

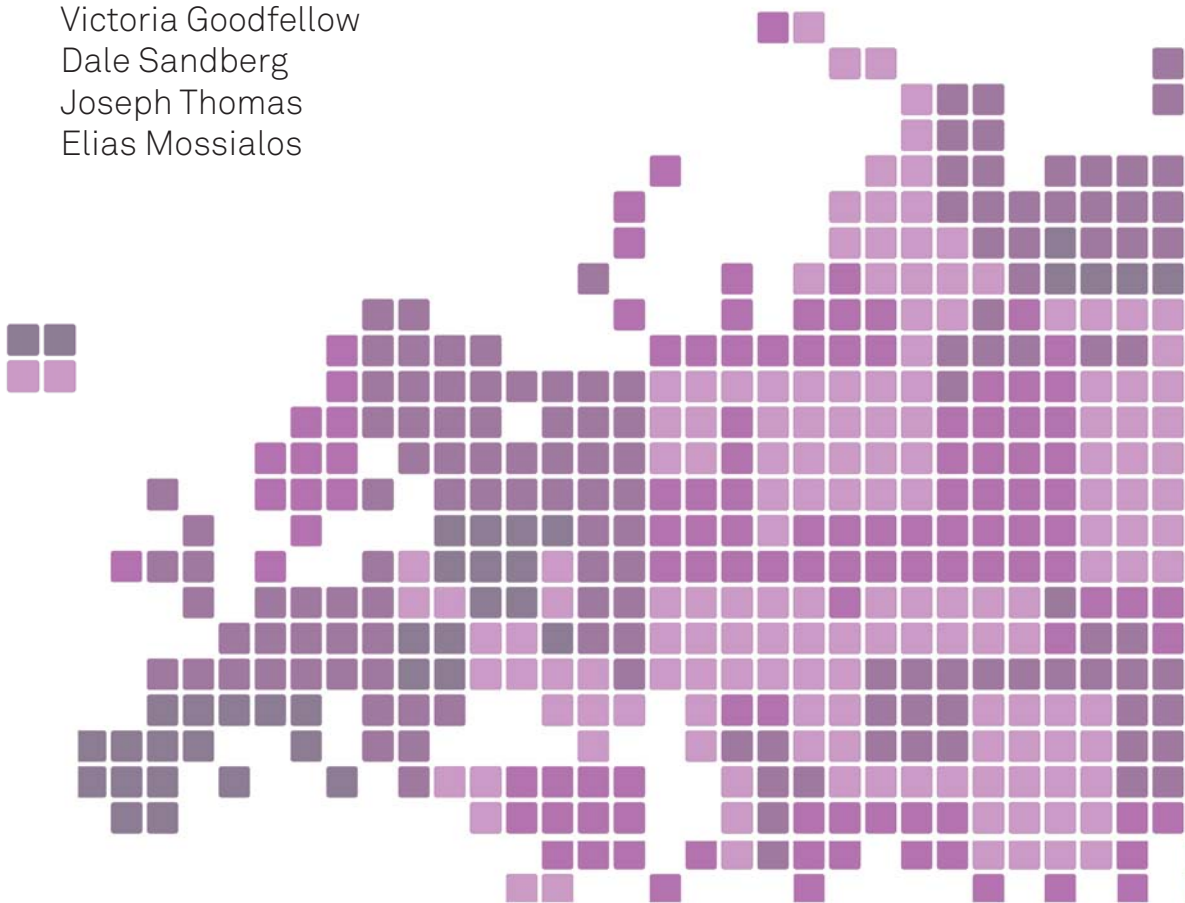
Ensuring innovation in diagnostics for bacterial infection

44

Observatory
Studies Series

Implications for policy

Edited by
Chantal Morel
Lindsay McClure
Suzanne Edwards
Victoria Goodfellow
Dale Sandberg
Joseph Thomas
Elias Mossialos



Ensuring innovation in diagnostics for bacterial infection



The European Observatory on Health Systems and Policies supports and promotes evidence-based health policy-making through comprehensive and rigorous analysis of health systems in Europe. It brings together a wide range of policy-makers, academics and practitioners to analyse trends in health reform, drawing on experience from across Europe to illuminate policy issues.

The Observatory is a partnership hosted by the WHO Regional Office for Europe; which includes the governments of Austria, Belgium, Finland, Ireland, Norway, Slovenia, Sweden, the United Kingdom, and the Veneto Region of Italy; the European Commission; the World Bank; UNCAM (French National Union of Health Insurance Funds); the London School of Economics and Political Science; and the London School of Hygiene & Tropical Medicine. The Observatory has a secretariat in Brussels and it has hubs in London (at LSE and LSHTM) and at the Technical University of Berlin.

Ensuring innovation in diagnostics for bacterial infection

Implications for policy

Edited by

Chantal Morel

Research Officer, LSE Health (London School of Economics and Political Science), Faculty of Medicine, University of Geneva

Lindsay McClure

Research Associate, LSE Health

Suzanne Edwards

Research Associate, LSE Health

Victoria Goodfellow

Research Associate, LSE Health

Dale Sandberg

Research Associate, LSE Health

Joseph Thomas

Research Assistant, LSE Health

Elias Mossialos

Professor of Health Policy, LSE Health

© World Health Organization 2016 (acting as the host organization for, and secretariat of, the European Observatory on Health Systems and Policies)

Address requests about publications to: Publications, WHO Regional Office for Europe, UN City, Marmorvej 51, DK-2100 Copenhagen Ø, Denmark.

Alternatively, complete an online request form for documentation, health information, or for permission to quote or translate, on the Regional Office web site (<http://www.euro.who.int/pubrequest>).

All rights reserved. The European Observatory on Health Systems and Policies welcomes requests for permission to reproduce or translate its publications, in part or in full.

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the European Observatory on Health Systems and Policies concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the European Observatory on Health Systems and Policies in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by the European Observatory on Health Systems and Policies to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either express or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall the European Observatory on Health Systems and Policies be liable for damages arising from its use. The views expressed by authors, editors, or expert groups do not necessarily represent the decisions or the stated policy of the European Observatory on Health Systems and Policies or any of its partners.

ISBN 978 92 890 50364

Printed in the United Kingdom

Cover design by M2M

Table of contents

Acknowledgements	ix
List of abbreviations	xi
List of tables and figures	xv
1. Introduction	1
2. Background	3
2.1 Trends in the use and misuse of antibiotics	3
2.2 Trends in the prevalence of resistance	7
3. Overview of the diagnostics market	13
3.1 Introduction	13
3.2 Shape and size of the market	13
3.3 Recent trends in the market	16
3.4 Exhibits: examples of recent breakthroughs in diagnostic development	25
4. Supply-side bottlenecks inhibiting development of priority diagnostics	33
4.1 Introduction	33
4.2 Drivers of resource allocation decisions by developers and prospective diagnostic developers	33
4.3 Scientific and technical barriers	40
5. Reimbursement-related signals received from procurement and reimbursement agencies	57
5.1 Introduction	57
5.2 Background: reimbursement in the United States	57
5.3 Coverage: determining clinical utility	58
5.4 Background: overview of reimbursement of diagnostics in the United Kingdom and Europe	77
5.5 Implications of being tied to indication	81
5.6 Variation across countries	84
5.7 Reimbursement case study	86

6. Regulation	89
6.1 Introduction	89
6.2 History of medical device regulation	89
6.3 Evolving needs for medical device regulation	90
6.4 Overview of regulatory processes for market entry in Europe and the United States	90
6.5 United States current regulatory structures/frameworks	92
6.6 EU current regulatory structures/framework	102
6.7 Reform under way in the United States	108
6.8 Reforms under way in Europe	115
6.9 Industry stakeholder involvement in European regulatory reforms	118
6.10 Evaluation of communication pathways between regulator and industry	118
6.11 FDA flexibility in antibiotic approval/trial design which may influence uptake of diagnostics	121
6.12 Flexibility in clinical trial requirements for antibiotic development	121
6.13 Regulatory comparison United States/EU	122
6.14 Harmonization of the diagnostics regulatory pathway in the United States and EU	125
6.15 Industry perspectives on harmonization	128
6.16 Stakeholder perception of overall regulatory processes for diagnostics	129
7. Intellectual property challenges	133
7.1 Introduction	133
7.2 History	133
7.3 Patent-related bottlenecks to diagnostic development	136
8. Demand-side issues	145
8.1 Introduction: complexity in demand expression	145
8.2 Engagement to improve developer understanding of demand	146
8.3 Determinants of and barriers to uptake of new POC diagnostics	148
8.4 Diagnostic and clinical guidelines	155
8.5 Prescribing culture	161
8.6 Patient barriers	164
9. Economic evaluation: the limited evidence base affecting both supply and demand for new diagnostics	165
9.1 Introduction	165
9.2 Background: economic evaluation and cost-effectiveness	165
9.3 Background: economic evaluation in the United States	167
9.4 Background: summary of the evidence from economic evaluations of rapid POC diagnostics	170
9.5 Challenges in making the “business case” for new diagnostics	178

9.6	Need for greater role of public sector in setting format priorities	182
9.7	Cost–effectiveness evidence in reimbursement decisions	183
9.8	Technical matters surrounding published cost–effectiveness studies of rapid POC diagnostics	185
10. Underlying and purpose-driven health system incentives affecting demand for diagnostics		193
10.1	Introduction	193
10.2	Reimbursement	193
10.3	Organization of budgets	200
10.4	Group purchasing	201
10.5	Performance assessment	203
10.6	Public performance monitoring	206
10.7	Financial penalties for poor performance	206
10.8	Financial bonuses for positive performance	207
11. Co-development of antibiotics and diagnostics for bacterial infection		209
11.1	Introduction	209
11.2	Potential of co-development	209
11.3	Background: the nature and underlying differences in the market for antibiotics and diagnostics	210
11.4	Considerations for co-development strategies	215
12. Policy response		235
12.1	Rationale for intervention in the diagnostics market	235
12.2	Initiatives to support diagnostics development	236
12.3	Final recommendations	259
Appendix A: Summary of studies on the cost–effectiveness of POCTs to diagnose sepsis		263
Appendix B: Summary of studies on the cost–effectiveness of POCTs to diagnose UTI		265
Appendix C: Streptococcal pharyngitis cost–effectiveness studies		269
Appendix D: United Kingdom HGC recommendations 2010		273
Appendix E: Recommendations of the SACGHS to the United States DHHS in 2010 report		275

Acknowledgements

The research for this report was undertaken from March 2012 through April 2013 and was made possible by a grant from the Pew Charitable Trusts. The material was updated in early 2015 in preparation for publication in book format. Much of the material presented here was drawn from extensive consultation with experts, including clinicians, lab technicians, hospital managers, industry representatives, insurance companies, public payers, regulatory agencies, managers from both public and private entities involved in diagnostics R&D and academics, with the aim of exposing potential bottlenecks and weaknesses in the current system and exploring innovative policy solutions. The authors would like to thank the many experts who agreed to be interviewed and are especially grateful to those who reviewed the draft in its entirety. Thanks also to those who helped at various stages of the evidence gathering process, including Julie Tran and Shannon McGrath.

List of abbreviations

ADEPT	Autonomous Diagnostics to Enable Prevention and Therapeutics
AHRQ	Agency for Healthcare Research and Quality
AMA	American Medical Association
AMCP	Academy of Managed Care Pharmacy
APC	Ambulatory Payment Classification
APEC	Asia-Pacific Economic Cooperation
ASPR	Assistant Secretary for Preparedness and Response
AWARE	Alliance Working for Antibiotic Resistance Education
BARDA	Biomedical Advanced Research and Development Authority
BBMRI	European Biobanking and Biomolecular Resources Infrastructure
BCBS	BlueCross BlueShield Association
BIVDA	British In Vitro Diagnostics Association
CAD	Canadian dollars
CDC	Centers for Disease Control and Prevention
CDDEP	Center for Disease Dynamics, Economics & Policy
CED	Coverage with evidence development
CEN	European Committee for Standardization
GENELEC	European Committee for Electrotechnical Standardization
CER	Comparative effectiveness research
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMS	Centers for Medicare and Medicaid Services
CPI	Consumer price index
CPT	Current Procedural Technology
QUIN	Commissioning for Quality and Innovation
DAP	Diagnostics assessment programme

DARPA	Defense Advanced Research Projects Agency
DECIDE	Developing Evidence to Inform Decisions about Effectiveness
DG	Directorate-General
DHHS	Department of Health and Human Services (United States)
DNA	Deoxyribonucleic acid
DRG	Diagnosis-related group
EARS-Net	European Antimicrobial Resistance Surveillance Network
EC	European Commission
ECDC	European Centre for Disease Prevention and Control
EDMA	European Diagnostic Manufacturers Association
EEA	European Economic Area
EPCs	Evidence-based practice centers
ESAC-Net	European Surveillance of Antimicrobial Consumption Network
ESO	European Standards Organization
EU	European Union
EUA	Emergency Use Authorization
EUDAMED	European Database on Medical Devices
FDA	Food and Drug Administration
FDASIA	Food and Drug Administration Safety and Innovation Act
FDC	Federal Food, Drug, and Cosmetic Act
FP7	7th Framework Programme for Research and Technological Development
GAS	Group A β -haemolytic streptococcus
GBP	British pound
GHTF	Global Harmonization Task Force
GPs	General practitioners
GPOs	Group purchasing organizations
HAI	Hospital acquired infections
HGC	Human Genetics Commission
HRGs	Health-related groups
ICU	Intensive care unit
IDE	Investigations Device Exemption
IDSA	Infectious Diseases Society of America

IMDRF	International Medical Device Regulators Forum
IMI	Innovative Medicines Initiative
IP	Intellectual property
IPPS	Inpatient Prospective Payment System
IRB	Institutional review board
ISO	International Organization for Standards
IUO	Investigational use only
IVD	In vitro diagnostic/s
IVDD	In Vitro Diagnostic Medical Devices Directive
JEREMIE	Joint European Resources for Micro to Medium Enterprises
LCD	Local coverage decisions
LDT	Laboratory-developed test
LOS	Length of stay
LPAD	Limited population antibacterial drug
LSIF	Life Sciences Innovation Forum
MAC	Medicare administrative contractors
MDR	Multi-drug resistant
MDUFA	Medical Device User Fee Amendments
MDUFMA	Medical Device User Fee and Modernization Act
MHRA	Medicines and Healthcare products Regulatory Agency
MODERN Cures Act	Modernizing Our Drug and Diagnostics Evaluation and Regulatory Network Act
MRSA	Methicillin-resistant Staphylococcus aureus
MS-DRG	Severity-adjusted diagnostic related groups
MTB	Mycobacterium tuberculosis
NBs	Notified Bodies
NCD	National coverage decisions
NHS	National Health Service (United Kingdom)
NIAID	National Institute of Allergy and Infectious Diseases
NICE	National Institute for Health and Clinical Excellence
NIH	National Institutes of Health (United States)
NIHR	National Institute for Health Research
NLA	National limitation amount
OPPS	Outpatient prospective payment system
PCOR	Patient-centered outcomes research

PCORI	Patient-Centered Outcomes Research Institute
PCR	Polymerase chain reaction
PHC	Personalized health care
PMA	Pre-market approval
POC	Point-of-care
POCT	Point-of-care tests
POCTRN	POC Technologies Research Network
PPP	Public–private partnership
PwC	PricewaterhouseCoopers
QALY	Quality-adjusted life year
QSR	Quality System Regulations
R&D	Research and development
RCT	Randomized control trial
RHSC	LSIF Regulatory Harmonization Steering Committee
RNA	Ribonucleic acid
RUO	Research use only
SACGHS	Secretary’s Advisory Committee on Genetics, Health, and Society
SBIR	Small Business Innovation Research
SBRI	Small Business Research Initiative
SIRS	Systemic inflammatory response syndrome
SME	Small- and medium-sized enterprises
SSI	Surgical site infection
STI	Sexually transmitted infection
STTR	Small Business Technology Transfer
TB	Tuberculosis
TEC	Technology Evaluation Center
TPPs	Target Product Profiles
TSN	The Surveillance Network
TTIP	Transatlantic Trade and Investment Partnership
UDI	Unique Device Identifier
USPSTF	United States Preventive Services Task Force
USPTO	United States Patent and Trademark Office
UTI	Urinary tract infection
VA	United States Department of Veterans Affairs

List of tables and figures

Tables

Table 4.1	General venture capital decision-making process	37
Table 5.1	Ratings scale for coverage decisions used by USPSTF	62
Table 5.2	BlueShield California Technology Assessment Forum evidence levels	63
Table 5.3	Hayes Rating system	64
Table 5.4	Variation in direct core pathology test costs across trusts in England 2009	84
Table 5.5	Reimbursement of trastuzumab companion diagnostics HER-2/neu and K-RAS in selected European countries	87
Table 6.1	FDA regulatory classes for IVD devices	94
Table 6.2	Relative proportions of CLIA designated laboratories	95
Table 6.3	Complementarity of the United States system for regulating IVD devices	96
Table 6.4	A selection of the 33 provisions, signed into law in July 2012, in the Food and Drug Administration Safety and Innovation Act (FDASIA) relating to medical device regulatory improvements	110
Table 6.5	Summary of the response to the public consultation of the IVDD revisions	117
Table 6.6	Priorities of the new international forum (IMDRF) for facilitating global regulatory harmonization for medical devices	126
Table 8.1	NICE DAP diagnostics guidance to date (published and in progress)	161
Table 10.1	Hospital acquired conditions that are not reimbursed	206
Table 12.1	Merits of incentive types	236

Figures

Fig. 2.1	Consumption of antibiotics for systemic use in the community in EU/EEA countries, 2010	4
Fig. 2.2	Consumption of antibiotics for systemic use in the community by antibiotic class, 42 European countries (based on data from 2011)	5
Fig. 2.3	The average number of dispensed outpatient antibiotic prescriptions per 1 000 inhabitants by US state in 2010	6
Fig. 2.4	Available national data on resistance for nine selected bacterial/antibacterial drug combinations in 2013	9
Fig. 2.5	Percentage of <i>Klebsiella pneumoniae</i> isolates with resistance to fluorquinolones	9
Fig. 2.6	Cross-country comparison of resistance levels based on 2009 data	11
Fig. 3.1	IVD market by segment and growth profile	14

Fig. 3.2	The global IVD and molecular diagnostics markets (US\$ million), 2004–2016	15
Fig. 3.3	Global IVD industry – key players	15
Fig. 3.4	Global pharmaceutical R&D expenditure (Pharmaceutical Research and Manufacturers of America member firms)	17
Fig. 3.5	European IVD market revenues (€ million)	18
Fig. 3.6	Molecular diagnostics market overview	21
Fig. 3.7	Molecular tests approved in the United States by therapy area	21
Fig. 3.8	Market overview of companies where molecular diagnostics are primary area of focus	22
Fig. 5.1	Stakeholders and factors influencing coverage decision	59
Fig. 5.2	Clinical laboratory services payment system	73
Fig. 5.3	Health care structures in United Kingdom	78
Fig. 6.1	DHHS organizational chart showing medical device regulatory oversight in the United States	93
Fig. 6.2	General controls	97
Fig. 6.3	510(k) pathway	98
Fig. 6.4	Pre-market approval	99
Fig. 6.5	Categorization of medical devices according to the EC’s IVDD	104
Fig. 6.6	Impact of MDUFA reforms on FDA fee revenues for medical devices	109
Fig. 6.7	Comparison of time to market in PMA and reimbursement processes between the United States and the EU	125
Fig. 9.1	Mean LOS for non-infected patients and those with HAI at various sites	173
Fig. 9.2	Mean hospital cost for non-infected patients and those with HAI at various sites	173
Fig. 11.1	The scientific and commercial potential of companion diagnostics	210
Fig. 11.2	Estimates of cost and time to approval for molecular diagnostics developers	215
Fig. 11.3	Typical components required to develop a companion diagnostic (separate from drug development)	216
Fig. 11.4	Potential time-line for co-development of drug and companion diagnostic	217
Fig. 11.5	Life-cycle for co-development of a predictive diagnostic	218
Fig. 11.6	Increase in Dx/developers’ collaborations within Roche	219
Fig. 11.7	Number of companion diagnostic partnerships by disease area, 2009–2010	221
Fig. 11.8	Key pharmaceutical–diagnostic deals by company and therapy area	222
Fig. 11.9	Idealized external agreement pharmaceutical–diagnostic time-line	223

Chapter 1

Introduction

The evolution of bacterial resistance to antibiotics opens the door for the resurgence of infectious diseases which have long been considered curable, posing a major challenge to global health. Strains that are resistant to entire classes of antibiotics are now emerging in both hospital and community health settings around the world. It is without question that this resistance is in large part a result of the misuse of antibiotics. Over-prescription and, in some settings, self-medication with antibiotics without prior diagnosis have provided the selective pressures to drive the evolution of resistance.

As traditional diagnostic methods such as culture and drug susceptibility testing can require days to produce results (even for rapidly growing bacteria), few infections can be microbiologically confirmed in a time span sufficiently short to inform treatment decisions. Infections are therefore very often treated empirically, inevitably leading to the inappropriate treatment of viral infections as bacterial infections, incorrect treatment of bacterial infections (i.e. treatment with the wrong antibiotic), and over-prescription of broad-spectrum antibiotics where narrow-spectrum antibiotics were available and would have sufficed.

Advances in biotechnology have led to the development of new devices that can rapidly detect pathogens, and in some cases resistance, at the point of care. Indeed the widespread availability and appropriate usage of point-of-care tests (POCTs) has the potential to significantly improve prescribing practices. However, despite the known threat of antibiotic resistance and the seemingly immense potential of POCTs in helping to slow its growth, few of these devices have found their way to care settings. This inability to get these devices to the market and ultimately into the appropriate treatment pathway reflects important failures in health, science and innovation policies.

By exploring the unique challenges facing diagnostic devices – such as ambiguous regulatory hurdles and short life-cycles that limit return on investment – this report aims to highlight the need for rapid innovation in the industry, not only in technology but also in policy. Solving the problem of antibiotic resistance will require innovative approaches that increase cross-sector collaboration, integrating scientific and medical research with regulatory, health care, industrial and pharmaceutical policies to overcome bottlenecks and incentivize continued

2 Ensuring innovation in diagnostics for bacterial infection

innovation in this area. The policy response to this situation must be multifaceted and broad, from rallying governments to increase public funding for antibiotic resistance research, down to conducting proper economic assessments of POCTs to understand their value in slowing resistance. The concluding recommendations of this book highlight the policy areas that will be most critical, those with the greatest potential for better promoting both research and development (R&D) and uptake of effective point-of-care (POC) diagnostics, and those where important efficiency gains can be made compared to current practice.

Chapter 2

Background

2.1 Trends in the use and misuse of antibiotics

Despite knowledge of the link between antibiotic use and resistance, there is significant worldwide misuse and overuse of antibiotics. The IMS Institute for Healthcare Informatics has estimated this problem is costing health systems US\$ 54 billion per year, equivalent to 0.9% of global total health expenditure.^{a, 1}

In Europe, trends in antibiotic consumption in the community are monitored by the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) which is coordinated by the European Centre for Disease Prevention and Control (ECDC). Fig. 2.1 provides an overview of antibiotic consumption data for 29 European countries in 2010 that was collected through ESAC-Net; consumption is presented as the number of defined daily doses per 1000 inhabitants.²

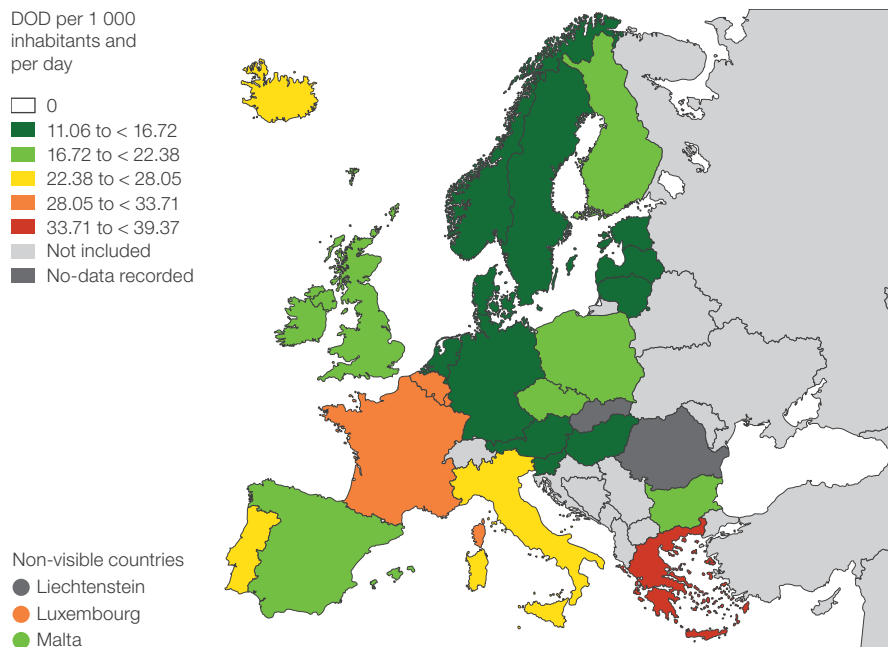
The WHO Regional Office for Europe has complemented the ECDC work by supporting European countries that are not in the European Union (EU) in the surveillance of antimicrobial consumption.³

Data from 2011 indicate an almost fourfold difference between the lowest (the Netherlands) and the highest (Turkey) antibiotic users among 42 countries and regions in the WHO European Region (within and outside the EU).⁴ While overall antibiotic prescribing rates have been increasing over the past 10 years, there are a number of countries, including Bulgaria and Slovenia, where reductions have been documented.⁵

Fig. 2.2 breaks down antibiotic use in the community by antibiotic type for 42 European countries. The proportionally greater use of broad-spectrum antibiotics in the southern and eastern Mediterranean is thought to be a contributing factor to the higher levels of resistance seen in these countries.⁶

a Global information about the costs of antibiotic overuse and/or misuse is sparse. The IMS Institute used information from the literature to create an index value for avoidable cost and then applied this to 186 countries, making country-level adjustments for a range of factors that drive cost differences such as oral antibiotic use per capita.

Fig. 2.1 Consumption of antibiotics for systemic use in the community in EU/EEA countries, 2010



Source: ECDC data.⁷

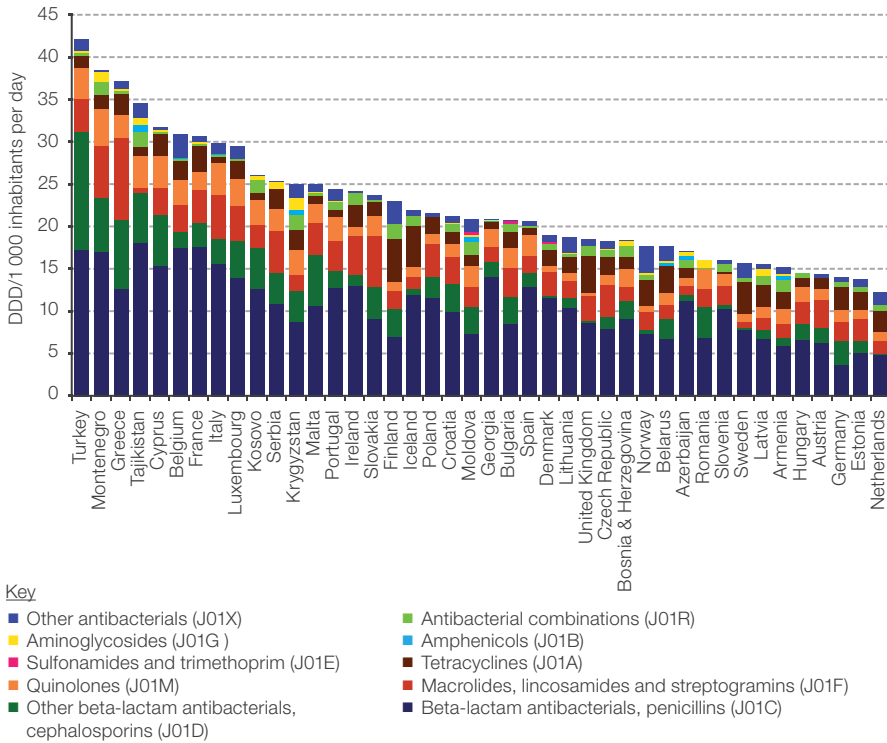
A similar data set is available for the inpatient care setting where prescribing rates of cephalosporins and other beta-lactams such as carbapenems are generally higher than in the community.⁸

In the United States, antibiotic prescribing rates are believed to have reduced by 17% since 1999.⁹ Unlike in Europe, however, there is not a comprehensive source of information in the public domain about antimicrobial usage – a problem that has recently been highlighted by the Infectious Diseases Society of America (IDSA).¹⁰ Published studies have used a range of different data sources¹¹ and methodologies,¹² making comparison difficult.

In 2009, the national United States antibiotic use rate was estimated at 0.86 prescriptions per capita which, although lower than the highest consuming countries in Europe, is still higher than many northern European countries such as the Netherlands.¹³

A frequent research finding has shown geographical variation in utilization with southern states having the highest consumption rates.¹⁴ One recently published study that used Medicare Part D data from 2007 to 2009 to study patterns in

Fig. 2.2 Consumption of antibiotics for systemic use in the community by antibiotic class, 42 European countries (based on data from 2011)



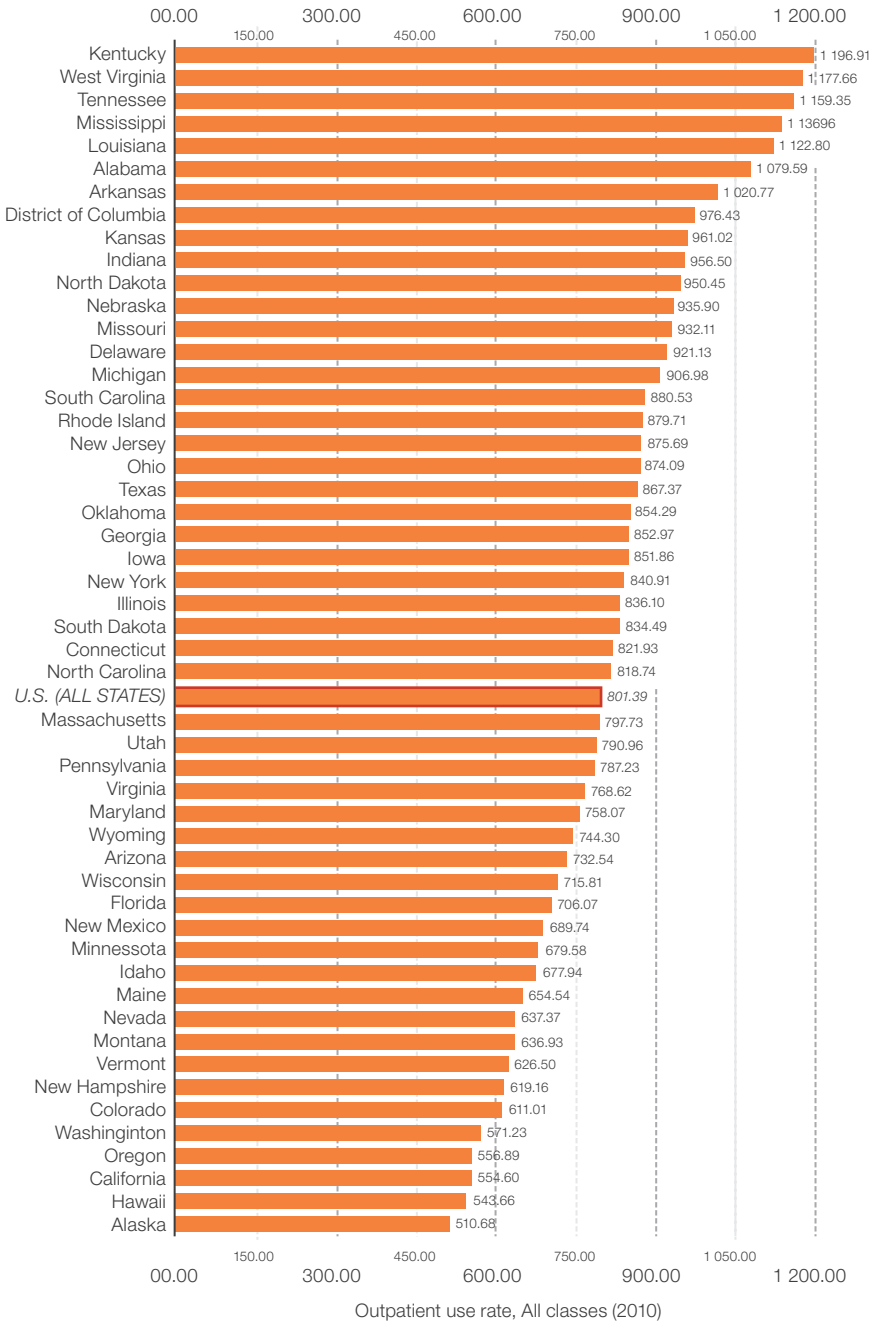
Source: WHO Regional Office for Europe data.¹⁵

Note: Reporting was not consistent across all countries. For example, some countries (e.g. Cyprus, Iceland, Lithuania and Slovakia) provided only total care data that included the hospital sector. Other countries (e.g. Romania and Spain) provided reimbursement data, which excluded non-reimbursed drugs such as those accessed without prescription.

prescribing for seniors, found that 21.4% of patients were prescribed an antibiotic per quarter in the South compared to 17.4% in the West; a variation that could not be explained by differences in clinical need.¹⁶ In an analysis undertaken by the Center for Disease Dynamics, Economics & Policy (CDDEP), using 2010 data from IMS Health, antibiotics were found to be prescribed twice as frequently per capita in the East South Central region than in Pacific states.¹⁷ Fig. 2.3 provides an overview of regional variation in consumption across the United States.

As well as changes in the overall volume of antibiotics prescribed, researchers have also identified a shift in the nature of prescribing over the past 10 years; in the United States, newer antibiotics such as fluoroquinolones and macrolides are increasingly being prescribed, risking accelerating the emergence of resistant microbes.¹⁸

Fig. 2.3 *The average number of dispensed outpatient antibiotic prescriptions per 1 000 inhabitants by US state in 2010*



Source: CDDEP.¹⁹

However, new initiatives in terms of pharmaceutical services – for example related to management of sore throat – have been started in the United States.²⁰ This type of task shifting, making use of reliable points of care at the pharmacy, indicates that more can be done using points of care to strengthen collaboration between health professionals and offer advantages for patient care, without compromising patient safety.

Limited information is available on antibiotic use in low-income countries with the infrastructure and resources required for surveillance often not available.²¹ One recent estimate published by WHO is that in low- and middle-income countries, antibiotics are inappropriately prescribed for about 50% of acute cases of viral upper respiratory tract infections and viral diarrhoea.²²

A range of factors are thought to influence antibiotic prescribing rates including the prevalence of infections, social and cultural factors, public awareness of the role of antibiotics and resistance, and the nature of the health system, including the availability of resources.²³ Researchers in Europe have also demonstrated a correlation between the number of branded antibiotic products marketed in a country and consumption. In this case, however, a causal relationship has not been established, and this phenomenon may simply be explained by higher consumption countries offering a more attractive market.^{24, 25}

Antibiotic stewardship programmes and rapid POC testing can help improve the appropriateness of prescribing, both ensuring that antibiotics are only prescribed where they will be clinically beneficial and helping to shift prescribing from broad- to narrow-spectrum agents. For example, a large randomized control trial (RCT) that was undertaken in the United Kingdom between January 2002 and February 2005 involving women aged 17–70 with suspected urinary tract infections (UTIs) demonstrated that using a POC dipstick test reduced antibiotic prescribing by 20–25%.²⁶ Similarly, in a recent Dutch study, general practitioners (GPs) with access to the c-reactive protein POCT prescribed antibiotics to 31% of patients presenting with the symptoms of an upper tract infection compared to 53% of patients when the GP did not have access to a test.²⁷ In the management of suspected sepsis, the use of rapid molecular diagnostics has been shown to enable earlier switches from broad- to narrow-spectrum therapy, targeted to the pathogen causing the infection.²⁸

2.2 Trends in the prevalence of resistance

In the early part of the 20th century, Alexander Fleming and Selman Waksman revolutionized the treatment of infectious disease by isolating penicillin and streptomycin²⁹ however, by the time they collected Nobel Prizes for their respective achievements, there was already evidence that the inappropriate use of antibiotics

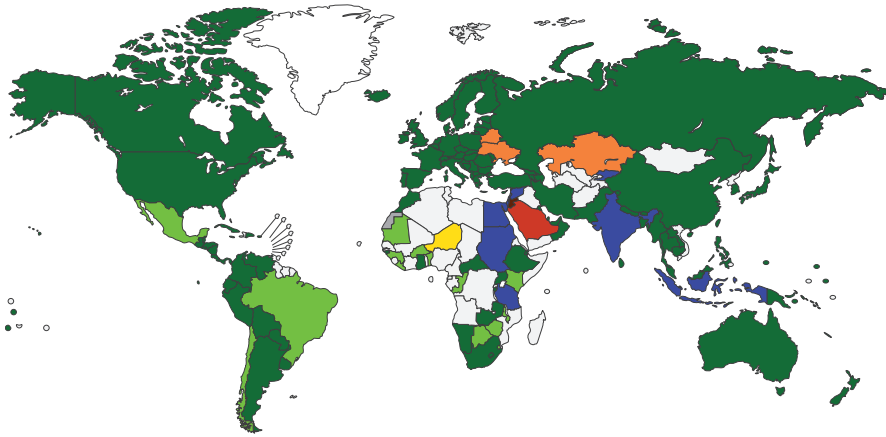
could lead to antimicrobial resistance.^{30, 31} Today, as a consequence of microbes developing resistance through mechanisms such as mutation and gene transfer,³² maintaining the effectiveness of antibiotics is a constantly evolving challenge; as new antibiotics have been introduced, it has only been a matter of time before resistance has emerged.³³

To monitor the spread of resistance, a range of surveillance systems have been established which capture data at health care organization level and use this to identify national, regional and global trends (Fig. 2.4). For example, in Europe, the European Antimicrobial Resistance Surveillance Network (EARS-Net) publishes data collected from hospitals and laboratories in 26 European countries (e.g. Fig. 2.5).³⁴ In addition, the Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CEASAR network) has been created by WHO Regional Office for Europe using methodology compatible with that of EARS-Net and currently collects data from additional six eastern European countries.³⁵ A similar initiative in the United States is the National Healthcare Safety Network (NHSN), which is managed by the Centers for Disease Control and Prevention (CDC);³⁶ however, fewer health care acquired infections are monitored through this network compared to EARS-Net and, as information is published at aggregate level, it is not possible to make geographical comparisons – perceived weaknesses of the network that some stakeholders would like to see corrected.³⁷ The ECDC's point prevalence survey is currently monitoring the incidence of health care acquired infections and antimicrobial usage in acute care hospitals in the EU.³⁸ There are also microbe-specific surveillance systems such as the CDC's Gonococcal Isolate Surveillance Project,³⁹ which tracks resistant strains of *Neisseria gonorrhoeae*, and networks operated by commercial providers such as The Surveillance Network (TSN).⁴⁰

While historically resistance has been seen as a problem linked to inpatient care settings, there is growing recognition that antimicrobial resistance can also compound the impact of common community acquired infections.⁴¹ For example, since 2000, numerous developed countries have reported rapid growth in community acquired methicillin-resistant *Staphylococcus aureus* (MRSA) infection rates.^{42, 43} As well as making the skin and tissue infections caused by *S. aureus* more difficult to treat, resistant strains have been linked to a toxin that causes tissue necrosis.⁴⁴ Going forward, initiatives such as the European Commission (EC) funded APRES – appropriateness of prescribing antibiotics in primary health care in Europe with respect to antibiotic resistance – project are likely to increase the availability of data on resistant strains circulating in the community.⁴⁵

A range of factors can facilitate the development of resistance, the most significant being medical, agricultural and environmental exposure to antibiotics.⁴⁶ Researchers have repeatedly demonstrated that an association exists between

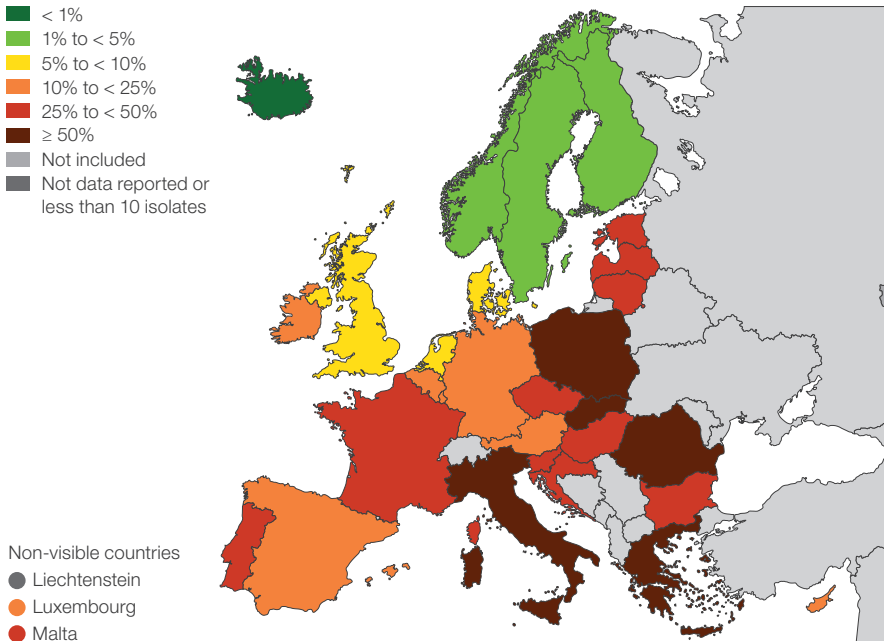
Fig. 2.4 Available national data on resistance for nine selected bacterial/antibacterial drug combinations in 2013⁴⁷



Number of requested bacteria/antibacterial medicine resistance combinations for data was obtained:

- < 5 (n=89)
- 2-5 (n=22)
- 1 (n=3)
- No information obtained for this report, some centres participate in some ANSORP Projects (n=2)
- No information obtained for this report, some centres participate in some RusNet Projects (n=3)
- No information obtained for this report (n=60)
- Not applicable
- National data not available (n=15)

Fig. 2.5 Percentage of *Klebsiella pneumoniae* isolates with resistance to fluorquinolones



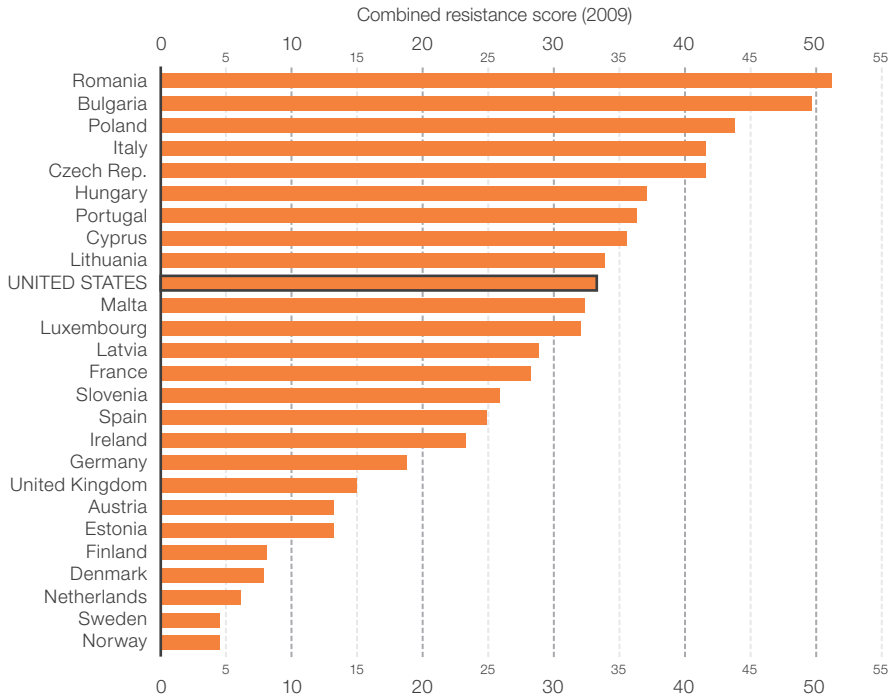
Source: EARS-Net.⁴⁷

the consumption of antibiotics and the prevalence of resistance, for example, in Europe, a north/south divide in resistance patterns has been identified correlated to antibiotic usage; countries such as Denmark, where antibiotic use has historically been carefully controlled, have been found to have lower concentrations of resistant bacteria than their higher-consuming, southern counterparts.⁴⁹ Similarly, studies have shown that actions to reduce the frequency of antibiotic prescribing have been effective in controlling the spread of resistance. In London, for instance, researchers at St George's hospital were able to demonstrate a strong association between reductions in MRSA rates and the introduction of a policy to reduce the prescribing of cephalosporins and ciprofloxacin.⁵⁰

There can be significant differences in resistance patterns between countries. CDDEP, a Washington-based think-tank, has used data from the TSN to develop the "Resistance Map", an open-access resource which provides regional and cross-country comparative resistance data for a number of pathogens.⁵¹ Using amalgamated data for various antibiotic/organism combinations, they have calculated a combined resistance score for countries in Europe and North America; as illustrated in Fig. 2.6, while the United States has lower resistance levels than certain eastern and southern European countries, its levels are higher than northern European countries, including the United Kingdom and the Nordic nations. Resistance levels can also vary significantly within countries. For example, in a study on samples collected from across the United States in 1999–2000, resistance to penicillin among *Streptococcus pneumoniae* isolates varied from 24.8% in the South Atlantic States to 8.3% in New England.⁵²

The prevalence of drug-resistant microbes varies depending on the combination of the microorganism and the antimicrobial agent.⁵³ A particular concern is the emergence of multidrug-resistant (MDR) organisms which can leave physicians with few treatment options and, in the worst case, can result in a "therapeutic dead end", a scenario that has occurred with extensively resistant tuberculosis (TB).⁵⁴ Other microbes that have been found to have MDR isolates include *Acinetobacter baumannii*, *Burkholderia cepacia*, *Enterococcus faecium*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Ralstonia pickettii*, *Staphylococcus aureus*, *Stenotrophomonas maltophilia* and *Streptococcus pneumoniae*.⁵⁵

A current key concern is rapid growth in drug resistant strains of *E. coli*, a microbe often responsible for urinary tract and bloodstream infections.⁵⁶ In Europe, 2011 data collected through EARS-Net indicated that up to 77.6% of *E. coli* isolates were resistant to aminopenicillins and over a third of European countries reported an increase in combined resistance to third-generation cephalosporins, fluoroquinolones and aminoglycosides.⁵⁷ Similar results have been found in the United States, with a recent study using data from TSN finding that resistance

Fig. 2.6 Cross-country comparison of resistance levels based on 2009 data

Source: CDDEP.⁵⁸

to the fluoroquinolone, ciprofloxacin increased from 3% to 17.1% between 2000 and 2010 and resistance to trimethoprim-sulfamethoxazole increased from 17.9% to 24.2%.⁵⁹

The proportion of drug-resistant *K. pneumoniae* isolates has also been increasing in Europe, a microbe linked to the disease, Klebsiella pneumonia. Almost a quarter of the isolates reported through EARS-Net in 2011 were resistant to at least three antimicrobial classes,⁶⁰ with the consequences of resistance including the need for more invasive care and an increased mortality rate.⁶¹ There has been a growing number of reports of resistance to the drug of last resort, colistin, with recent outbreaks of colistin-resistant, carbapenem-resistant *K. pneumoniae* occurring in a number of countries including Italy⁶² and the United States.⁶³

A. baumannii infections are often identified in intensive care units (ICUs) in patients who are immunosuppressed or who have had invasive surgery; they are associated with a high mortality rate.⁶⁴ In recent years, the trend towards increased resistance has been expedited by wounded soldiers returning from Iraq and Afghanistan carrying MDR strains.⁶⁵ Some strains of *A. baumannii* have been shown to be resistant to all major classes of antibiotics with evidence of growing

resistance to the drug of last resort, colistin,⁶⁶ which is an older antimicrobial agent linked to high degrees of toxicity.

The resistance of *Neisseria gonorrhoeae* is also displaying a worrying trend; data from the Gonococcal Isolate Surveillance Project has suggested growing *N. gonorrhoeae* resistance to third-generation cephalosporins in the United States, the treatment option now recommended by the CDC for gonorrhoea after the microbe developed resistance to other antimicrobials, including penicillins, macrolides and fluoroquinolones.⁶⁷

There are also some positive trends. Proactive work to contain resistance is thought to be responsible for stabilizing and in some cases decreasing resistance levels, for example in the case of *S. pneumoniae* in Europe⁶⁸ and the United States,⁶⁹ a bacterium responsible for ear infections and pneumonia. There is also a promising decline in MRSA. In the United States, the number of patients with MRSA requiring hospital treatment more than doubled between 1999 and 2005.⁷⁰ Since then the trend has reversed; hospital data collected through the National Healthcare Safety Network indicates a reduction in infection rates between 2001 and 2007⁷¹ and surveillance data from the CDC's Emerging Infections Program suggests that hospital acquired MRSA infections decreased by over a quarter between 2005 and 2009 while community acquired infections decreased by 17% in the same period.⁷² A similar trend has been seen in Europe.⁷³ One contributing factor to the decline is thought to be the active screening of patients using diagnostics tests, including using culture or rapid molecular diagnostics.⁷⁴

Chapter 3

Overview of the diagnostics market

3.1 Introduction

This chapter provides an overview of the current diagnostic market, describing the recent activity of key players in the industry and laying out important emerging trends affecting R&D in this area. The chapter concludes with a series of short case studies highlighting important developments in the search for better POC diagnostics to identify bacterial infection.

3.2 Shape and size of the market

Generally speaking *in vitro* diagnostics (IVD) tests are considered medical devices.^a They may be reagents, techniques, instruments, or a combination of these used *in vitro* for the examination of specimens such as blood, urine or tissue with the goal of obtaining a diagnosis from assays in a controlled environment outside a living organism.

Diagnostic tests are usually conducted in laboratories, private or public, equipped with appropriate and sometimes expensive instrumentation and staffed with trained and qualified personnel to perform the tests. As will be described in further detail later in this report, POC testing which occurs at or near the site of patient care, is sought after in the field of infectious bacterial diagnostics to allow the care team to receive the results more quickly and allow for immediate and informed management decisions to be made.

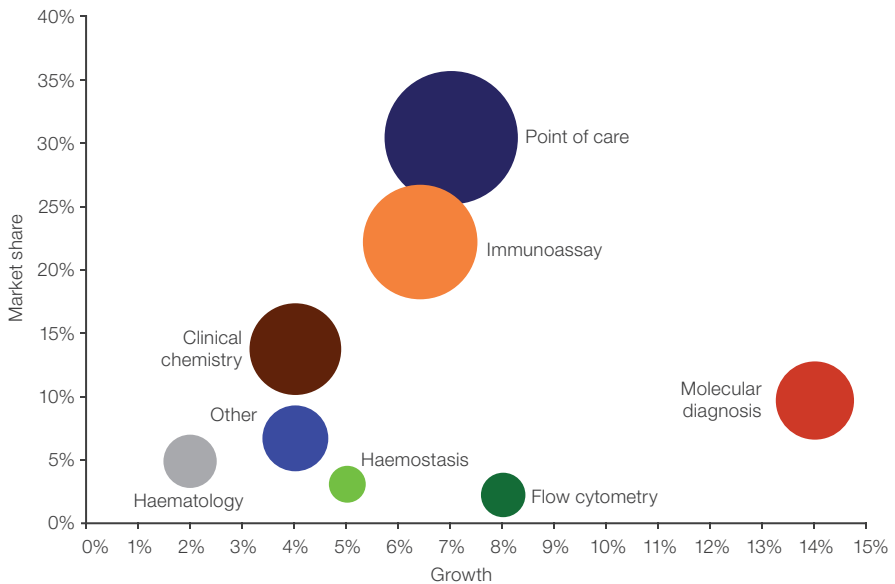
A number of analyst estimates^{1,2} approximate the overall global diagnostics market to be worth US\$ 40–45 billion with POC diagnostics contributing US\$ 12–13 billion. The bulk of the IVD market is concentrated in developed countries, with the United States (US\$ 19 billion), Europe (US\$ 14 billion) and Japan (approx. US\$ 4 billion) accounting for over 80% of global sales.³ An industry report by Cowen & Company⁴ suggests the aggregate market value of diagnostics for infectious disease is worth in excess of US\$ 3 billion annually

^a In Europe however IVDs have their own, separate Directive.

in the United States. This compares to aggregate industry global antibiotic sales estimated at US\$ 14 billion,⁵ with the market shrinking in dollar terms as key blockbuster drugs (such as Augmentin, Cipro, Zithromax) have faced patent expiry. Growth in the overall antibiotics market is also hampered by a slowdown in product launches: the Food and Drug Administration (FDA) approved 16 new antibiotics between 1983 and 1987, 5 between 2003 and 2007, and two since 2008.⁶ Estimates show that there are currently 37 novel antibiotics in development.⁷

The total IVD market, which includes various classes of assays, represented in Fig. 3.1 is expected to grow at a compound annual growth rate of 5% (2010–2016)⁸ with global sales forecast to pass the US\$ 50 billion mark in 2014,⁹ although as Fig. 3.2 demonstrates, the industry remains dwarfed by the size of the prescription pharmaceuticals market.

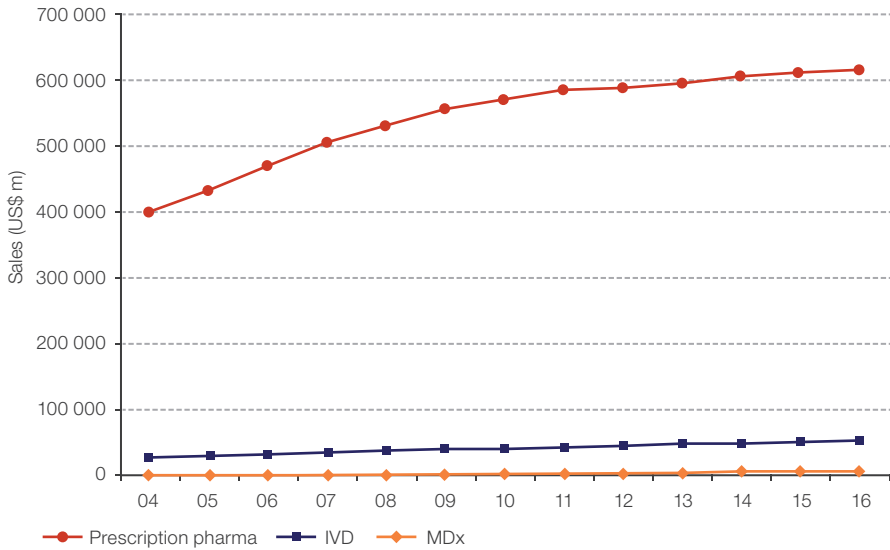
Fig. 3.1 IVD market by segment and growth profile¹⁰



Overall the IVD market is dominated by six key players: Roche Diagnostics, Abbott Diagnostics, Siemens, Johnson & Johnson Medical Devices and Diagnostics, Beckman Coulter and BioMerieux (Fig. 3.3).¹¹ Smaller players tend to be highly specialized, as in the broader IVD market a lack of product differentiation makes scale economies essential.¹²

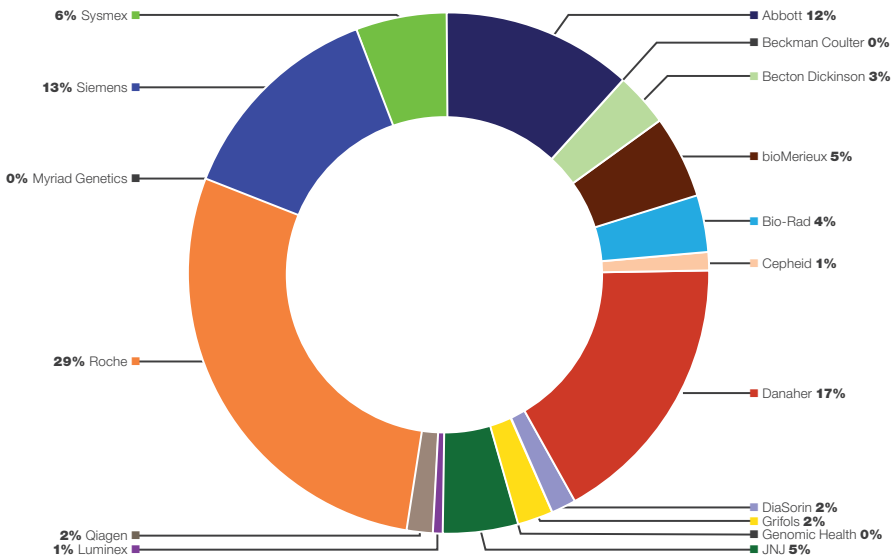
In recent years in the prescription pharmaceutical markets there has been much focus on sales of “blockbuster” drugs with sales in excess of US\$ 1 billion annually; however, in stark contrast there are few diagnostic products (or indeed markets)

Fig. 3.2 The global IVD and molecular diagnostics markets (US\$ million), 2004–2016¹³



Source: company-reported information; Roche Diagnostics PHC Investor Day, 2011, presentation for the 2010 and 2015 market numbers for IVD and MDx sectors (extrapolated to 2016 by Datamonitor); prescription pharmaceutical market forecast obtained from the PharmaVitae Explorer (October 2011)

Fig. 3.3 Global IVD industry – key players ^{14, 15}



with annual revenues in excess of US\$ 100 million,¹⁶ although the IVD markets for human immunodeficiency virus (HIV) (est. >US\$ 400 million) and human papilloma virus (est. US\$ 300–350 million) are notable exceptions in the field of infectious disease: this generally means diagnostic manufacturers need to seek a broad portfolio in order to achieve scale.

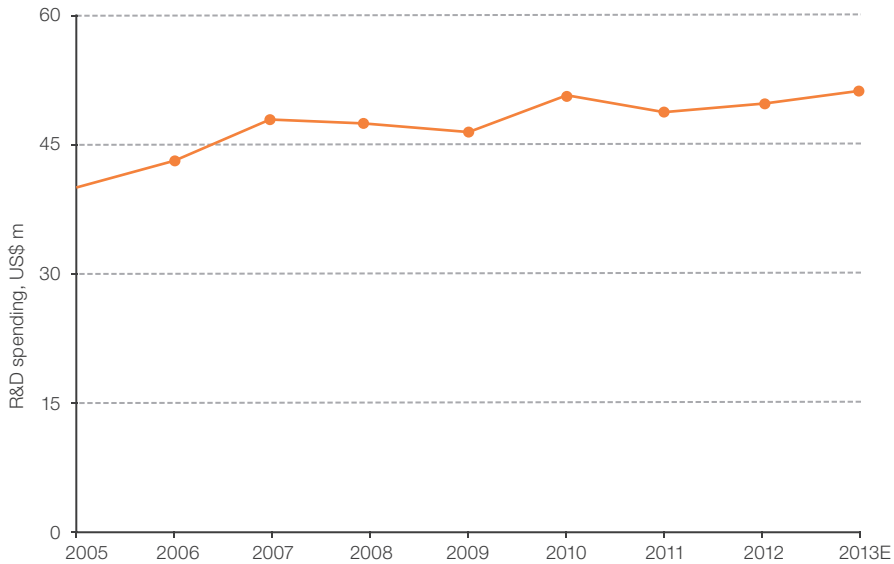
3.3 Recent trends in the market

3.3.1 Overall IVD market

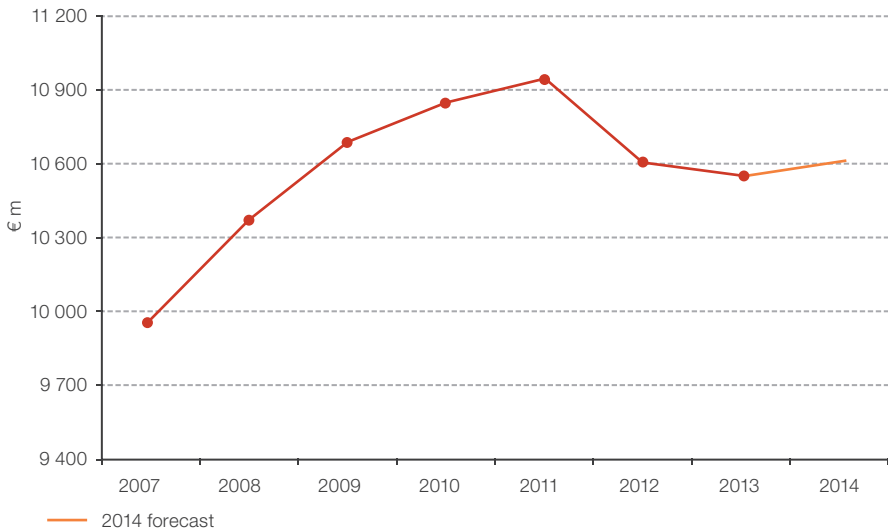
The impact of the broader economic backdrop on the diagnostic market is important to consider since diagnostics companies are more sensitive to changes in the macroeconomic cycle than other parts of the health care system. Around 20–25% of the sector's revenue generation capability comes from exposure to industrial (as opposed to clinical) end markets such as food testing, which often carries greater macroeconomic sensitivity.¹⁷ Furthermore, cuts to government funding for scientific research are likely to have an impact on diagnostics companies. Illumina is an extreme example, with 80% of its sales to either government institutions, such as the National Institutes of Health (NIH), or academic organizations supported by government funding.¹⁸ Illumina is a dominant player in the gene-sequencing market, selling gene-sequencing platforms and assays to a primarily research-focused end market and, as such, is particularly exposed to changes in government funding. As with many diagnostic companies, they sell the capital equipment at low margins and make the bulk of their revenues from the sales of consumables. Although most companies in the sector generally have less than 25% exposure to government funding,¹⁹ cuts to, for example, the United States' NIH budget and the move away from the use of Regional Development Funds in the United Kingdom may be an important concern for certain companies. The broader United States budgetary battles have had important ramifications for NIH spending, and while the approximately US\$ 31 billion NIH budget is inconsequential to the overall fiscal picture in the United States, cuts have had a dramatic impact on public medical research funding encompassing the money which is allocated to diagnostics research. Anecdotal reports already suggest many NIH funding streams are on hold until there is further clarity regarding the cuts.²⁰ The triggered sequestration of 2013 resulted in a 5%, or US\$ 1.55 billion, cut to the fiscal year 2013 NIH budget. This cut affected every area of medical research.²¹ In Europe, the European Research Council, which funds scientific and medical research, was allocated €13.1 billion for the period between 2014 and 2020 as part of the EU's Horizon 2020 research programme.²² The global decline in R&D spending among pharmaceutical companies is also an important factor

and, while absolute levels of R&D spending remain as high as they have ever been, recent trends (see Fig. 3.4) indicate that further growth may be anaemic at best.

Fig. 3.4 Global pharmaceutical R&D expenditure (Pharmaceutical Research and Manufacturers of America member firms)²³



Fiscal pressures not only impact publicly funded research budgets, but are also squeezing health budgets across key western markets. While in the medium-term this may be expected to drive rationalization of resource use, in which effective diagnostics may play a role, the short-term impact of budgetary constraints often leads to immediate cost control. This raises potential reimbursement challenges, particularly for more innovative and often higher priced diagnostics. A full analysis of reimbursement challenges is covered in section 10.2, but it would suffice to say here that reimbursement challenges are consistently flagged as an ongoing issue for diagnostic manufacturers.²⁴ Data from the European Diagnostic Manufacturers Association's (EDMA) 2011 report on the IVD market in Europe document the impact that macro pressures are putting on the IVD market, noting particularly negative growth of the market size in both Greece (-9%) and Portugal (-10.5%) in 2010/2011.²⁵ Data from 2012 show that the European IVD market has continued to decrease, but that this decrease is not as drastic as had been forecast (-0.6% instead of a forecast -2.1%) (Fig. 3.5).²⁶ Continued budget constraints, measures such as reductions in the number of reimbursed tests, and moves to consolidate lab operations are among the drivers of this market decline.²⁷

Fig. 3.5 *European IVD market revenues (€ million)*²⁸

Sales of consumables, as opposed to capital equipment (the razorblade in the “razor/razorblade” business model), offer a degree of certainty even when the macro backdrop is challenging given the often long-term nature of the contracts entered into. Given the high cost of many diagnostic platforms, it is common for manufacturers to lease equipment instead of selling technology outright to end users with the lease tied to contracts to purchase associated reagents or assays for the equipment over the life of the contract. Indeed many diagnostic companies have in excess of 75% of sales from consumables such as assays and reagents. However, tying clinical facilities to long-term contracts for these consumables may be a double-edged sword. While they reward companies for innovative diagnostics that are taken up, when contracts are long-term the uptake of new technology may be hampered as end users are locked into existing agreements that prevent the upgrading or switching of technology from being cost-effective. Regarding technological progress more generally, there is a clear industry trend for greater automation that looks set to continue.²⁹ Technology that offers the potential to reduce other lab overheads, in particular labour, may present a compelling option for hospitals and labs looking to reduce costs in the face of budget cuts. For example, Guy’s and St Thomas’ clinical pathology unit recently part-funded trials of a gastro-intestinal infection diagnostic (Luminex’s xTAG GPP molecular platform) on the basis that it offered the potential for significant reductions in lab technician hours needed to process samples.³⁰

The shortage of both physical space and skilled staff faced by many labs may drive consolidation of testing onto a smaller number of platforms. There is an

increasing demand for panel rather than single pathogen diagnostics given the flexibility they may offer labs and clinicians. There is some industry feedback indicating that panel diagnostics may be favoured by payers given the potential for economies of scope from the multi-function capabilities. Further, this creates a push incentive for industry consolidation on the diagnostics side and manufacturers are driven to divert resources to a smaller number of platforms to match this demand.³¹

3.3.2 POC diagnostics market

The global POC market is estimated to be worth in excess of US\$ 15 billion annually (2011 data),³² with growth estimated at 7% per annum.³³ This is dominated by over-the-counter self-testing (US\$ 9.6 billion), which is largely glucose testing and home pregnancy tests; professional POC testing is estimated to be worth in the region of US\$ 5.6 billion annually, again dominated by glucose testing, with infectious disease testing comprising US\$ 810 million annually. Estimates of the size of the professional POC market for infectious diseases vary: a 2011 report by Kalorama³⁴ put the global POC infectious disease testing market at US\$ 810 million annual sales, whereas an industry overview from investment bank Morgan Stanley³⁵ estimated 37% of the US\$ 3 billion professional POC market in the United States alone is dedicated to the area. Key players in the POC market are Roche, Siemens, Johnson & Johnson, Beckman Coulter/Danaher, and Abbott, although given the diversity of products on offer in this market segment there is no clear industry leader: particular sub-segments, however, tend to be dominated by a few companies.³⁶ The United States dominates the overall POC market (>50% global market share), and POC diagnostics are estimated to comprise 12% of the total IVD market in the United States.³⁷ This reflects more widespread use of POC devices in professional settings; self-testing uptake in the United States is lower than in some European countries. Delays in decisions by Medicare to reimburse self-testing products may explain this trend.³⁸ Adoption of POC diagnostics across Europe varies widely however: Germany, the Netherlands and Scandinavia are strong adopters, whereas uptake is low in France (where POC testing is not approved in physician setting), and the United Kingdom.³⁹ In general, there has been an increasing focus on near-patient testing across a number of settings, including physician offices and walk-in clinics or self-testing for chronic disease management; given the rise in chronic conditions such as diabetes, segments such as glucose testing are likely to remain an important part of the POC market. Already, the primary market for infectious disease POC testing is in non-hospital settings, with the industry leaders in this segment being Alere (35% market share), Beckman Coulter/Danaher (15%), Meridian and Quidel (c. 8% each).⁴⁰

Certain areas of infectious disease, such as influenza testing, already have well established POCTs, with almost 80% of flu testing performed at physician level in the United States. Competition in this POC market segment is already intense, leading to pricing pressure in the absence of meaningful developments in product differentiation.⁴¹ Concerns over sensitivity and specificity of rapid tests have led to a push towards the development of molecular assays, although these come at a significantly higher cost (>US\$ 100 per patient, versus c. US\$ 15 per patient for the rapid POCTs), which is likely to limit the volume growth of these tests outside of narrow patient populations (e.g. immuno-compromised) if consumable cost alone is accounted for.

While estimates of the growth potential for POC testing remain positive, POC devices may be particularly vulnerable to budgetary pressures, meaning achieving sales of devices is not a given. The burden is on the manufacturer to provide evidence of improved outcomes, but these outcomes can only be achieved through an improved care pathway. In many cases the realities of how patient care is managed may mean that, despite robust device design, inflexibility in the patient care pathway or poor understanding by diagnostics manufacturers of the clinical realities of managing patients may limit acceptance of POC devices.⁴² The developing world may provide a source of future growth for POC devices given the paucity of clinical pathology facilities in many countries, however reimbursement may be a challenge in these settings with limited purchasing power from fiscally squeezed health ministries; Cepheid's TB platform, which was launched in India with funding from the Bill & Melinda Gates Foundation, exemplifies this issue, as the public-private partnership (PPP) agreement dictated that the device be made available to government facilities at cost, although the firm is free to sell to private facilities at market prices.⁴³ Furthermore, diagnostics devices used in a laboratory often need to be modified and/or miniaturized to be adapted to POC delivery – a difficult and expensive undertaking that can slow commercialization.

3.3.3 Molecular diagnostics market

To develop effective rapid diagnostics, developers are increasingly moving away from the classical methods requiring culture of the pathogens and turning to scientific advances from a range of fields. One of the fastest growing areas in infectious disease identification is molecular diagnostics (for an overview of the market see Fig. 3.6), which include techniques such as DNA (deoxyribonucleic acid) microarray analysis, mass spectrometry and nucleic acid amplification.^{44, 45}

Estimates put the size of the molecular diagnostics (Mdevelopers) market at between US\$ 3 and US\$ 5 billion in annual global sales,^{46, 47} amounting to approximately 10% of the overall IVD market. With compounded annual growth estimated at 10–15% between 2012 and 2015,⁴⁸ molecular diagnostics is thought to be the fastest growing segment of the IVD market in the coming years.⁴⁹ Currently just over 50% of the molecular diagnostics market is focused on infectious disease testing. Fig. 3.7 demonstrates the dominance of this field in approved molecular devices in the United States to date. However, continuing

Fig. 3.6 *Molecular diagnostics market overview*⁵⁰

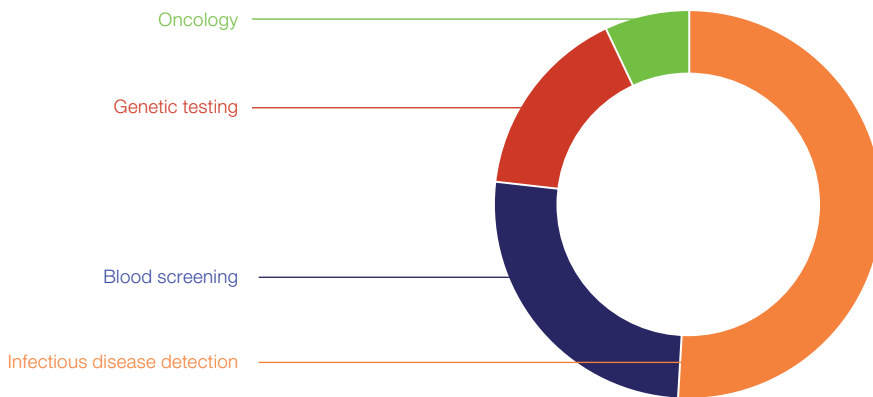
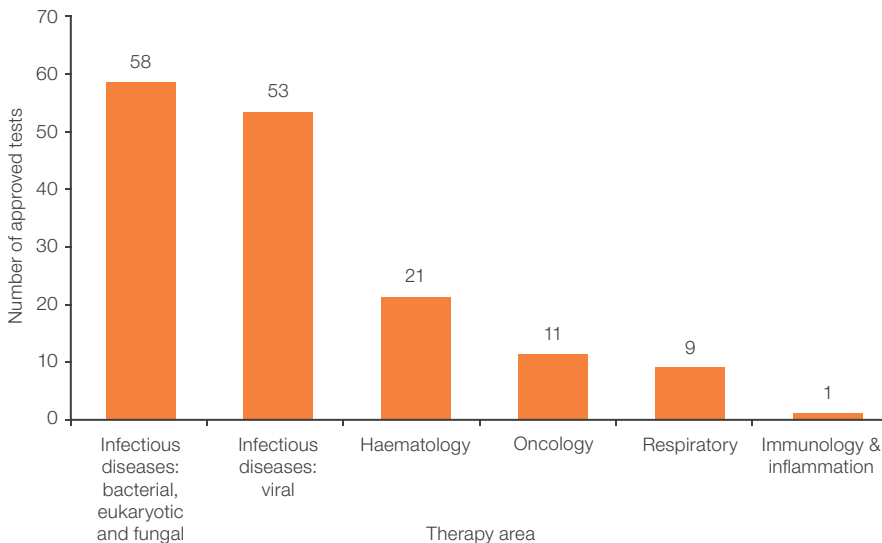


Fig. 3.7 *Molecular tests approved in the United States by therapy area*⁵¹

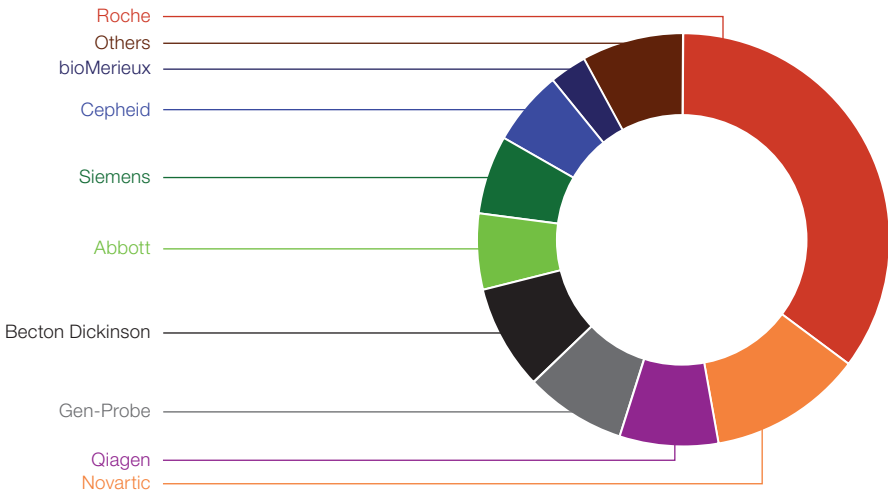


Source: Datamonitor; adapted from Association of Molecular Pathology

development in other areas and the uptake of tests in the oncology field may drive future growth in the sector. Further, the demand for personalized medicine across other disease areas is also expected to expand, particularly as cost pressures and poor efficacy rates of therapies demand a more targeted approach to prescribing.

Market leaders consist of a blend of diversified players such as Roche, Novartis, Abbott, Alere and Siemens, as well as niche companies that are more highly specialized in molecular diagnostics such as Qiagen, Gen-Probe, Cepheid and bioMerieux (see Fig. 3.8).⁵²

Fig. 3.8 Market overview of companies where molecular diagnostics are primary area of focus⁵³



Given the growth profile of the molecular diagnostics market, it has been an area of focus for deals and consolidation. Many diagnostics firms that were under-represented in this area have sought partners or acquisitions to gain exposure, reflecting the growing interest in personalized medicine. Acquisitions by Qiagen (developersS) and LabCorp (Monogram Biosciences) are key examples of this trend.⁵⁴ This is a trend that may continue given the relatively favorable growth outlook and the potential for premium pricing, and given the role molecular diagnostics may play in improving the clinical decision-making process. This may be exemplified by the market for *Clostridium difficile* testing, in which molecular testing is growing in importance: about 2 million of the 5–7 million tests performed for *C. difficile* each year in the United States are now based on molecular diagnostics, a trend which is expected to continue given the superior accuracy and speed of available molecular tests on the market.⁵⁵ The fact that the product with the largest market share in this category, Cepheid, maintains a

significant advantage, despite premium pricing relative to competitor products^a reflects the value users put on ease of use.

3.3.4 Consolidation

Consolidation at both the diagnostic manufacturer^{56, 57} and lab service^{58, 59} levels has been a prominent theme across a number of jurisdictions for the diagnostics industry. On the manufacturing side, while the number of deals in the sector remained relatively unchanged over the period 2008–2010, the IVD market has witnessed accelerating levels of consolidation in terms of deal values throughout 2010/11 (up 57% to US\$ 4.7 billion in 2010 from US\$ 3 billion in 2009), with particularly large deals by Danaher and Thermo Fisher making 2011 a strong year. A large number of these deals have been cross-border, highlighting the global nature of the industry.⁶⁰ Interested acquirers are a diverse range of entities, including private equity firms, clinical laboratories and life sciences firms. Pharmaceutical companies have been notably absent from major acquisitions of diagnostics companies, and have instead opted for partnerships with them (Novartis' US\$ 330 million acquisition of Genoptix being a notable exception). However, the number of partnership arrangements between pharmaceutical and diagnostic companies has tripled between 2008 and 2010,⁶¹ with these types of companion partnership arrangements addressed in more detail in Chapter 11. In terms of deal outlook, an industry report by PricewaterhouseCoopers (PwC) in 2011⁶² forecast a likely continuation of the positive trend for deals. This trend is supported by a number of factors, including new entrants to the IVD market, existing players aiming to cement their position, and potential ongoing interest from private equity in niche players in the most attractive segments of the IVD market such as molecular diagnostics. For example, Switzerland's Biocartis raised US\$ 44.5 million in 2012 from a range of investment partners to commercialize its molecular platform.⁶³ More recent reports, however, suggest venture capital early-stage interest in molecular diagnostics has cooled as firms become wary of regulatory and reimbursement risks in the sector, with interest instead shifting to "safer" fields of diagnostics such as imaging.⁶⁴ Finally, as the trend for drug–diagnostics co-development takes off, interest from large pharmaceutical companies may increase as acquiring diagnostics businesses may become more compelling for pharmaceutical firms when scale is applied to the trend for companion diagnostics. Note, however, that if large drug companies do become more actively involved in acquiring IVD companies rather than partnering, the most likely targets are niche players with specific capabilities which may enhance either the development or marketing of a particular drug rather than the large diverse

a Cepheid test cost of approx. US\$ 35 per test versus c. US\$ 22–25 per test for the products of competitors Meridian and Beckman Coulter/Danaher.

diagnostic firms which may fit less well with the existing product suite or pipeline of the pharmaceutical firm. Larger, more diverse acquisitions are also likely to be more difficult to execute and integrate into existing pharmaceutical businesses.

The drive for panel diagnostics demand may be particularly acute in equipment-heavy segments of the market, such as molecular diagnostics, in part driven by pressure on both physical lab space and availability of skilled staff to execute the diagnostic tests. This may also drive consolidation on the manufacturer's side, given the need to streamline the number of platforms marketed to end users, the route to which may involve integrating a number of technologies into a single platform. Consolidation has also been particularly prominent in the POCT market, with dominant market players continuing to make acquisitions in 2010.^a

The robust near-term outlook for further consolidation is driven by a number of factors, including recent entrants to the IVD market looking to grow their portfolios and established players responding to the changing competitive landscape by actively seeking acquisitions to cement market position and prevent growth of competition. Further consolidation will also be driven by continued interest from private equity firms (subject to capital market conditions) and the potential for major pharmaceutical firms to acquire IVD businesses (particularly molecular/tissue) as the trend for companion diagnostics takes off and the dynamic reaches a point where it makes more sense for pharmaceutical manufacturers to bring the diagnostic business in-house rather than manage the process through partnerships.

In many developed countries such as Australia, Scandinavia, the United Kingdom and the United States, there is a trend to try to keep patients out of hospital, bring care closer to home, and involve pharmacies and other retail outlets. In the United States, decentralization of the pathology market is an important theme; that is, the shift of certain types of testing from larger reference labs towards POC.⁶⁵ The extent to which this has happened varies by indication.⁶⁶ Given cost pressures throughout the health care system, many hospitals are aiming to consolidate either lab operations or volumes in order to exploit scale economies: to the extent that new diagnostics can bypass the need to use larger reference labs towards instead using hospital labs, they may be able to benefit from this consolidation trend.⁶⁷ From a pathology facility perspective, this same trend may squeeze smaller hospital labs as larger facilities attempt to exploit the scale economies and keep as much testing in-house as possible.

In the United Kingdom the prominent review of pathology services led by Lord Carter in 2006⁶⁸ highlighted the need for consolidation of pathology services across the United Kingdom in order to improve efficiencies across the service. This has led to the creation of a number of "pathology networks", whereby

a In January 2010 Alere announced US\$ 255 million acquisition of Epcocal and a US\$ 217 million offer to acquire majority stake in Standard Diagnostics.

groups of hospitals aim to more effectively share pathology services. The potential ramifications for diagnostics manufacturers are conflicting: the “arms race” for consolidation following the publication of the Carter review did lead to larger labs looking to cement their position and act as consolidators, by expanding equipment and capacity^{69, 70} However, the potential for larger pathology networks with greater purchasing power may mean pressure on diagnostic pricing. The full effects of changes in the United Kingdom pathology environment are as yet unclear, not least because the drive for consolidation has been beset by political issues at hospital/trust level,⁷¹ and the trend is yet to fully play out. Recent changes to commissioning in the United Kingdom have added further uncertainty to the sector and these issues are likely to present challenges for the diagnostics sector in the foreseeable future.

3.4 Exhibits: examples of recent breakthroughs in diagnostic development

Recent breakthroughs in diagnostic development highlight the advantages of rapid POC diagnostics in infectious disease.

3.4.1 Xpert MTB/RIF test: a game-changer in global TB diagnosis

TB is a major global killer; in 2011, an estimated 1.4 million people died from the disease.⁷² Delays in diagnosis contribute significantly to unnecessary TB-related morbidity and mortality.⁷³ The traditional diagnostic gold standard, sputum culture, can take 6–8 weeks⁷⁴ and requires a biosafety infrastructure that limits its use to reference laboratories.⁷⁵ Smear microscopy can be used to achieve a faster diagnosis but this approach has lower sensitivity and needs to be undertaken by specially trained staff.⁷⁶

The Xpert MTB/RIF test (Cepheid), which became available in 2009,⁷⁷ is revolutionizing TB identification, bringing diagnosis closer to the point of care. The cartridge-based, fully automated nucleic acid amplification test (NAAT) can be used by a relatively unskilled health worker to simultaneously detect both the presence of the *Mycobacterium tuberculosis* pathogen and whether the strain harbours common rifampicin resistance related mutations in less than 2 hours.⁷⁸ The test was found to be highly sensitive and specific by a large multi-country study in 2008/2009: the test correctly identified 98.2% of smear-positive TB, 72.5% of smear-negative cases, and 99.2% of cases where the patient did not have TB.⁷⁹

In one recent study using the test at the point of care in a primary health care centre in South Africa, evidence suggested an increase in case detection, same-day treatment initiation in over 80% of new cases, and real-time contact

identification when a patient was accompanied by a partner or relative.⁸⁰ Using data from implementation studies, researchers have estimated that the Xpert test will increase TB diagnosis by approximately 30% per year with up to 70% greater diagnosis of MDR strains.⁸¹ This improvement in diagnosis is expected to translate into better health outcomes. One study estimates that the technology could prevent over 4 million deaths between 2015 and 2050.⁸² With the support of the WHO,⁸³ over 1 million tests have been purchased by low- and middle-income countries since December 2010.⁸⁴

Xpert is not an ideal POCT;⁸⁵ it is expensive due to the large equipment investments required. But its development marks a key milestone on the journey towards a simple and reliable dipstick for community-based diagnosis.⁸⁶

A key benefit of the GeneXpert System that supports the Xpert MTB/RIF test is that, through interchangeable cartridges, the system can be used to detect a number of other pathogens. Health workers can load a sample to test for TB in one module while testing for another pathogen, such as MRSA or *C. difficile*, in another module.⁸⁷

3.4.2 Syphilis POC screening: helping cut unnecessary syphilis-attributable stillbirths and perinatal deaths

Each year, there are approximately 11 million new cases of syphilis worldwide.⁸⁸ When syphilis occurs in pregnancy, the consequences of the disease can be devastating. The WHO estimates that in 2007 syphilis contributed to 650 000 fetal and neonatal deaths worldwide,⁸⁹ deaths that could have been prevented if patients had been screened and treated for the disease.

A problem with traditional testing methods in low-income countries has been diagnostic delays. For example, in one study in Botswana in 2000, researchers found that the median time for women to present to antenatal services was 20 weeks into the pregnancy and there were delays of up to five weeks while blood samples were sent to a central laboratory to be tested.⁹⁰ Where there are delays, patients often don't return for test results and treatment.⁹¹

POCTs are helping to cut deaths by providing rapid results. Generally easy to use, with results available in 15–20 minutes, more than 20 syphilis POCTs are now commercially available.⁹² In 2012, the results of a large multi-centre project funded by the Bill & Melinda Gates Foundation found that introducing POC devices can dramatically increase access to testing in some settings; in maternity hospitals in Lima and Callao, Peru, the percentage of sexually active individuals screened for syphilis increased from 51% to 95%, and in Kampala hospital and rural antenatal clinics in Uganda, testing increased from 1.7% to 90.3%.⁹³ In a recent systematic review of interventions to improve syphilis screening,

Hawkes et al. also found that introducing POC testing and same-day treatment increased the frequency of testing and concluded that it could support decreasing the incidence of perinatal death and stillbirth.⁹⁴ The researchers estimated that interventions to improve the coverage and effectiveness of antenatal syphilis screening, such as introducing POC testing, could reduce syphilis-attributable stillbirths and perinatal deaths by up to 50%.⁹⁵

3.4.3 Syphilis: a modern approach to identifying an old disease in hard-to-reach patient groups

There is a range of barriers to patients seeking testing for syphilis at health clinics, including structural problems such as accessibility, clinic hours, financial barriers, patient knowledge of syphilis, and the silent nature of the infection.⁹⁶ POC testing is overcoming these barriers by enabling health workers to carry out rapid testing in the community on mobile and hard-to-reach at-risk groups.

In Edinburgh, Scotland, the ROAM (Resources, Outreach, Advice for Men) project, which is part of National Health Service (NHS) Lothian's Harm Reduction Team, offers services for men who have sex with men in public sex environments. In a pilot project in October 2008, sexual health workers carried out POC testing at three of the city's saunas. Of 63 patients tested, three were found to have undiagnosed syphilis, with almost half of the men being tested for the first time.⁹⁷

Using POCTs to support screening has also been found to improve treatment coverage in settings where there is a high risk of loss to follow up. For example, in a 2010 study funded by the Bill & Melinda Gates Foundation, female sex workers attending fixed and mobile sexually transmitted infection (STI) clinics in Bangalore, India, were more likely to accept a test where it could be performed rapidly on-site and individuals who had access to POCTs were found to have significantly higher treatment coverage.⁹⁸

3.4.4 Reducing unnecessary isolation bed days through rapid MRSA screening

MRSA is a leading cause of secondary infections that are acquired during hospital stays and in long-term nursing facilities.⁹⁹ One infection control approach is to place patients with suspected MRSA in isolation, but this can be costly for hospitals.

A large multi-centre study across the ICUs of 12 Dutch hospitals between 2005 and 2008 confirmed that the use of rapid MRSA screening tests has the potential to significantly reduce hospital costs by reducing the time patients were kept in

isolation unnecessarily. Where testing was undertaken using traditional cultures, patients would typically spend 96 hours in isolation. This was reduced to 27.6 hours where patients were screened with the GeneOhm™ MRSA polymerase chain reaction (PCR) test (Beckman Coulter/Danaher) and 21.4 hours when staff used the GeneXpert MRSA/SA test (Cepheid).¹⁰⁰ Tests were undertaken by a central laboratory and the benefit to the hospitals concerned was between €121.76 and €136.04 per isolation day avoided.

The quicker results gained from using rapid tests have also been shown to improve the appropriateness of antibiotic prescribing. A study in northern Australia by Davies et al. found that performing the GeneXpert MRSA/SA test on 151 positive blood cultures with gram-positive cocci led to earlier appropriate prescription of vancomycin for 54% of patients with MRSA.¹⁰¹ This can translate into clinical benefits; in a 2010 study covering 167 patients with *S. aureus* bacteremia at the Ohio State University Medical Centre, researchers found that the adoption of the GeneXpert MRSA/SA test reduced the average length of stay (LOS) by 6.2 days compared to traditional blood culture, and decreased average hospital costs by US\$ 21 387. The impact of the test in this study may have been enhanced by the close involvement of an infectious disease pharmacist in guiding prescribing.¹⁰²

While most studies to date have involved rapid tests being undertaken by a central laboratory, an additional advantage of the Xpert test is that it is sufficiently simple to use that testing could be undertaken by clinical staff at the point of care.¹⁰³ A recent feasibility study in a British hospital found that when testing was undertaken at the point of care, the results were available over 10 hours faster than from the lab. Testing at the point of care was particularly beneficial in the evenings and weekends when the lab was closed.¹⁰⁴

3.4.5 T2 *Candida* assay: using magnetic biosensor nanotechnology to diagnosis candidemia

The presence of the *Candida* pathogen in blood, a condition known as candidemia, is a major cause of morbidity and mortality in the inpatient care setting¹⁰⁵ and is associated with both prolonged hospital stays and high treatment costs.¹⁰⁶ Delays in treatment are associated with increased mortality.¹⁰⁷ Since clinical symptoms are non-specific¹⁰⁸ and conventional diagnostic methods take 48 hours,¹⁰⁹ prescribers have had little option but to prescribe broad-spectrum antifungals empirically.¹¹⁰

In recent years, a range of new tests has been developed to improve the speed of candidemia diagnosis using technology such as PCR and molecular techniques.¹¹¹ The T2 *Candida* assay is a promising one that uses magnetic biosensor nanotechnology designed to enable detection of DNA, ribonucleic acid (RNA), protein,

small molecules and other targets from a single blood sample in a one-step process that can be undertaken by non-specialist staff.^{112, 113} Although it is still early days in the clinical testing of the product, the manufacturer has reported that two independent research groups from Massachusetts General Hospital and University of Houston College of Pharmacy have confirmed that the test had equivalent sensitivity and specificity to blood cultures but provides results within 2 hours compared to 48.¹¹⁴ Formal clinical trials are planned¹¹⁵ to assess the assay's potential benefits, which may include reduced mortality and lower health system costs.¹¹⁶

The device which supports the test, the T2developers, is versatile. Since it is capable of detecting a range of substances, including bacteria, cancer cells and viruses, and of processing almost any sample, including whole blood and urine, there is potential for it to be developed for a wide range of clinical uses.¹¹⁷

3.4.6 Speeding up the detection of respiratory pathogens with multiplex devices

There is a broad range of causative organisms responsible for respiratory tract infections, making them difficult to diagnose. This problem is compounded by the fact that conventional diagnostic techniques can take up to 72 hours.¹¹⁸ To overcome these challenges, there has been a recent trend towards the development of multiplex devices: devices designed specifically to rapidly detect a variety of bacterial, viral, or fungal pathogens in a single test.¹¹⁹

Techniques used in these devices include real-time PCR, PCR microarray technology and mass spectrometry.¹²⁰ While some techniques are better suited to high-throughput laboratory testing, others are designed to support near-patient diagnosis.¹²¹

One newly developed device is the Unyvero™ solution (Curetis AG), which has investigational device status in the United States and conforms to the CE-mark (*Conformité Européenne*) requirements in Europe.¹²² While the device is not necessarily “simple”, requiring the technician to perform multiple steps to prepare a sample, it supports a “sample to answer” approach to diagnosis. Patient samples are loaded directly into the device without prior preparation, the sample is then screened for a broad panel of pathogens with simultaneous detection of some antibiotic resistance determinants (overall predictive value of 60%), and results are presented on an integrated screen within 4 hours.¹²³ Unlike some molecular tests on the market, the device can be operated by staff without specialist training¹²⁴ and, when used in a decentralized setting, this can improve access to the technology, particularly at nights and weekends when central laboratories are often closed. The device currently supports the diagnosis of pathogens associated

with pneumonia, with the company's pipeline including panels for implant and tissue infections, bloodstream infections (sepsis) and TB.¹²⁵

Given the product's novelty, there is still limited independent evidence of the benefits of the device (the sensitivity, which depends on bacterial species, ranges between 35% and 100%)¹²⁶ but it holds considerable promise. Studies of similar multiplex devices targeting respiratory infections have suggested that earlier detection of causative pathogens may improve the appropriateness of prescribing antibiotics, which in turn can help minimize antibiotic resistance.^{127, 128} An economic analysis undertaken by Curetis indicates that it may also help reduce overall health care costs and improve patient quality of life.¹²⁹ Oliver Schacht, PhD, Chief Executive of Curetis, reported that an additional multi-centre interventional trial is being planned to gather real-world evidence on the health economic benefits of the device.

3.4.7 Using a simple dipstick to improve diagnostic precision in suspected UTIs

A significant proportion of patients with suspected UTIs receive antibiotics unnecessarily.¹³⁰ One tool that can help improve appropriate prescribing is the simple urine dipstick test that has been used in clinical practice for over 30 years.¹³¹

Using clinical symptoms alone cannot accurately diagnose a UTI. In a 2003 prospective cohort study involving eight GPs in the United Kingdom, Fahey et al.¹³² investigated how a patient's symptoms influenced the likelihood that GPs would opt for a dipstick test, urine culture or empirical antibiotic prescribing in the management of suspected UTIs. The study found that GPs were more likely to prescribe antibiotics as a clinical strategy when patients presented with a history of frequency and dysuria or a history of dysuria alone, yet less than 30% of cases that presented with these symptoms were later found to have a UTI. A dipstick test provides the physician with additional information on which to base their clinical decision. In a health technology assessment funded by the United Kingdom's National Institute for Health Research (NIHR), Little et al. provided evidence that using a dipstick to test for the presence of either nitrite or a combination of blood and leucocytes modestly improved diagnostic accuracy.¹³³ This conclusion has been supported by a number of systematic reviews,^{134, 135} despite heterogeneity in the findings of individual studies.¹³⁶

Using a dipstick to target prescribing may also offer value for money. The study by Little et al. found that using a dipstick to target prescribing was cost-effective if the cost of a patient avoiding a day of moderately bad symptoms was valued at over £10.¹³⁷ However, other economic evaluations have provided conflicting results. In a study in 2000, Fenwick et al.¹³⁸ concluded that empirical antibiotic

treatment was the most cost-effective strategy in managing suspected UTIs in general practice, however this did not take into consideration the long-term costs of increased antibiotic resistance – a factor that the researchers recognized could influence their study outcome.

A key weakness of dipstick tests is that, while they can aid prescribing decisions, they do not provide the gold standard of microbiological identification data and susceptibility information. Fortunately, it is likely to only be a matter of time before next-generation devices become available that can support rapid and definitive diagnosis at the point of care.^{139, 140}

Chapter 4

Supply-side bottlenecks inhibiting development of priority diagnostics

4.1 Introduction

This chapter seeks to explain how investments flow into the diagnostic market – from basic research, to development, to the point of care – and to elucidate how that flow is guided at each stage of the process. By following existing and potential streams of funding to support the POC diagnostics industry, the chapter helps expose both where and why investment may be being diverted from its optimal path, where it is most likely to yield truly useful devices.

The chapter also highlights some of the technical and scientific bottlenecks inhibiting the development of POCTs in this area. The chapter concludes with a series of case studies meant to delve into subtle complexities and resulting challenges that arise when implementing and assessing the effectiveness of diagnostic POCTs.

4.2 Drivers of resource allocation decisions by developers and prospective diagnostic developers

As would be expected, the overarching process driving investment decisions by diagnostic developers is underpinned by horizon scanning for areas of unmet clinical need. This may be either because no diagnostic currently exists, or there is the potential to develop a product with a competitive advantage to existing diagnostics for an indication. Improvements may be in the form of superior sensitivity, specificity, speed, ease of use, the ability to simultaneously assess a broader range of potential pathogens, or antibiotic resistance identification capabilities. Once the potential gap in the market has been identified, however, the ultimate investment decision involves overlaying the specific market opportunity with a complex process of business, strategic and financial decisions affecting how resources are allocated in the R&D process.

The particular challenge in developing innovative diagnostics in the field of infectious disease is that the gold standard, cultures, are a well-established and

cheap method, particularly relative to more innovative rapid diagnostics and those employing molecular technology. For rapid diagnostics in particular, this places a heavy onus on the producers to prove the clinical and/or cost benefits that increased speed of diagnosis brings to the care pathway. Furthermore, POC diagnostics are often used in conjunction with cultures, making them an additional cost in the care pathway, rather than offering any savings on existing diagnostic methods.

Diagnostics developers employ a number of strategies to gather information to inform their investment decisions. These include market research, estimations of expected reimbursement levels; cost–effectiveness analysis, analysis of how a new product fits within existing portfolio, and an evaluation of the funding environment (both internal and external).

4.2.1 Market research

Diagnostics firms may conduct or outsource market research to understand the competitive landscape for the relevant product/indication, including existing diagnostics that are covered by the same diagnosis-related group (DRG) or therapeutic grouping; reimbursement levels for similar products; and the broader macro backdrop as regards health system funding, hospital economics and budget constraints.

4.2.2 Price expectations

Critical to the investment case is forming estimates of potential reimbursement levels for the intended product. A consistent issue raised by manufacturers involved in this study is that diagnostics are not reimbursed on a basis that takes account of the value that they add to the care pathway. While this issue will be addressed in Chapter 10, in terms of the barriers this may present to investment, from a reimbursement perspective this makes price estimations more straightforward. Many developers have indicated to us that anticipated pricing is largely estimated on a cost-plus basis to ensure sufficient profit margin, rather than a more complex value-based approach.

4.2.3 Health economic analysis

Following from the above, feedback from participants in this study indicates there is less consensus on the timing of assessing the *value* of the potential product (and the role, therefore, that health economic analysis plays in resource allocation decisions, as opposed to pricing negotiations). Particularly within small- and medium-sized developers (small- and medium-sized enterprises [SMEs]), views were divergent. Some indicated that prospective cost–effectiveness

studies and modelling take place before investment decisions are made,¹ while others indicated that robust health economic studies are only performed at a late stage of the development cycle and form the basis of price negotiations rather than investment decisions.² Among smaller developers, this may be reflective of the resources and expertise in this area that they have access to. One developer indicated that the cost of even a basic health economic study could be greater than £20 000. This may present a barrier to some developers to employing such analysis early in the development process, when capital may be in short supply and returns on investing in the project at their most uncertain.³ A further consideration when employing cost–effectiveness studies (addressed in more detail in Chapter 9) is the population used in modelling. While the primary driver of this will be the anticipated principal end-market (for example, hospital or primary care setting), there may be a tendency for studies, at the marketing stage at least, to focus on the highest cost segment of the potential patient population, in order to make the cost–effectiveness argument more compelling. In hospitals, for example, this could lead to a focus on evidence generation for segments such as the ICU, where patient costs may be highest (and therefore savings from quicker, more accurate diagnosis potentially greatest). This raises the prospect of a lack of focus of evidence generation in lower-cost settings, such as primary care, where either the potential savings from altering care pathways may be lower, or around which it may be harder to generate robust estimates.

4.2.4 Portfolio analysis

Of more relevance to larger diverse diagnostic developers is the strategic fit any new development would have within the company's existing product portfolio. Large manufacturers have indicated that there are benefits attached to being a “full service” diagnostics provider (i.e. where a company as a single supplier can meet as broad a range of a customer's diagnostic needs as possible). This increases the likelihood that development decisions at larger players may be influenced by the incentive to invest in less innovative platforms to fill a gap in their current offering, as the potential returns (or lower potential lost revenues) from being able to offer a broad portfolio of diagnostic testing may outweigh anticipated benefits from a novel and yet unproven diagnostic.

4.2.5 Funding landscape

Key sources of funding for diagnostic companies include internal funding streams generated from existing business lines, private capital such as angel investors or venture capital firms, government research funding and donor programmes.

In-house funding

Internal availability of funding is an issue of more relevance to larger, multi-product diagnostics firms. Depending on organizational structures, different sectors may face internal competition. For example, diagnostics for infectious disease may have to compete against diagnostics for other indications; POC diagnostics may have to compete against lab-based platforms, etc. This has been highlighted as a particular challenge facing investment in POC diagnostics, as the high initial investment required in building a POC platform may compare unfavourably to the development of, for example, a new assay on an existing lab-based platform marketed by the company. While it is likely that the costs of developing a whole new lab-based platform are higher than that of a POC device, the multi-assay and multi-indication nature of many of the lab-based platforms means they offer greater flexibility and potential to add future assays than a specific POC cartridge may be able to offer. Stakeholders in POC businesses have indicated that this means the onus to prove potential value is higher than for other areas of diagnostics. This may prove to be a limiting factor on investment in this area.

Private capital

There are a number of venture capital firms that focus on the diagnostics market. A scan of recent investment online journals (*Elsevier Business Intelligence*, 2012 [for example, Micklus and Surprenant];⁴ *Fierce Medical Devices*, 2012 [Hollmer]⁵) shows that there is growing interest in the diagnostics market. For instance, in early 2012 alone, recent venture capital investments across different markets include:

- £1.1 million+ investment for MODE Diagnostics, a University of Glasgow spinout with a focus on producing diagnostics for cancers and infectious diseases.⁶ The funding was provided by IP Group PLC, Scottish Investment Bank, Parkwalk Advisors Glasgow University Holdings, Kelvin Capital. MODE Diagnostics currently has a rapid diagnostic for bowel health; there are plans to focus this next round of funds to infectious diseases.
- £5 million investment for Lab21, a United States based biotech with molecular diagnostics products for infectious diseases including malaria, Chagas, syphilis and cytomegalovirus (CMV) – supplied globally to screen blood supplies.⁷ The funding was provided by Clydesdale Bank. Lab21 currently has a biological assay for the rapid diagnosis of TB and specific drug-resistant forms of the disease, and is now using the same technology to develop new diagnostics for other bacterial pathogens. The following new products are in late stage development:

FastPlaque MAP (for the rapid detection of *Mycobacterium avium paratuberculosis*) and FastPlaque Listeria (for the rapid detection of Listeria species.)

- US\$ 12 million investment for GeneWeave Biosciences, developer of a platform for the rapid detection of infectious disease for the United States and China markets.⁸ The funding was provided by Decheng Capital, Claremont Creek Ventures and X/Seed Capital GeneWeave Biosciences is currently working on commercializing a rapid test to detect toxic *E. coli* bacteria and the bacteria that cause Johne's Disease in cattle.
- US\$ 10 million of financing for Xagenic Inc., a Canadian privately held molecular diagnostics company (a collaboration between MaRS Innovation and the University of Toronto) developing a new technology for decentralized, rapid diagnostic testing for quicker diagnosis of conditions ranging from infectious disease to cancer.⁹ The technology developed by Xagenic Inc. competes with PCR for sensitivity, but is easily automated and multiplexed. These characteristics are intended to allow the diagnostic to detect multiple infectious diseases at a high throughput.¹⁰ The funding was provided by the financiers CTI Life Sciences Fund (CTI) and the Ontario Emerging Technologies Fund (OETF) with significant participation by QIAGEN N.V. The latter is a provider of assay diagnostics.¹¹
- US\$ 1 million and US\$ 6 million in two rounds of investment in MedMira Inc., another Canadian manufacturer of rapid diagnostics for infectious diseases, which has products in the global market.¹² Both rounds of funding were provided by Andurja Beteiligungen AG, a Swiss based firm. A MedMira product includes a test that detects *Helicobacter pylori*, a bacterial species associated with peptic ulcer disease and cancers of the gastro-intestinal tract.

Venture capital firms invest in companies with products that have the potential to change the way health care is delivered in a sizeable market. Their stated decision-making generally follows similar lines, outlined in Table 4.1.

Table 4.1 General venture capital decision-making process

Product criteria	Leadership criteria	Business strategy criteria	Market criteria
Breakthrough technologies with the potential to revolutionize health care delivery; strong intellectual property (IP) protection	Demonstrated track record of success, exceptional leadership, and the commitment to grow the company into a substantial enterprise	Clear strategy of product development, launch and revenue building; executable roadmap (e.g. key milestones identified, identified capital required along the way)	Addressable markets where there is a significant unmet need for the company's products and technology

In the area of infectious disease, however, there have been some concerns on the part of these investors. Unclear requirements and inconsistency in the application of regulatory requirements have been cited as challenges of the 501(k) process (National Venture Capital Association, 2010).¹³ This, in turn, can be a lengthy process and there are some comments made by the National Venture Capital Association¹⁴ in 2010 that state that these barriers can deter venture capital firms from investing in early-phase molecular diagnostics companies. The National Venture Capital Association has lobbied for the establishment of well-characterized clinical sample repositories, to limit the need for repetitive, expensive clinical trials and supports rapid, efficient development and approval of new molecular diagnostic tests.

As noted earlier, however, if there is a large unmet need in the market, the FDA has been known to recognize this. There is some evidence that this may reduce the complexities of the regulatory process. The case of Great Basin, a biotech in the United States using novel molecular technology to produce low-cost alternatives to popular infectious disease tests, perhaps illustrates this point. Its first rapid diagnostic for *C. difficile* was approved by the FDA in April 2011 and its CEO has noted that: “because the disease has high prevalence and because it’s well-known to FDA, we knew it would be a simple, fast trial, and we weren’t going to have a lot of issues with FDA”.¹⁵

Furthermore, some biotech firms have recognized the potential regulatory complexities and have taken steps to use the certification process to attract more venture capital investment. For instance, Curetis AG, an innovative molecular diagnostics company that focuses on IVD products for infectious disease testing, made the strategic move to receive its International Organization for Standards (ISO) 13485^a certification in 2010.^{16, 17} This was a strategic move to demonstrate its implementation and use of a quality management system that conforms to the highest international quality management standard for medical devices, including IVD products. Shortly following the company’s ISO certification, it announced that it had received venture capital funding (€1.5 million).¹⁸ It should be noted that these specific regulatory hurdles are not typically an issue with antigen-based IVD technologies.

a ISO 13485:2003 specifies requirements for a quality management system where an organization needs to demonstrate its ability to provide medical devices and related services that consistently meet customer requirements and regulatory requirements applicable to medical devices and related services. In Europe, ISO 13485 certification is seen as the first step in achieving compliance with regulatory requirements. The United States, on the other hand, currently has its own quality auditing processes and therefore ISO 13485 is not a regulatory requirement. There is currently a pilot programme in place, however, that allows manufacturers that are ISO certified to voluntarily submit their ISO audits in lieu of the FDA’s third-party audits (see FDA, *Guidance for Industry, Third Parties and Food and Drug Administration Staff – Medical Device ISO 13485:2003 Voluntary Audit Report Submission Pilot Program*. [<http://www.fda.gov/RegulatoryInformation/Guidances/ucm212795.htm>, accessed 5 October 2012]).

External support and incentives

Several existing initiatives, both public sector and donor-led, have offered support to diagnostic development efforts. The types of resources available to support initiating or continuing research and/or development vary depending on the nature of the developer (e.g. research institute, SME or large company), the type of device that is being developed and the relevant stage of the production process. This heterogeneity of need is mirrored in the diverse mix of public and private initiatives that have been established to support R&D. Key current initiatives and lessons that have been learned can be found in the following section.

In order to try to better outline market needs, the WHO has developed a series of Target Product Profiles (TPPs).¹⁹ Importantly, these guidelines push the traditional boundaries of what defines a POCT by discarding restrictions that POCTs must necessarily be very cheap and equipment free.²⁰ TPPs clearly outline the operational and performance characteristics that manufacturers should strive to meet. TPPs have already been developed for POC sectors including HIV/syphilis tests. Further TPP development could be expanded to all public health priority areas where POC devices could play a role.

Public bodies such as the National Institute of Allergy and Infectious Diseases in the United States and the NIHR in the United Kingdom offer funding, typically grants, through a mixture of general and targeted schemes. In the private and non-profit sectors, there are examples of more innovative funding approaches, such as prize funds, being adopted. There is also collaboration between the two sectors, for example publicly backed venture capital funding is offered through the organization Finance Wales in the United Kingdom.

Each scheme is different in terms of the level of funding available, the proportion of actual costs covered and whether funding is paid up-front or linked to defined targets being achieved. There are also differences in the range of developments supported. Some funders have chosen to focus on supporting basic scientific discoveries while others have opted for translational research to progress basic research through to product development stages. Most initiatives are open to many types of developers, including large businesses, SMEs and academic institutions but there are often restrictions on the eligibility of foreign organizations. The level of involvement from funders also varies, at one extreme are funders such as the Innovative Medicines Initiative (IMI), which provide funding but leave the day-to-day project management to the recipient project coordinator. The converse is organizations such as the Wellcome Trust, which tightly monitor and manage many of the projects that they fund and offer a range of project support, including advice on IP arrangements.

A growing trend that may in future support device developers is “crowd-funding”,²¹ which enables access to funding from the broader community. A diagnostic developer currently seeking crowd-funding is Cervia Diagnostic Innovations (Cerviadevelopers), a social entrepreneurship company working to develop a POC diagnostic to screen for cervical cancer.²² The potential of this approach is as yet unknown but there are clear challenges, such as establishing acceptable IP or alternative reward arrangements.²³

In addition to funding, there are initiatives to improve access to specimens and affordable trial sites with appropriate target populations, as well as projects to support manufacturers with needs assessment, evaluating prototype devices and gathering evidence of a device’s real-world impact.

4.3 Scientific and technical barriers

Conventional culture-based assays by definition involve a single live cell yielding a visible colony of cells, usually on the surface of an agar plate.²⁴ However, this process can take from one to five days²⁵ when, for many infections, test results are needed much more quickly. In managing sepsis, the critical time window for initiating appropriate treatment is estimated to be on average 6 hours²⁶ or less. Survival is approximately linearly correlated with time to antibiotic treatment, so each hour-long delay increases the chance of mortality by 7.6%.²⁷ Culture-based assays have a range of limitations, for example some microorganisms grow poorly in culture media and there is no single medium capable of detecting all pathogens.²⁸ If patients are receiving antimicrobials, this can inhibit cell growth in the culture.²⁹ Both time and storage conditions during transport to the laboratory can cause cell death, undermining the integrity of specimens.³⁰ A difficulty specific to bloodstream infections is that there are often very few pathogens present in a given volume of blood. Taking a large sample of up to 30 ml can help, but this increases the risk of blood clots in the syringe, making inoculation of culture bottles difficult.³¹ As a consequence of these challenges, the diagnostic sensitivity of cultures can be low,³² a problem that is unlikely to be overcome by simply enhancing culture techniques.³³

To develop effective rapid diagnostics that are appropriate for use in clinical settings, developers are increasingly turning to scientific advances in a range of diverse fields, including biochemistry, immunology and molecular biology.³⁴ One of the fastest growing areas in infectious disease detection is molecular diagnostics, which encompasses techniques such as nucleic acid amplification, DNA microarray analysis and mass spectrometry.³⁵ Each of these approaches presents developers with their own set of technical and practical challenges.³⁶

PCR, a technique involving the amplification of DNA fragments to support the detection of the genetic material from a pathogen, is much faster than conventional cultures, but is hampered by problems differentiating between the DNA of live pathogens and unviable chromosomal DNA that remains after cell death.³⁷ The high proportion of false positives generated by these tests³⁸ means that in making a final diagnosis, all other clinical and laboratory data should be taken into consideration. For example, in the case of TB, whether the patient has responded to recently prescribed anti-TB medication^{39,40} must be considered. Other drawbacks of PCR include the inability to differentiate between infection and carriage (relevant for some infections, such as urine). In addition, if the gene has mutated, PCR can provide a false negative diagnosis because primers will not bind as intended (as happened with chlamydia in Sweden in 2007).⁴¹ Dr Anna Zorzet explains that if PCR is used to detect resistance genes, complications can be more considerable since resistance genes are not as conserved as the genes (usually 16S rRNA) used to identify species. The detection of a gene generally thought to confer resistance does not automatically imply that the organism is resistant; in some cases the gene is deactivated. Similarly, new resistance genes will not be targeted and hence not picked up by PCR. Another molecular approach, mRNA (messenger RNA) detection, has advantages, such as being able better differentiate dead cells, but this method has the potential to be more technically complicated if, for example, there is a need to first remove DNA contamination from an RNA extract.⁴²

Mass spectrometric analysis is used to acquire knowledge on molecular structure based on mass spectral pattern. The technique can be used to detect amplified products of a PCR reaction,⁴³ unique proteins or amino-acids identified as “finger-prints” of organisms or resistance to drugs, for example mass spectrometry has been used to detect genetic markers for cephalosporin resistance in clinical strains of Enterobacteriaceae.⁴⁴ Mass spectrometry methods are rapid, have high sensitivity and specificity but are far from being routinely used in clinical laboratories because they have not achieved the standards of reproducibility and performance expected of clinical tests.⁴⁵ The added challenge for POC diagnostic delivery is that the instruments are extremely expensive and large. However, progress is being made to reduce the size of instruments and the upfront cost may be offset by the low cost per test and the ability to run multiple detections on a single sample. A 2013 study appears to provide proof of concept for using this technology for early diagnosis of *Staphylococcus aureus* infection and determining antibiotic resistance.⁴⁶

A challenge that molecular tests share with bacterial cultures^a is differentiating between active infection and colonization;⁴⁷ pathogens such as *S. aureus*,

a While rough, culture methods can give an impression of the quantity of bacteria, which can give an idea of whether the infection is due to contamination/colonization.

Streptococcus pneumoniae and Enterobacteriaceae can be present at detectable concentrations without causing any symptoms or signs of infection⁴⁸ (for certain types/sites of infection). Unless a diagnostic test includes a quantification step to assess the density of microbes⁴⁹ and a cell volume threshold has been predefined,⁵⁰ it may not be possible to distinguish between the harmless presence of an organism and the existence of infection.⁵¹

Another barrier to developing any new diagnostic is access to well-characterized clinical samples to support both assessing the clinical utility of tests and test validation.⁵² Shared specimen banks offer a possible solution, improving access and maximizing the efficiency of diagnostic development, but there is a range of risks that need to be managed in setting up a bank. If stored samples have been collected from the sickest patients this can lead to inflated estimates of diagnostic accuracy.⁵³ Similarly, if specimens are not representative of the diverse mix of patients that are targets for the test, this can lead to ethnically biased research findings.⁵⁴ The quality of specimens can be reduced over time through storage and there is a wide range of operational challenges, including security and patient consent arrangements.⁵⁵ More information about specimen banks and how these challenges can be overcome can be found in section 12.2.5.

An important recent advance is the emergence of single tests that identify multiple pathogens.⁵⁶ While the benefits of this approach are clear, the validation process is more time consuming and costly when compared to single-analyte assays.⁵⁷ There is a need to ensure that individually performed reactions would generate identical results, leading to increased complexity of controls, evaluation and reporting.^{58, 59} Obtaining appropriate control and reference materials can also be difficult, if not impossible.⁶⁰ In a study on the effectiveness of a respiratory pathogen microarray, researchers from the Center for Biomolecular Science and Engineering in California found that where the test identified multiple organisms, confirmatory testing was not always possible because of a lack of validation materials.⁶¹

One key decision for developers is which type of sample will be collected from patients. In a study on sampling methods in the diagnosis of lower respiratory tract infections, Loens et al. identified possible invasive and non-invasive sampling techniques, such as blood samples, thoracentesis, bronchoalveolar lavage, sputum collection and nasal or throat swab,⁶² with some approaches, by necessity, having to be undertaken under sterile conditions. Each approach has different advantages and disadvantages. A particular challenge in the diagnosis of lower respiratory tract infections and TB, for example, is that the traditional sampling method, sputum collection, is extremely challenging. Some patients cannot produce an adequate sample size⁶³ and poor collection technique can lead to the sample being contaminated with saliva and pharyngeal secretions.⁶⁴ As a

consequence, specialist training is typically required to collect a sample, which limits the settings in which it can be undertaken.⁶⁵ In a recent study assessing the impact of the Xpert MTB/RIF test for POC diagnosis of TB in primary care in South Africa, Clouse and colleagues reported that the workload was such that a minimum of two staff were required to supervise collection and processing of an average of 15 sputum samples per day.⁶⁶ There was also a need for careful infection control and biosafety measures to protect staff.

Breath samples have low concentrations of pathogens and changes in humidity can influence the profile of the volatile substances absorbed in breath.⁶⁷ Stool samples usually require extensive purification to remove materials that could inhibit DNA amplification when molecular diagnostic techniques are used.⁶⁸ However, this depends on the molecular technique used as some, such as padlock probes, can work well for faeces.⁶⁹ Changing sampling approach, for example moving from collecting blood to sputum, may require developers to identify novel techniques to ensure equivalent clinical performance to existing tests.⁷⁰

Once collected, samples need to be prepared for use in a diagnostic device; this represents a major bottleneck in POCT development.⁷¹ Traditional sample preparation methods can be time consuming, involve use of multiple pieces of equipment such as centrifuges and bead beaters, and require reagents that must be stored in a fridge. However, for use at the point of care, devices need to be small, stable at room temperature and provide quick results.⁷² As Professor Herman Goossens, a Belgian microbiologist from the University of Antwerp, put it: the challenge facing the developers is comparable to “shrinking a huge laboratory filled with people and equipment onto a single chip the size of a matchbox”.⁷³ Fields such as microfluidics and nanotechnology could hold the key to miniaturization,⁷⁴ but a key challenge for manufacturers is establishing multidisciplinary scientific and engineering teams with the necessary skills to undertake development, as well as having appropriate manufacturing facilities to support prototyping and small batch pre-production.⁷⁵ If these hurdles can be overcome, the technology offers the potential of cheaper, more portable and easier-to-use POC devices that can detect infectious diseases from a small sample size and could even be disposable after use to enhance biosafety.⁷⁶

Finally, it should be noted that the technical challenges – including the ability and necessity to create an entirely “stand-alone” POCT – are very different for tests intended for the inpatient and outpatient setting.⁷⁷

4.3.1 Case study 1: *Streptococcal pharyngitis – a success story*

Symptoms related to the throat was the fifth most common complaint in outpatient visits in the United States, accounting for 2.1% of all sick outpatient visits in

the year 2008, including 6.2 million visits for children under 15 alone.⁷⁸ Group A β -haemolytic streptococcus (GAS) can be a cause of pharyngitis – most often in school-age children, less in adults. GAS is the cause of pharyngitis in 20–30% of children and 5–10% of adults, but viral infection is the cause of the majority of cases.⁷⁹ Untreated, the patient is infectious for approximately one week and symptoms may last 10 days without treatment.^{80,81} Antibiotic treatment reduces infectivity and duration if begun early. Treatment also reduces progression to more severe (but rare) sequelae such as rheumatic fever, pharyngeal abscess, glomerular nephritis and local or systemic spread. The cost of streptococcal pharyngitis is estimated at US\$ 205 per episode, or between US\$ 224 million and US\$ 539 million annually.

While other studies have accounted for some of the cost, this estimate, from a United States paediatric clinic provides the most complete economic picture of care delivery in the United States. It includes not only medical costs (office visit, prescription, testing) but non-medical costs related to care of the child with streptococcal pharyngitis as well (transportation, work-time lost, child care, etc.).⁸² Such costs can vary by setting in the United States, with pharyngitis visits and treatment in outpatient settings costing significantly less than emergency room care.⁸³ As well, European costs can be expected to be less, as shown in a Spanish study which tabulated the medical costs at about US\$ 65 compared to the United States studies, which estimated the same costs between US\$ 110 and US\$ 166.⁸⁴

Rapid strep screening tests can be purchased by the provider at a cost of US\$ 2–5. Hospital charges vary widely, but current Medicaid reimbursement is approximately US\$ 14 for the rapid screen and US\$ 7 for a throat culture.⁸⁵ Treatment is most often penicillin for 10 days, at a cost of approximately US\$ 10–20, while a course of treatment with a cephalosporin can be as much as US\$ 100 or more for a brand name, but similar to the cost of penicillin for the generic.

Diagnosis

Diagnosis involves assessment of physical findings, interpretation of test results as well as the consideration of the probability or likelihood of GAS infection. Pharyngitis as part of a larger viral syndrome may include symptoms not commonly associated with GAS such as rhinorrhea, cough and hoarseness. The identification of signs and symptoms associated with pharyngitis has led to the development of clinical decision tools. Some have included not only signs and symptoms as likelihood calculators for GAS pharyngitis, but also consideration of local prevalence and diagnostic accuracy of the test (e.g. sensitivity and specificity) to determine which patients should receive testing, as unnecessary testing risks producing false positives and additional cost.

Systems such as those by Centor or McIsaac⁸⁶ use a scoring system which incorporates objective observation of signs and symptoms (e.g. fever, absence of cough, age) to identify a risk category for patients – who should be tested and/or treated. The McIsaac scoring system has been shown to reduce not only the use of antibiotics, but also the use of diagnostic testing.^{87, 88} However, such systems can overestimate the likelihood of strep throat and are only able to predict a positive culture 51–55% of the time which, in the absence of diagnostic testing, would lead to significant overtreatment of patients. Also, the ascertainment of physical findings is key to the utilization and value of such scoring algorithms, but a practitioner's failure to identify such signs or symptoms may further limit its utility.⁸⁹

Testing

Culture has been the gold standard for strep testing, but results take up to 48 hours, and are rarely performed outside a laboratory. Antigen testing, in its simplest form, was known at the turn of the last century, when it was discovered that antibodies and their corresponding antigen produced complexes. Developments in testing were later designed to identify these complexes, often by labelling the antibody in some detectable way. This led to radioimmunoassays, enzyme or optical immunoassays, and latex agglutination as microbiological test methodologies, all of which are still in use today. Rapid antigen strep tests are often enzyme based, and were first licensed for use in the United States in 1983.⁹⁰ Prior to this time throat cultures were often performed in office laboratories, but the introduction of the Clinical Laboratory Improvement Amendments regulations in the United States (CLIA 1988) classified cultures as moderate-complexity tests requiring an elevated standard for labs, and some physicians stopped performing them in their clinic or office.^{91, 92} However, most rapid antigen tests are considered “waived” or simple complexity, meaning anyone can perform them accurately, including the untrained patient at home.⁹³

Since their introduction to the market around 1986, rapid antigen tests have become highly specific (up to 99%), and sensitive (77–95%) compared to culture, and take just a few minutes in the outpatient setting.⁹⁴ Collection swabs are stable and suitable for testing for up to 48 hours at room temperature by some manufacturers. However, sensitivity and specificity may vary widely from manufacturer's report, and should be validated in a particular setting.⁹⁵ The type of personnel performing the test may significantly affect the diagnostic accuracy. Tests performed by clinical staff in one study resulted in poorer sensitivity and specificity than those performed by laboratory staff.⁹⁶ POCTs in general have been found in one study to be frequently subject to error from different sources, including operator incompetence and non-adherence to test procedures.⁹⁷ Due to

the lower sensitivity, the current recommendation from the IDSA is to confirm negative rapid tests with culture in children only, as this age group is most likely to develop rheumatic fever if unidentified and untreated.⁹⁸ Neither rapid detection nor culture can differentiate carrier status from infectious cause, and 10–15% of children may be GAS carriers.^{99,100} Despite testing variability, the introduction of rapid strep testing has produced a significant reduction in antibiotic prescribing in ambulatory settings, without additional adverse effects.^{101,102}

When evaluating cost–effectiveness, studies vary widely on different testing, treatment, provider type, payer options evaluated, and the metrics reported. While there is diagnostic value in both the clinical decision tools, such as a scoring system, and the rapid testing, their integrated use is necessary to maximize effective patient care.¹⁰³ Several studies have found that the combined use of clinical decision tools and rapid antigen testing can be cost–effective by pre-selecting those who get tested by the presence of clinical symptoms. This pre-selection method by symptoms, when compared to either empirical treatment or culture, cost US\$ 15 per patient appropriately treated, while the others were US\$ 26, and US\$ 32, respectively. This method produces nearly ideal treatment of patients presenting with pharyngitis, preventing complications and reducing unnecessary antibiotic use.¹⁰⁴ One study estimated that use of the rapid test alone was the most cost–effective way to prevent cases of rheumatic fever (when compared to other test-all or treat-all methods), resulting in a cost to society of US\$ 727 000 per case of rheumatic heart disease prevented (as cases of rheumatic heart disease are rare and strep screenings are frequent).¹⁰⁵ This included estimates of antibiotic allergy reactions and likelihood of death, as well as outcomes of failed therapy. A European paediatric study found similar results, but included a clinical scoring system and found the score plus the rapid test to be the most cost–effective for the payer (cost–effectiveness ratio of €50.72). This same study showed that the sensitivity of the scoring system was relevant, and the rapid test was the most cost–effective when the score sensitivity was lower.¹⁰⁶ However, there are numerous published guidelines on how to incorporate patient presentation and microbiological testing into diagnosis and treatment. Some guidelines do not favour microbiological testing or treatment, as the disease is viewed as benign and self-limiting (which can create different problems, such as ones surrounding public awareness and education).¹⁰⁷

In the absence of clinical complications, it would be unnecessary to test or treat any patient for GAS, but the small probability of the rather serious complication of rheumatic fever drives both test and treatment. Models demonstrate that treating all symptomatic patients with penicillin incurs the lowest immediate cost in test/treat strategies and is most effective for reducing sequelae, however the cost of penicillin-allergy-induced treatments is quite high.^{108,109} This method incurs the greatest “health lost” (in quality-adjusted life years [QALYs]) due to risk of

complications, in one study.¹¹⁰ Incidence of rheumatic fever in the United States is quite low (0.5 cases per 100 000 persons annually) and has decreased steadily since the 1940s, although outbreaks do still occur.¹¹¹ However, worldwide rates vary widely by country, with the aboriginal population of Australia having rates as high as 241 per 100 000.¹¹²

Treatment

Penicillin is the recommended treatment for non-allergic patients due to the fact that it has a narrow spectrum and is an inexpensive antibiotic (averaging less than US\$ 1 per pill). Dosing is oral or intramuscular. A narrow-spectrum cephalosporin such as cephalexin is the recommended alternative for allergic patients, although cost can be significantly higher.^{113, 114} While GAS pharyngitis is often self-limiting, progressing to complications in only rare cases, antibiotic therapy reduces symptoms and duration, as well as infectivity. However, data from United States national ambulatory health surveys show that antibiotic treatment for adults with upper respiratory illness is as high as 50–75% in emergency room or outpatient settings.^{115, 116}

Data suggest that antibiotic use rates for upper respiratory tract infections in the United States have decreased since the 1990s. Penicillin and cephalosporin use has decreased, but macrolide and quinolone use is increasing and more than half of all paediatric visits for respiratory tract infections result in antibiotic prescription.¹¹⁷ Overall per-person antibiotic use in Europe has increased over the same period, with up to 60% of all primary care antibiotic prescriptions in the United Kingdom alone given for respiratory infections.^{118, 119} A United Kingdom study demonstrated that patients who received antibiotics in an outpatient clinic for sore throat were more likely to return to the clinic for an episode of sore throat within the following year than patients who did not receive antibiotics.¹²⁰ However, the availability and implementation of rapid testing has been shown to reduce antibiotic prescribing in ambulatory settings by as much as 27–39% in several studies.^{121, 122, 123}

Rapid testing for streptococcal pharyngitis has proven a very successful tool in the management of the patient. Bacterial antigen testing is most useful when there is one single organism under study which is unique in its environment, just as group A streptococcus is an intruder in the upper respiratory tract and not part of the normal flora. Rapid testing has provided physicians a bedside decision tool that eliminates return visits, additional phone calls and, most importantly, unnecessary antibiotic use. While severe adverse effects due to strep throat infection are rare, rapid strep testing has provided the means to prevent them.

4.3.2 Case study 2: MRSA – a success story

The antibiotic methicillin was introduced in 1959, and within a few years MRSA was observed. Hospital outbreaks occurred in the 1970s, and researchers began work to find the source of resistance within the organism. The penicillin-binding protein was discovered in the 1980s, and not long afterwards, the gene that codes it called *mecA*.¹²⁴

Once resistance was discovered, clinicians focused on infection control measures in hospitals to prevent transmission. Patient isolation, improved hand hygiene, cautious antibiotic use and active surveillance measures were implemented. Some countries also undertook elimination policies aggressively treating all MRSA carriers. The methods had significant effects, and rates of MRSA in hospitalized patients began to decrease.^{125, 126, 127} Transmission of MRSA was determined to be the predominant cause of new cases, as opposed to antibiotic pressure.

Identifying patients who were infected or carriers was the first step. Surveillance cultures of the nares have been employed in different patient populations, allowing hospitals to identify, isolate and/or treat patients. However, the method for identification has traditionally been agar plate growth or a microbial antibiotic panel, both requiring up to 72 hours for identification of the organism and its resistance patterns. One study showed that patients admitted to hospital who were carriers of MRSA would have already contaminated their environment within the first 36 hours, before their test results were back and before they could be isolated from other patients. The need for faster identification was clear.

Enriched culture media were developed to enhance identification of MRSA, but bacterial growth still requires at least 18–24 hours. In the late 1990s, rapid phenotypic assays were developed such as the BBL Crystal MRSA ID and Denka MRSA screen assay, but both required microbial growth first, and only the sensitivity of the organisms was actually rapid. The development of PCR assays to identify the *mecA* gene significantly decreased the time to identification, but were initially quite complex and performed only in specialty laboratories. The Beckman Coulter/Danaher GeneOhm assay was FDA-approved in 2008, and Cepheid's GeneXpert for MRSA in 2010. Both tests are simpler PCR assays that take less than 2 hours. Compared to culture media, the Xpert assay has a sensitivity and specificity of 80–100% and 93–100%, respectively.¹²⁸ The use of a rapid test has been shown to reduce MRSA burden and transmission in a hospital unit.¹²⁹

4.3.3 Case study 3: Sepsis – persisting challenges

Sepsis, severe sepsis and septic shock are often the result of bacterial, fungal, viral or parasitic infection contributing to systemic alterations and creating an

inflammatory response that may lead to organ failure and death. Incidence is estimated between 1 and 3 cases per 1000 population cases each year (750 000 in the United States annually).^{130, 131} Rates of mortality from sepsis have declined in recent decades, and are currently approximated at 17.9–48%, depending on severity of illness at presentation and age.^{132, 133, 134} The hospital cost is estimated at between US\$ 22 000 and US\$ 38 000 per case, and US\$ 1.67 billion annually.^{135, 136, 137} More than half of cases are admitted to ICU care, where studies have found an average LOS from 9.2 to 15.7 days.^{138, 139} Studies in Europe and Canada have estimated daily costs of hospital care of sepsis patients to be between €710 and €1033.^{140, 141} A review of European and American studies finds that approximately 40–60% of care costs are personnel costs in hospital (with ICU care being the most expensive), and about 30% is drug cost.¹⁴² Autopsies show that patients continue to die from failure to identify and treat sepsis.¹⁴³ Studies have shown that patients who received inappropriate antimicrobials for their blood stream infections had significantly higher in-hospital mortality than those who received appropriate antimicrobials for the pathogen.^{144, 145, 146}

Diagnosis and diagnostic tools

Diagnosis of sepsis is often made on the physical assessment of the patient, guided by widely accepted algorithms developed by several international groups including the International Sepsis Forum, the American College of Chest Physicians, American College of Emergency Physicians, Canadian Critical Care Society, European Society of Clinical Microbiology and Infectious Diseases, European Society of Intensive Care Medicine, European Respiratory Society, and the Japanese Association for Acute Medicine.¹⁴⁷ The rapid identification and treatment (both supportive and curative) of sepsis are crucial to better patient outcomes. Initial diagnosis is made based on fever, blood pressure, signs of poor tissue perfusion, and organ dysfunction. Diagnostic tests include blood culture for recovery of pathogens, blood cell counts for elevated white blood cells, coagulation testing for alterations in haematologic process (disseminated intravascular coagulation), organ-specific function tests (liver and kidney), and tests for tissue perfusion (lactate, blood gases). With the exception of blood culture, turn-around time on blood tests is in a hospital setting is usually less than 2 hours.

An increasing number of identified symptoms indicate an increased disease severity. Systemic inflammatory response syndrome (SIRS) is an inflammatory response that may be triggered by infectious or non-infectious incident, trauma or burns. Similar symptoms may be produced by myocardial infarction or pancreatitis. If sepsis is in the differential diagnosis, it is helpful to identify a probable source, such as respiratory infection or UTI, wounds or abscesses, or recent surgery. Imaging studies may be useful for diagnosing pneumonia,

gastrointestinal disruptions or abscesses as a potential source. Imaging studies are often available to physicians in short time in most emergency rooms and acute care hospitals.

Whether the source of the sepsis is a primary bacteraemia or another source, pathogenic organisms can be captured in the bloodstream. Blood culture is often part of a treatment algorithm, but can take several days to isolate and identify an organism. The positivity rate of blood cultures increases with increasing disease severity. However, a true pathogen is recovered only 30–50% of the time in sepsis cases.

Not all pathogens are recovered in the blood; in cases of pneumonia the organism may or may not migrate to the bloodstream. A respiratory source has been found in several studies to be the leading cause of sepsis, with the urinary tract, intra-abdominal, primary bacteraemia, and skin or soft tissue sources next in frequency.^{148, 149, 150, 151} When possible, specimens can be gathered directly from the site of probable infection, such as sputum or urine specimens, or drainage from an abscess. When a pathogen is recovered from a septic patient, aerobic gram-positive and gram-negative bacteria have been found with nearly equal frequency (with a slight predominance of gram-positives in some studies), and both greatly outweighing anaerobes and fungi.^{152, 153, 154, 155}

The Surviving Sepsis Campaign is the product of a consortium of more than a dozen international medical organizations dedicated to identifying and treating sepsis through reviews of evidence and the publication of guidelines.¹⁵⁶ The most recent set of guidelines was published in 2012, and for the first time mention the use of biomarkers, though only procalcitonin is mentioned specifically. Its potential to identify sepsis has been variable in the literature, and the guidelines do not recommend the use of procalcitonin as a diagnostic tool for sepsis (“rule in test”), but instead recommend utilizing a low test value (“rule out test”), below which bacterial infection is unlikely and antibiotic therapy might be discontinued.

New diagnostic developments

Numerous biomarkers and inflammatory proteins have been identified and tested as potential indicators in sepsis and bacterial infection in pneumonia, though few have yet emerged with a strong predictive value, sensitivity, speed and usable diagnostic algorithm, and none is yet capable of being used as a stand-alone indicator of sepsis.^{157, 158, 159} The utility of any of these markers or tests depends on whether the clinician is interested in determining (1) if the patient has an inflammatory response occurring, (2) if there is organ failure, (3) how severe the illness is, (4) what the cause is, or (5) what the outcome might be. Possibly due to individual host response and severity of illness, markers do not demonstrate

consistent activity in studies, with wide variability in diagnostic performance, and different performance in adult versus paediatric population.¹⁶⁰

Markers also provide different types of information, as in one study that found that procalcitonin levels rise in the presence of infection, but remain low when organ dysfunction is less severe; while C-reactive protein rises with low levels of organ dysfunction, but does not increase with increasing disease severity.¹⁶¹ Another small study found that mean interleukin-8 levels are higher with increasing severity of disease, but there is a large amount of overlap in the range at each stage of organ failure, making it difficult to discern the patient's level of illness, yet potentially still helpful in predicting mortality.¹⁶² Other biomarkers may only identify the process taking place, and not the cause. Effective antibiotic treatment must be guided to the pathogen.

The use of procalcitonin as a biomarker of infection has shown promise as an adjunct diagnostic tool.¹⁶³ Levels of procalcitonin correspond linearly to increasing severity of disease (SIRS, sepsis, severe sepsis, septic shock).¹⁶⁴ It has had limited success in predicting outcomes, but has shown more useful in guiding antibiotic therapy. An elevated procalcitonin level indicates probable bacterial infection (in the absence of other systemic inflammatory instigators such as trauma or burns), and may be used as a decision-making tool for initiating antibiotic therapy.¹⁶⁵ Monitoring trends in procalcitonin levels by use of an algorithm can indicate progress in resolving infection, and identify the appropriate time to de-escalate or discontinue antibiotics. Several studies show a decrease in frequency and duration of antibiotic use in hospital using such an algorithm without detriment to the patient, however a meta-analysis of procalcitonin-guided therapies finds that overall they did not improve outcomes or decrease admission to or LOS in ICU.¹⁶⁶ Several assays are commercially available, including tests for automated clinical chemistry analysers KRYPTOR by Brahms AG; (Henningsdorf, Germany), and for VIDAS by bioMérieux; (Marcy L'etoile, France). Time to result is approximately 20 minutes. Both use low-volume (0.5 ml or less) serum or plasma samples, kept refrigerated or frozen, which are obtained by venipuncture, intravenous line sampling or even umbilical cord blood.^{167, 168}

While many inflammatory markers are under investigation, some other analytes are in use or in development. Serum lactate levels are one test in widespread use in sepsis detection as part of the Surviving Sepsis Campaign guidelines for identifying unapparent shock and tissue hypoperfusion. The production of lactic acid from anaerobic metabolism is a by-product of sepsis pathology. Blood plasma sample is the specimen type, obtained from a simple venipuncture. Automated tests are available from numerous manufacturers, with time to result 30 minutes or even less. Interpretable clinical ranges exist for this test. Coagulation abnormalities are not uncommon in sepsis patients who develop disseminated intravascular

coagulation. Several small studies have found an increased frequency in biphasic aPTT waveforms in patients with bacterial infection,¹⁶⁹ although the predictive value is unclear.

Despite what may be a clear clinical presentation of sepsis, to target treatment physicians still search for the source and the pathogen, often with cultures. Blood cultures have notoriously poor recovery rates for bacteraemia in septic patients, and a focus has moved to molecular diagnostics. Septifast (Roche Diagnostics, Mannheim, Germany) is a multiplex PCR assay for the detection of pathogens in blood samples, which is in use in Europe but has not received FDA approval for use in the United States. A recent study shows it to be non-superior to blood culture when used alone, but useful as an adjunct for identifying the pathogen in sepsis.^{170, 171} While it detected pathogens more often than the blood culture, that detection rate was still only 14% (compared to 10% in blood culture) in a population of suspected sepsis patients. A study of a eubacterial PCR method found similar results – although there was some overlap, the PCR and blood culture each identified bacteria the other did not.¹⁷² Anecdotal evidence suggests that the lack of sensitivity in the technology may be related to the very small volume of blood in the test sample, making it difficult to detect a small quantity of bacteria.

More promising is the Verigene system (Nanosphere, Inc., Northbrook, Illinois) that uses microarray nucleic acid testing to detect bacteria. A multiplex panel assay was approved by the FDA in 2012 for the detection of gram-positive organisms in positive blood cultures.¹⁷³ After inoculation of a blood culture bottle, the bottle is incubated, and when detected to be positive for microbial growth (as many large laboratories use an automated detection system), the bottle is sampled for the assay. This removes the time it takes to culture a specimen, and the assay takes only 3 hours at this point. However, time to growth detection in a blood culture bottle may be several hours to several days.

Blood cultures have remained the gold standard, but for many years were the only method. They have limitations, including sensitivity that is dependent on sampling technique (contamination with skin flora may result from imperfect collection or the collected volume may be insufficient to recover the pathogen), long turn-around times, and difficulty identifying certain fastidious organisms.^{174, 175} Biomarkers such as cytokines require extensive sample preparation by skilled technologists and instrumentation that is not available in every laboratory. While the PCR has a remarkable 6 hour time to result, it currently serves only as an adjunct to blood culture, not a replacement, and organisms captured by blood culture but not by PCR still require a wait of several days for comparison. These new diagnostics and molecular tests that promised increased sensitivity and speed have been complex, expensive, and yet still remain subject to one of

the same concerns plaguing blood culture: how should negative results be interpreted? And, especially in the case of *Staphylococcus epidermidis*, is the organism identified really the pathogen?

While bacterial cultures are often the focus of sepsis diagnosis, symptoms of sepsis syndrome may be caused by a dysregulated immune response to trauma or extensive burns (SIRS) and not by microorganisms. In special situations, other types of pathogens may be considered. Only when cultures do not grow an organism, and the patient remains severely ill is another type of pathogen considered, according to one critical care physician. Viruses can trigger the same inflammatory response as bacteria, but the diagnosis can be more difficult for several reasons. First, a viral culture is highly technical, and requires a specialist laboratory and expertise. The specimen (which may be a bronchial washing, spinal fluid, tissue, blood or faeces sample) is often usable only for a few days, must be maintained in special media, and kept cold. In addition, viral culture can be quite slow, with results taking days. Faster and more direct methods include direct fluorescent antibody staining or PCR, but the test must be ordered for a specific virus, and not a panel.

Another concern is that viral diagnostics may identify any virus present, even if it is not a pathogen in the patient. As with bacteria, it then becomes difficult to determine if the result represents the causal pathogen, or an innocent bystander. Certain viral illnesses are more likely and may be expected in compromised patients, such as transplant recipients. Recent literature focuses mostly on viral sepsis in neonates, and epidemiological incidence of viral (versus bacterial) sources is estimated at 58% in one study.¹⁷⁶ When analysing epidemiology of sepsis in children, one study assessed only bacterial and fungal cultures, while acknowledging very unique epidemiology of sepsis in paediatric populations by both age group and co-morbidities.¹⁷⁷

Treatment

While identification of a pathogen and a source is necessary in treating sepsis, immediate concern is also for preservation of life and supportive care. Sepsis may progress quickly to septic shock. Respiratory failure is supported by mechanical ventilation, and hypotension by fluids in large quantities or vasoactive medications. Treatment is guided towards physiologic goals, such as haemodynamic parameters, with fluids, medications and ventilator support. The 2012 Surviving Sepsis guidelines have an algorithm for resuscitation interventions within the first 6 hours, including initiation of antibiotics within the first hour for patients with severe sepsis, well before blood culture results or nucleic acid testing would be available. While some studies have demonstrated an increase in mortality as

time to antibiotic increases, one recent study shows that the time to *appropriate* antibiotic treatment was more predictive of mortality, with increases for each hour of delay. However, identification of a potential source of infection may narrow antibiotic choice, as certain pathogens may be more or less likely in a certain body site. As studies have shown that identification of the causative organism happens, at most, 55% of the time, identification of a probable source should guide antibiotic treatment, although the algorithm utilizes broad-spectrum therapy as first treatment.^{178, 179, 180} There are currently some emergency medical services teams beginning sepsis treatment pre-hospital. Once the new guidelines are published, more hospitals may institute pre-hospital treatment.

Even in the absence of an identified pathogen, early aggressive supportive treatment aimed at increasing fluid volume and improving oxygen delivery (called Early Goal Directed Therapy, or EGDT) has been shown to decrease hospital cost and mortality significantly, even among sepsis survivors, who often incur longer lengths of stay than patients who die.^{181, 182} It can also be cost-effective with one study calculating an increase of “1.3 QALYs and at a willingness to pay threshold of US\$ 50 000 per QALY”, and an increased hospital cost of approximately US\$ 7000.¹⁸³ While also not cost-saving (additional costs of US\$ 8800), another study found that a similar integrated treatment protocol including antibiotics and insulin was also cost-effective, at US\$ 16 309 per QALY gained.¹⁸⁴ Considering that a large portion of sepsis care cost is hospital staffing, any treatment that reduces the LOS is cost-saving.¹⁸⁵ However, patients receiving protocol therapy as mentioned here tend to survive longer and incur longer stays.¹⁸⁶

With cytokine testing requiring specialized laboratory staff and equipment, blood cultures providing poor recovery of organisms and long turn-around times, and patient survival dependent on rapid diagnosis and treatment, sepsis has seen none of the success in diagnostics that has been achieved with streptococcal pharyngitis. This complex syndrome of infection and inflammation has not yet benefited from a simple diagnostic tool (with some experts expecting that it is not possible), and improvements in diagnostic speed can only be applied to a test that actually works.

Sepsis is an enormously complex illness to diagnose and treat. With myriad microbiological causes from any number of body sites, it may occasionally rival the needle in the haystack. When physicians are fortunate enough to identify a probable source from which a specimen can be obtained, they are hampered by slow cultures and contaminating or coexisting organisms. Simple bacterial antigen testing that has seen success in other areas of microbiology is limited in sepsis because these tests are aimed at just a single or even a few organisms, while sepsis needs a panel. Nucleic acid testing has shown promise in microarrays and PCR, but both the costs and the technical expertise required limit the

general availability and potential POC capabilities, although fully automated systems are coming to market.¹⁸⁷ Whether the target is viral, fungal or bacterial, the majority of available methodologies cannot clearly rule out whether the organism recovered is truly the pathogen. Left guessing half the time, physicians must deploy broad-spectrum antibiotics and supportive care.

The ideal sepsis test:

- would identify the organism and differentiate between sepsis and SIRS, and provide some measure of certainty or likelihood that it is, in fact, the pathogen;
- would identify a probable site of infection if an organism cannot be recovered;
- would provide some antibiotic guidance, or resistance analysis;
- has a time from sample to test result of less than 6 hours for organism identification, or less than 3 hours for definitive determination of microbial sepsis, or to definitive rule out.

Chapter 5

Reimbursement-related signals received from procurement and reimbursement agencies

5.1 Introduction

Diagnostic developers receive much information on market demand through the filter of procurement and reimbursement agencies. Signals from the agencies involved are therefore critical in directing developer investment. However, current discord and considerable variation in evidence requirements leave significant uncertainty surrounding coverage and reimbursement levels, pushing developers towards less risky, less innovative technologies. This chapter outlines the key reimbursement and procurement processes and identifies critical areas where improvements should be made, especially in terms greater harmonization and transparency.

5.2 Background: reimbursement in the United States

In the fragmented United States market, with multiple insurers and varying legislative contexts, diagnostic developers face a number of differing incentives and disincentives when deciding what kinds of new diagnostic to invest in. Additionally, even within providers reimbursement varies significantly according to the care setting, as well as often by insurance plan type. There are three main payer “types” that a developer will consider: first, Medicare (part A and part B); second, Medicaid; third, commercial (private) health plans of both for-profit and not-for-profit nature. There is also an emerging fourth category of payer, the Health Insurance Marketplaces, authorized under the Patient Protection and Affordable Care Act, which will become effective on 1 January 2014. This means that a developer faces multiple purchasers, rather than a single national purchaser as is often the case in countries with systems akin to the United Kingdom’s NHS.

Having said this, there was general consensus among project participants that in many contexts Medicare is a de facto coverage determiner and price setter,

being the largest single payer in the country, serving over 50 million beneficiaries and contributing an estimated 21% of national health spending.¹ Medicare is responsible for more than 29% of the nation's laboratory bills for inpatient and outpatient services, and Medicare laboratory services spending grew by an average of 5.5% per year between 2002 and 2011, primarily volume-driven increases. Medicare is the largest single purchaser of clinical laboratory services and in 2011 payments for these services totalled US\$ 8.9 billion, 1.6% of total Medicare spending.²

In summary, the United States coverage and reimbursement landscape presents significant challenges for developers of novel diagnostics. Currently the system is built upon a reimbursement structure that was designed in the context of relatively simple, traditional diagnostics. Coverage decisions are driven by strength of evidence and, although there are clear hierarchies of evidence, the processes lack transparency and vary across payers. This means that developers face uncertain evidence requirements as well as uncertainty about coverage, leading to increased financial risks. Coding and payment are intricately linked, and although coding for some molecular tests has recently undergone major changes, there remain significant challenges in motivating accurate descriptive codes. This leads to irrational payment structures and few opportunities for assigning a price that reflects the value to the health system, or society.

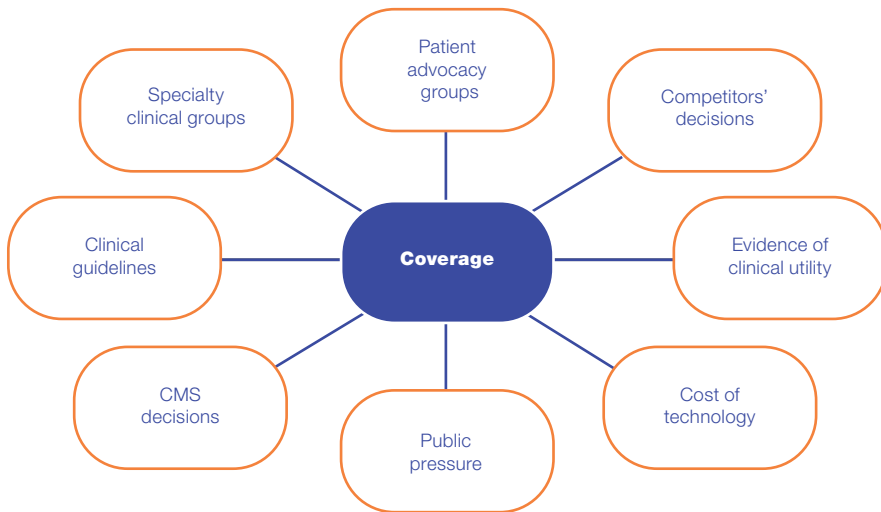
In the case of diagnostics used in the lab setting, it should be added, requests for tests are often made before reimbursement status is known. Expensive molecular and esoteric testing are often proprietary, only performed in a few reference labs that direct bill the laboratory for their services. The laboratory and/or hospital where the lab is located pays the cost of the test and then attempts to be reimbursed from patient's insurance or Medicare. They bear the full risk in the case of ex-post coverage refusal. In some cases reference labs agree to "third party" a bill, meaning that they accept a specimen with the understanding that the hospital lab will cover the cost of the (lab-developed) test in the event that the patient's insurance refuses to pay.

5.3 Coverage: determining clinical utility

Coverage decisions determine whether or not a technology will be included in services offered to health plan beneficiaries. Coverage decisions for diagnostics lack formality and payer organizations' reflections identified variability in the processes and evidence requirements. Payers' decisions are influenced by a variety of factors, and variability in the strength of influence makes it very difficult to predict coverage decisions. One large private payer identified a number of factors that would influence their medical directors' coverage decisions on a

novel diagnostic for infectious diseases and it is shown in Fig. 5.1. CMS stands for Centers for Medicare and Medicaid Services, a branch of the United States Department of Health and Human Services (DHHS), which administers Medicare and Medicaid.

Fig. 5.1 Stakeholders and factors influencing coverage decision



Variable processes exist for Medicare. Medicare coverage decisions can be made at a national level, using national coverage decisions (NCDs). In reality, however, these decisions are only for high-impact or high-cost technologies. Rather, coverage decisions are usually driven from the individual, local level upwards. New technologies are often identified through the claims processing procedure with regional contractors; if a claim includes no procedure code or an item without an established price it will automatically be passed on for review as a once-off coverage decision. Apart from this, external sources such as physicians, manufacturers, clinical associations or advocacy groups may request coverage for a new treatment or device and then the process begins of determining whether or not the technology's clinical utility can be demonstrated and whether the treatment is deemed necessary within the individual care pathway. Physicians can motivate for coverage of a new technology on a case-by-case basis. This area is where sales representatives from diagnostic companies can influence physician uptake in the hope of increasing sales until a coverage decision can be reached. Dealing with claims supporting documentation for uncovered, case-by-case reimbursement decisions places significant financial and time burdens on physicians. This leads to reluctance to use innovative products. In this way use of and coverage for many low-cost or low-impact items will be decided on an ad-hoc case-by-case basis at local level.

However, sometimes payers, physicians and patients are at loggerheads, or the technology is subject to controversy, or has the potential to have high impact for beneficiaries, or could have significant impact on the payer programme through high volumes and/or expenditure. In these instances, coverage decisions are requested by interested parties (including patients, practitioners or clinical specialty groups). Topics that are accepted for review will then have coverage decisions made that are binding for providers. The CMS and its contractors – Medicare administrative contractors (MACs), fiscal intermediaries and carriers – are authorized to develop local coverage decisions (LCDs) for most items. In some instances, however, CMS produces NCDs that are binding for all contractors (MACs, fiscal intermediaries and carriers) as well as quality improvement organizations and quality independent contractors, administrative law judges and the Medical Appeals Court (Stakeholder interviews).³ Overall, coverage decisions are made on an ad hoc basis, as and when the payers deem a decision to be necessary in response to various factors, including patient pressure.

NCDs, LCDs and private payer coverage decisions are guided by the strength of evidence for the new care path, technology or medicine's *clinical utility*. Determining clinical utility requires that the health intervention or technology demonstrate safety and efficacy data where the benefits outweigh the potential harms, as well as, increasingly, effectiveness data showing benefits in an everyday clinical setting. This term, "clinical utility", also refers to the probability that a diagnostic or intervention will improve patient outcomes by (a) changing care decisions based on the findings and (b) showing whether the patient benefits from the changes to his/her care pathway. Currently, data from RCTs are given most credence, with the findings of less rigorous studies being considered thereafter. This creates an accepted evidence "hierarchy" and, for a product to receive favourable review, it must be accompanied by robust, peer-reviewed evidence from scientific trials.

The Social Security Act governs what Medicare does and does not cover, based on whether the technology falls within an existing benefit category and is not being specifically excluded. Additionally, since 1965 Medicare coverage decisions have been guided by the mandate that coverage be limited to services that are "reasonable and necessary", that is, if the technology is needed to diagnose or treat a medical condition, and if it meets accepted standards of clinical practice. Within the context of increasing health care costs, budgetary pressures and the relentless march of technology, it becomes a complex challenge to find acceptable definitions of what can be considered necessary or reasonable. Neumann and Chambers (2012)⁴ present a cogent overview of the challenges of the enduring struggle to define exactly what "reasonable and necessary" means. Care is usually defined as necessary within the Medicare system based on the strength of clinical evidence showing safety and efficacy.

In 1989, Medicare proposed a definition of “reasonable and necessary” as care that is safe, effective, non-investigational, appropriate and cost-effective. This last criterion was rejected on the grounds that cost considerations would lead to patients being denied “necessary” care. As a result, Medicare is legally barred from considering cost and the country’s health plans, providers and patients are stuck in a bizarre dance of semantics and double thinking where, as one respondent said, cost is both the “deal breaker” and the enormous elephant in the room. Participants did, however, suggest that cost plays an implicit role in determining which aspects come up for coverage review; technologies that are high cost or that are likely to have high budget impact have a greater probability of being reviewed for NCD or LCDs.

As described earlier, Medicare contractors are permitted to set LCDs when there is no NCD in place, or when the NCD needs further defining. An LCD determines whether or not a fiscal intermediary or carrier will cover a service. These are made within each Medicare jurisdiction separately, although collaboration can take place. Stakeholder perceptions highlight that areas with a culture of medical research, the medical “meccas” like Boston, are often more likely to consider evidence-based approaches and innovative areas of treatment (Stakeholder interview). Because LCDs serve as guides in the absence of NCDs, and many unspecified decisions are left to local determination, there is wide variation between what services are available under different contractors.

Large private payers have the capacity and ability to consider costs of new technologies and health technology assessments may include economic data. They are also, however, often subject to intense public pressure and patient advocacy groups because of the large populations they serve, and explicit cost considerations are unpopular. Stakeholders from private payers were recalcitrant about the degree to which cost is incorporated into coverage decision-making.

Smaller private payers have less capacity to conduct extensive technology assessments and are more likely to gather assessments conducted by other payers, tweaking them to apply to their own beneficiary groups. Internal advisory bodies and expert physician committees were mentioned by stakeholders as influential in this regard.

All interviewees identified the critical role played by peer-reviewed, clinical evidence. Coverage decision frameworks use reports and evidence synthesized or generated within national or regional research groups: the most important of these are the Agency for Healthcare Research and Quality, the United States Preventative Services Task Force, the ECRI Institute (an independent non-profit-making research group) and private groups like the BlueCross BlueShield Association (BCBS) Technology Evaluation Center (TEC), BlueShield California and consultancy groups like Hayes. Medical specialty groups within the NIH

also play a role in guiding research and synthesizing evidence. These research groups are described below.

The AHRQ guides coverage decisions through evaluating evidence of new technologies. The AHRQ exists within the DHHS, with the mandate of improving safety and quality of care. The AHRQ targets a range of stakeholders, from provider to payer, federal to state policy-makers, and private and public bodies. Its influence was confirmed across the board by participants in this report. Private health plans will often look to national research bodies such as the AHRQ for guidance on the clinical utility of a new technology, influencing coverage. The AHRQ oversees a group of “evidence-based practice centers” (EPCs), usually based within universities, which are contracted for five-year periods to review existing evidence for technology assessments aimed at guiding coverage decisions, among other things. Reviews are housed online,⁵ and used by both providers and payers, as discussed later. The BCBS TEC, Johns Hopkins University, Kaiser Permanente Research Affiliates, Brown University, ECRI Institute at Penn Medicine are a few of the EPCs. These groups also support the work of the United States Preventive Services Task Force (USPSTF).

The USPSTF makes recommendations for coverage for treatments pertaining to preventative health based on clinical utility defined as a balance of clinical benefit and harm. Reports from the USPSTF are also available online.⁶ The rating scale used is presented below in Table 5.1.⁷

Table 5.1 *Ratings scale for coverage decisions used by USPSTF*

Grade	Definition
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgement and patient preferences. There is at least moderate certainty that the net benefit is small.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.
I Statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.

An example of a Medicare NCD influenced by USPSTF relevant to infectious diseases was issued in 2011 on screening for STIs and high-intensity behavioural counselling to prevent STIs. This coverage determination found that the evidence was adequate to conclude that screening for chlamydia, gonorrhoea, syphilis and hepatitis B, as well as high-intensity behavioural counselling was sufficiently supported by the grade A and B recommendations from the USPSTF. Coverage

is therefore granted for the “appropriate” FDA approved/cleared tests, used in compliance with the CLIA regulations.^{8, a}

The ECRI Institute conducts health technology assessments and is an EPC. The Institute’s Health Technology Assessment Information Service is a membership-based consulting service for hospitals and health plans. The Institute assists in coverage and procurement decisions through conducting systematic reviews of published evidence. Reports are only available to members.⁹

The BCBS TEC has its own “scientific criteria for assessing medical technologies [for clinical effectiveness] through comprehensive reviews of clinical evidence”.¹⁰ It is recognized as an influential body for evidence-based technology assessments and non-BCBS health plans are able to use the findings. For example, Kaiser Permanente and the CMS make use of the assessments produced by the TEC. There are between 10 and 15 assessments per year. Reports are available on the web site and may be used by any interested party with the permission of the TEC.¹¹

Private health plans like BlueShield California also follow similar methodologies with their in-house assessments, focusing on determining clinical utility, without consideration of financial costs. The BlueShield California Technology Assessment Forum uses key criteria to guide decision-making for coverage guides. (1) First the technology must have final approval from the relevant government regulatory body and then (2) the scientific evidence must permit conclusions concerning the effectiveness of the technology insofar as it impacts positively on health outcomes. The evidence on effectiveness is graded using a structured “rating scale” drawn from Cook et al. (1992).¹² Level 1 studies are the top of the evidence hierarchy while level 5 evidence is unlikely to lead to the intervention being considered for coverage as described in Table 5.2.

Table 5.2 *BlueShield California Technology Assessment Forum evidence levels*

Level 1	Randomized trials that had enough power to demonstrate a statistically significant health outcome
Level 2	Randomized trials with results that were not statistically significant but where a larger trial might have shown clinically important difference
Level 3	Non-randomized concurrent cohort comparisons between contemporaneous patients
Level 4	Non-randomized historical cohort comparisons between current patients and former patients (from the same institution or from the literature)
Level 5	Case series without control subjects

a Professor James Nichols notes that the USPSTF only makes recommendations for population screening of patients for specific diseases. The USPSTF does not review evidence for use of specific technologies in the management or treatment/prognosis of certain diseases after diagnosis, so the USPSTF only covers patients without symptoms for screening of chronic illnesses.

(3) The technology must improve net health outcomes, which for diagnostic tests relies on evidence that the test would result in improved medical management that would be of benefit to the patient. (4) It must offer at least the same benefits as any established alternative and, finally, (5) the improvement must be attainable in day-to-day practice, beyond a clinical trial setting. Recommendations from the BlueShield California Technology Assessment Forum are also available online.¹³

National consulting groups like Hayes consulting group are also drawn on for guidance, with many private payers purchasing subscriptions for this purpose. Hayes’ recommendations are only accessible with a paid subscription. Private payers also use the Hayes “strength of evidence” approach to determine clinical utility. With this approach, evidence is rated A–D, with published peer-reviewed, RCT data as the gold standard. The Hayes Rating system is detailed in Table 5.3, drawn directly from the Hayes web site.¹⁴

Table 5.3 *Hayes Rating system*

A	Established benefit.	Published evidence shows conclusively that safety and impact on health outcomes are comparable to or better than standard treatment/testing. Long-term safety and impact on health outcomes have been established, and other important questions concerning application of the technology have been answered. Drugs, biologics, and devices with an A rating have FDA approval, but not necessarily for the specific clinical application(s) under consideration.
B	Some proven benefit.	Published evidence indicates that safety and impact on health outcomes are at least comparable to standard treatment/testing. However, there are outstanding questions regarding long-term safety and impact on health outcomes, clinical indications, contraindications, optimal treatment/testing parameters, and/or effects in different patient subpopulations. Drugs, biologics, and devices with a B rating have FDA approval, but not necessarily for the specific clinical application(s) under consideration.
C	Potential but unproven benefit.	Some published evidence suggests that safety and impact on health outcomes are at least comparable to standard treatment/testing. However, substantial uncertainty remains about safety and/or impact on health outcomes because of poor-quality studies, sparse data, conflicting study results, and/or other concerns.
D1	No proven benefit.	Published evidence shows that the technology does not improve health outcomes or patient management for the reviewed application(s) or is unsafe.
D2	Insufficient evidence.	There is insufficient published evidence to assess the safety and/or impact on health outcomes or patient management.

Although most technology assessments follow similar evidence hierarchies the range of groups available for guiding decisions leads to inconsistencies and variability in coverage. For example, MAC directors naturally differ in their interpretation of evidence, particularly in the face of varying evidence sources and decision frameworks used across regions. Respondents noted that different carriers may have more specialists in a particular field, and lack expertise in others, which has implications for coverage decisions. Advocacy groups may be more or less active in certain regions, and patients may be more or less informed.

Medical directors will draw together published evidence, clinical expertise from clinical specialty groups and potentially patient advocacy groups in making a decision. Developers do not have official routes for lobbying coverage decision processes except through ensuring that published evidence of clinical efficacy, and potential economic impact, exists. Developers may also collaborate with specialty or advocacy groups in some cases. Payers differ in their perspectives about the role of developer-sponsored economic analyses. Some feel that economic data helps with motivating coverage while others see economic studies as marketing tools, to be used to ensure uptake rather than influence coverage and reimbursement decisions.¹⁵

5.3.1 Evidence challenges

The inconsistencies in methods and decision-making make it difficult for developers to anticipate what evidence will be required, by which bodies, to determine clinical utility. One large private health plan representative reported that they would use evidence from multiple decision frameworks, including the AHRQ, USPSTF, BCBS TEC, Hayes and internal assessments using medical expert panels or advisers. While the same data may be available to all decision-makers, the various frameworks being used leads to wide variation in evaluation outcomes and coverage decisions.

Private payers and CMS contractors highlight the challenges created by the complex, fragmented evaluation system. When there is no clear decision-making process it is very difficult for payers to send clear signals about what products would be regarded as high value. If payers cannot send clear signals, it is virtually impossible for developers to anticipate payer demands in (a) the types of technologies to develop and (b) the types of evidence required for assessment of these technologies. These challenges restrict the development and diffusion of innovative diagnostics.

Determining “clinical utility” increasingly requires evidence of effectiveness in day-to-day practice. This brings numerous additional changes to the evidence requirements faced by developers. Similarly, an increased focus on outcomes data will influence manufacturers and researchers in deciding which areas of technologies are worth investing in. For example, if the existing treatment context makes it difficult to change patient pathways, investing in a test is less attractive because it may be difficult to provide evidence of how the test will impact patient outcomes. One participant raised the example of warfarin: currently tests are able to identify patients who will respond negatively to treatment, but there is no mechanism for the physician to act on the information to *improve* patient outcomes by adjusting the dose, or moving the patient to alternative treatment.

Because the evidence requirements for diagnostics, including companion diagnostics, depart significantly from the requirements for drugs and biologics, making evidence-based and value-based decision processes is often challenging. Diagnostics come to the market either (1) as an FDA approved laboratory test kit (which is referred to as a device) or (2) as a laboratory-developed test (LDT). IVD manufacturers manufacture “devices” for commercial distribution. These devices are subject to the FDA Center for Devices and Radiological Health “premarket notification” (PMN or 510(k)) process, or “premarket approval” (PMA) process. These processes do involve some measure of safety and efficacy assessment but neither process will routinely include controlled trials for the evaluation of safety or efficacy.

LDTs are developed in-house by clinical laboratories that also use the tests. These tests rely on the CMS CLIA regulations of 1988 for overseeing laboratory processes. CLIA does not, however, include assessment of *individual* tests. The FDA does not exercise regulatory authority over LDTs at this stage.^{a, 16} Both routes to market access, therefore, result in less evidence generation than would usually accompany the development of a drug or biologic. The availability of a test, either through commercial distribution or laboratory development does not, therefore, guarantee evidence of clinical utility, nor does the lack of FDA approval mean that a test is of poor quality. It means that evidence is difficult to navigate and typically each circumstance requires individual consideration.

The FDA does not require clinical outcome studies for approval during regulatory states, so the evidence is not usually generated. This means that when technologies are assessed for evidence of clinical utility data on effectiveness are lacking. Additionally, because published, RCT data are preferred in all the rating systems described above, developers have to ensure that their product has been included in peer-reviewed, published reports.

In 2006 Medicare adopted the “coverage with evidence development” (CED) policy.¹⁷ This policy allows provisional coverage for medical technologies that could offer significant benefits through the NCD process, provided that the patients receiving the treatment are enrolled in a clinical trial gathering data on safety and efficacy as well as impact on patient outcomes. Data are primarily collected using RCTs. If adequate evidence is generated, the technology will continue to be covered and will be expanded to patients outside of the trial setting. Dealing with uncertainty in the evidence that is generated presents significant challenges, particularly because there are no standardized methods for gathering and processing data. Additionally, legal complexities exist since it is argued that the definition of “reasonable and necessary” is undermined: if CED aims

a The FDA has arguably always had the authority but has used “enforcement discretion”, that is, chosen not to intervene. http://www.nytimes.com/2013/07/08/opinion/the-gap-in-medical-testing.html?_r=0

to generate evidence, then the service cannot yet be considered reasonable or necessary in terms of its proved ability to improve health outcomes. The policy has recently come under review and some of the changes are outlined below.

Between 2011 and 2012 Medicare opened a CED Public Solicitation process to elicit comments from the public, including manufacturers, on the future direction for CED.^{18, 19} Comments from Eli Lilly Co. highlight the need to coordinate evidence requirements between CMS and the FDA. Stakeholders express concerns about the possibility that CED may be implemented through LCDs, where local Medicare contractors would collect data. Concerns relate to the implications of fragmented studies with incompatible endpoints, and low statistical power due to small sample sizes. Duplication of effort is also a concern. For example, in drug regulation there is currently the risk of FDA requiring a Risk Evaluation and Mitigation Strategy and CMS proposing CED separately.

Comments from the American Clinical Laboratory Association highlight the challenges that CED policies can pose for diagnostic technologies in particular. It is unusual for a laboratory to conduct prospective RCT trials to show that a specific test has clinical utility, particularly because of the indirect effect that a diagnostic technology usually has on outcomes. One commentator suggested that for diagnostics a substantive change in patient management should be considered the endpoint of interest, rather than overall patient health outcomes.

An example of a CED for a diagnostic test is the test for predicting responsiveness to warfarin. CMS determined that the pharmacogenomics testing of CYP2C9 or VKORC2 alleles to predict warfarin responsiveness does not provide sufficient benefit to Medicare beneficiaries to warrant coverage. This is because there was no evidence to demonstrate how the test would enable physicians to change treatment so as to improve patient outcomes. CMS did, however, allow for a CED approach for those patients enrolled in a prospective RCT to generate evidence on the topic.

The most recent draft guidance for the public (2013), industry and CMS staff of CED²⁰ identifies the AHRQ as a key body in coordinating stakeholder interests in designing, implementing and monitoring CED trials. It is also anticipated to play an increasingly important role in establishing PPPs for funding CED studies and maintaining confidentiality and data protection that should facilitate improved data sharing. This most recent guidance reaffirms that CMS recognizes a lack of evidence of real-world benefits in typical patient care settings. Additionally, the report identifies the need to re-evaluate older technologies when new evidence emerges, hinting at the expanding influence of comparative research approaches.

Responses to the new policy guidelines²¹ express concern about CED being used as a formal, routine mechanism for determining coverage, and that it should

rather be used sparingly when FDA approval is unequivocally inadequate for demonstrating clinical utility within the Medicare population. Because many private health plans follow Medicare's lead with coverage decisions, delays in implementing full coverage are likely to lead to delays in accessing other market segments. Data from the CED trials are expected to be published in peer-reviewed papers, after which they are included in the evidence base for or against clinical utility.

Even with the possibility of innovative coverage processes like CED, a developer of a new test faces significant uncertainty about coverage of a new product. Because no standard definition of "reasonable" or "necessary" exists for Medicare coverage, nor standard decision frameworks for private payers, coverage determinations are always open to some degree of interpretation, and will be influenced by the subjective perspectives of those involved in the decision. This adds to the unpredictability of coverage decisions.

5.3.2 Potential for harmonization of approach

MACs oversee the administration and processing of Medicare A and B policies, managing all coverage, billing and enrolment issues. Providers and suppliers are generally assigned to a MAC based on geographic location, while larger chain providers can request that all their reimbursement activities be handled under the MAC with jurisdiction over the chain's headquarters. This means that if tests are processed in a centralized laboratory, they are subject to that region's LCDs, even if the sample being analysed is from elsewhere. Developers whose tests are used in such a centralized laboratory would be able to focus on ensuring coverage in the relevant region, automatically ensuring coverage in other regions that use the same testing centre. This could, theoretically, lead to a situation where an LCD serves as a de facto NCD.

There are 15 national Medicare jurisdictions. These jurisdictions are made up of a number of states, normally geographically separate. Over the next several years CMS will consolidate smaller A/B MACs, reducing the number of jurisdictions to 10.²² This has implications for developers since the consolidation of the jurisdictions potentially means greater harmonization in approach and more streamlined market analyses. For developers this could mean a reduction in the burden of evidence requirements.

Beginning in 2014, all technologies rated as A or B by the USPSTF (coverage recommended) will become mandatory preventative services for coverage across health insurance providers of all types, creating universal coverage determinants for the defined population groups.²³ This will make the USPSTF decision-framework particularly important to developers.

The private health plan market is characterized by an increased number of mergers and acquisitions, leading to some consolidation of approach. Similarly, the National Association of Insurance Commissioners has encouraged greater coordination across the insurance market. These changes will not have significant impact for developers, however, since large variability will continue to exist and uptake at a local level remains the driving force for coverage consideration.

Coverage decisions have different implications across medical care settings where reimbursement contexts vary. These are presented below as clinical laboratory setting, physician outpatient setting, inpatient acute care and outpatient hospital setting. Clinical laboratory services receive the most attention, since this is where the greatest stakeholder interest exists.

Clinical laboratory services

Under Medicare part B (outpatient services), Medicare covers all medically reasonable and necessary services that are ordered by a physician or appropriately qualified non-physician practitioner. This includes diagnostic POCTs and tests from clinical laboratories. There are more than 1100 Healthcare Common Procedure Systems billing codes for laboratory services and these code arrangements are based on Current Procedural Technology (CPT) codes, created by the American Medical Association (AMA). In this way, although CPT coding is nominally a data capturing and administrative process, it is an integral part of assigning a value to a new diagnostic product because CMS reimbursement amounts are directly associated with the CPT codes for diagnostic technologies.

Coding. The Health Insurance Portability and Accountability Act of 1996 required that the Secretary of Health and Human Services establish a set of standard codes for health services and technologies in order to facilitate data collection and sharing between providers and payers. (Section 1173 (a)(1) of the Social Security Act (42 U.S.C. 1320d-2(a)(1))). Having a shared “language” should theoretically facilitate increased granular insight into where spending is taking place for payers, where the market demands are waning or waxing for suppliers, as well as improving monitoring capacities for performance and quality assessments. The AMA’s CPT codes were created for this purpose. The codes were supposed to be intuitive to use, flexible and encourage innovation. In contrast to other areas, they are designed to be standardized across the national level. CPT codes for diagnostic laboratory tests contain five digits and identify more than 9000 diagnostic tests.

When a new technology comes to the market it is classified as “not otherwise coded”. These uncoded technologies struggle to achieve both coverage and payment. The AMA, not CMS, is responsible for determining whether to add, delete

or revise CPT codes. In almost all instances, the AMA will assign a new test to an existing code (called “cross-walking”). However, proponents of new technologies, including physicians and industry, may submit requests to the AMA for a code to be assigned. Coding decisions are made by the CPT Editorial Panel. The Panel is made up of physicians nominated by the national medical specialty societies and physicians representing BCBS, America’s Health Insurance Plans, the American Hospital Association and, finally, the CMS. The last two seats on the Panel are for members of the CPT Health Care Professionals Advisory Committee, who support the work of the Panel. Payers are well represented on the Panel, and are predisposed towards excluding any technologies with weaker evidence from coverage.

Although not an official requirement, coding requests are more likely to receive favourable outcomes if a clinical specialty society motivates the submission. The specialty societies have quite significant advocacy power but strict “lobbying” rules apply to anyone who can influence the Panel in their decisions. Applicants submit dossiers, presentations and commentary to the Panel during an open meeting, or workgroup meeting, along with comments from other interested parties. Thereafter, Panel members may request additional information but applicants are prohibited from engaging in unsolicited communication with either the Panel or Committee, or lobbying decisions in any fashion. The AMA does, however, encourage medical societies to collaborate with applicants from industry and elsewhere in compiling submissions, and does accept queries from these specialty society advisers. Interviewees confirmed that the world of CPT coding is complex and can seem impenetrable and slow to implement changes, taking up to 18 months to develop or modify a code.

There are three categories of CPT codes. Category I codes are assigned to clinical technologies or procedures that are used routinely and have strong evidence of clinical efficacy. Once a test is used routinely, medical specialty societies, industry representatives, individual physicians, third-party payers and other interested parties can submit an application motivating for a CPT code to be assigned. Adequate, national, routine usage is difficult to demonstrate conclusively. Applicants can also suggest deletions and revisions of existing codes.²⁴ Most new technologies are assigned existing codes that describe tests with similar methods or technical components. New tests may be assigned to the same code for other tests for the same condition (e.g. tests for Strep A), or may be assigned to a code for an existing test for a different indication, but which uses the same testing methods as the new test (e.g. transcutaneous tests for different indications). Only tests that are entirely dissimilar to existing tests will have a new code created.

Category II codes are tracking codes, part of the physician quality reporting system used to monitor performance.

Category III codes are for “new and emerging technologies” and stakeholders view this category as a miscellaneous catch-all for any technology for which there is limited evidence of clinical utility or regular use in practice situations. Technologies coded category III are unlikely to receive positive coverage decisions and are usually paid for on a case-by-case basis. These technologies are also sometimes seen as “experimental” and therefore issued with blanked non-coverage decisions. CED may be considered to allow medical specialties and payers to observe the impact of a new technology. By assigning technologies to category III the onus is placed on proponent of the technology to increase the evidence body and motivate a move to category I and full coverage. New peer-reviewed literature is required to move from category III to category I coding. Some clinical stakeholders also view category III as a means to buy time for dealing with technologies that disrupt scope or payment in practice.

Clinical laboratory services reimbursement. The link between coding and reimbursement for clinical laboratory services is very influential. As mentioned, when a new technology comes to the market it is classified as “not otherwise coded” and getting the new technology coded is the first step towards formalizing reimbursement. Reimbursement for new technologies is determined on a case-by-case basis, through contracts and negotiation. Category III codes are usually the first to be assigned. If any coverage is granted for these technologies reimbursement is negotiated payer by payer. The implicit assumption is that if a technology *does* have clinical utility, it will be used more and more and eventually be coded to category I, facilitating payment. The aim for a developer is to move as quickly as possible from an unlisted not otherwise coded status to Category I.

Once a technology is assigned a category I CPT code and coverage has been agreed, Medicare sets a reimbursement amount. Medicare pays for laboratory tests through 56 carrier-specific Clinical Laboratory Fee Schedules. These Fee Schedules were created in 1985 based on the charges for CPT coded items from laboratories in each of the Medicare carrier-specific markets. Tests with similar processes and technical components are priced the same: if a test is deemed comparable to an existing test, the new test is “walked” across to the fees associated with the comparable test (the associated local carrier fee). This process, called “cross-walking” can also involve some interpolation, for example, walk to 30% of code X, or code X*6. If there is no diagnostic that is considered similar enough an entirely new payment schedule is created for the product. This process is called “gap-filling”. The latter is usually the case when a new test has been assigned a wholly new CPT code.

This system is referred to as a “legacy approach” system, since in the majority of cases technologies are “cross-walked” to existing, historically determined

payment schedules. This approach makes it difficult to reward innovation and value, and perpetuates historic pricing mistakes. The 1980s tests that form the foundations of this payment schedule were mature tests, suggesting they may have been priced at marginal cost. This means that the basis of new tests is the marginal-cost price, with little room for producer surplus. Some also question whether this “legacy” approach even covers the development costs of more innovative molecular tests, particularly in states where the historic fee schedule is low. The implications of rewarding a test that has had high development costs with a marginal-cost base price may have negative implications for the diagnostic market.

When a product is “gap-filled”, creating a new price rather than using an existing price schedule, there is some room for discussion of value to take place. Conversations with participants suggested that perceptions differ about whether developers would prefer this approach, or try to get their product cross-walked to a predictable reimbursement outcome. Although it may seem intuitive that a new price would be higher, the “gap-filling” method can result in a wide range of prices and is therefore considered unpredictable by producers.

When gap-filling a reimbursement amount, each MAC independently sets its rates based on (a) charges and discounts to charges from clinical laboratories, (b) local pricing patterns, (c) resources required for conducting tests, (d) data from other payers, (e) any other relevant data including payment for similar tests. Negotiation through contracting with developers also plays an important role. The tremendous variation in reimbursement amounts between different MACs leads to uncertainty over future returns.

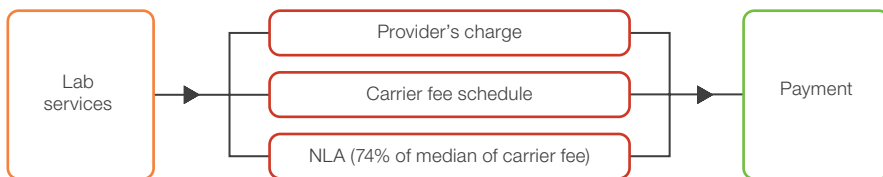
Having 56 different carrier-specific fee schedules (for both cross-walked and gap-filled tests) naturally results in wide reimbursement variations. In 1986 this prompted the creation of a national limitation amount (NLA) that acts as a ceiling for reimbursement for each CPT coded item. The NLAs are set at 74% of the median price of all carrier-specific rates for the each test. For tests that have been gap-filled, CMS calculates an NLA based on the median of the MAC reimbursement amounts after one year.²⁵ The price submitted by each MAC contractor has equal weight, regardless of the number of claims reviewed for the gap-filled product.

The process through which the codes are cross-walked or gap-filled includes opportunities for participation from pathologists, developers or other stakeholders. This was not always the case and signals a move towards a more “open” reimbursement-setting process, where stakeholder participation is valued.²⁶ There are still many concerns about the lack of transparency in weighing public comments. Industry comments highlight the fact that the public meetings risk losing their purpose without increased transparency about what motivates the

CMS decisions.²⁷ For both gap-filled and cross-walked technologies, CMS may review the payment amount in response to public comments at various points in time. The Clinical Laboratory Fee Schedule runs in calendar-year cycles, at the beginning of which calls for new or reconsidered payments are processed. After this the payment amount is not open to reconsideration until the following year. Reconsidering payment amounts requires getting a product cross-walked to a different code schedule, or putting it up for renewed gap-filling in light of inappropriate cross-walking in the previous year.

These NLAs were adjusted annually based on the consumer price index (CPI). Since 1987, however, Congress has specified lower updates and only three increases have taken place since 1997 (2003: 1.1%, 2009: 4.5%, 2012: 0.65%). In 2011 overall payment rates were also reduced to offset increased volumes. The reimbursement amounts have become completely market unrelated, with no reliable annual upward adjustments and some downward adjustments too. Payment will be the lowest amount of (a) the provider charge, (b) the carrier fee schedule and (c) the NLA (Fig. 5.2). In practice most of payments are set according to the NLA, which acts as a reimbursement ceiling.

Fig. 5.2 *Clinical laboratory services payment system*



Most private payers reimburse laboratory tests using Medicare NLA as a reference point. An influential 2001 Institute of Medicine report²⁸ found that the private mean payment amounts were similar to Medicare reimbursement amounts. Private payers are, however, able to negotiate with providers to achieve lower prices than Medicare. The ability to negotiate also allows some inclusion of “value” using pharmaco-economic models or risk-sharing mechanisms.

Challenges with the current system. Conversations highlighted that the current cross-walking, gap-filling approach presents barriers to innovation for a number of reasons.

If test A is dissimilar to any existing tests, with low probability that it could be linked to an existing CPT code, a new code is created and an associated price schedule is “gap-filled” by local carriers over a period of one year based on various factors. *This scenario results in high levels of uncertainty for developers, low incentive for investment in innovation.*

If test B^i is technically similar to test B, it will be “cross-walked” to an existing CPT code and an associated low payment, even though B^i offers vast improvements on the comparative technology (e.g. increased accuracy). Reimbursement is fixed based on historic prices for the cross-walked code, so there is no reward for innovation. *This scenario results in predictable payment outcome, but low incentive for investment in innovation.*

If a new test C^i used for identifying bacterial agents is technically similar to existing test C but has a much faster turn-around time (leading to improved patient outcomes for sepsis, for example), it will be rewarded based on the legacy fee for the existing CPT code, regardless of the costs-saving potential and improved health outcomes it brings to the clinical setting. An existing test C attracts a reimbursement that is relatively high compared to some other tests (perhaps because in the 1980s it was a newer, high-cost test). If test C^i is similar to test C, but test C^i offers some improvements on test C it is likely to be the test of choice in clinical setting. The cross-walked code attracts a high fee schedule compared to the low costs of investment faced for C^i . *This scenario leads to low levels of uncertainty for developers, and high incentives for investing in only incremental improvements.*

Interviewees from various stakeholder groups described the relationship between coding and reimbursement for clinical laboratory services, and the reimbursement approach, as ripe for change and full of illogical incentives and signals for developers of diagnostic products. A report by Foley Hoag LLP (2010)²⁹ argues that the administrative conventions of a legacy approach to pricing pose as great a barrier to innovation as the scientific challenges of developing and evidencing innovation. Although Foley Hoag is a strong advocate for industry, this view was also echoed by interviewees from research bodies, and payers.

Changes to the current system. Molecular pathology codes and payment schedules have recently (2012–2013) undergone significant changes. Previously, these complex tests were described by unwieldy “stacks” of codes linked to the individual technical components within the molecular testing process, and reimbursed based on the total value of all the stacked components. This stacking method made it virtually impossible for payers or industry stakeholders to know which tests were being used when, where or for what. Additionally, reimbursement for these stacked tests was difficult to keep track of, with test components being mixed up into variable amounts. The CPT Panel decided to assign entirely new codes that describe the tests as a whole, using their specific analytes in conjunction with a set of unique disease and mutation modifiers rather than the stacked codes. The stacked codes expired on 1 January 2013 and local contractors are in the process of gap-filling reimbursement amounts for the newly coded tests.

Although not an explicit objective of the recoding process, pathologists believe that assigning a single code will incentivize developers to streamline the technical aspects of these molecular tests now that they are bundled together for payment. This bundling also creates more transparency about usage and payment for third-party payers, and ultimately gives suppliers greater accuracy in estimating demand. With the stacking systems it is almost impossible to obtain a complete picture of the volumes of molecular diagnostics being performed, or what they were being performed for. More accurate information on the range of analytes being tested and the volumes for each procedure will be welcomed by developers and other stakeholders across the board.

Uncertainty about reimbursement and challenges unrelated to the actual clinical value of the product are significant disincentives for innovation. The changes to molecular coding have been welcomed, but there is still much uncertainty about the gap-filled prices that will emerge from this change over the course of 2013.

Physician outpatient

Since 1992 Medicare has moved from payment by charges to the Medicare Physician Fee Schedule, which identifies payment for over 10 000 physician services based on a resource-based relative value scale. Price amounts are weighted to reflect the variation in practice costs from within a geographic area using a geographic practice cost index. The payment is composed of three components, called “relative value units” for work, practice expenses and malpractice, with physician work and practice expenses valued highest. Pricing the expenses portion is the job of the Practice Expenses Review Committee, which considers direct expenses relating to supplies and non-physician labour, as well as the *pro rata* expense calculation for equipment used in providing services.

Calculating the physician work component is a more nebulous affair, and includes valuing time, technical skill, physical and mental effort required, as well as stress factors. This component has been subject to some controversy, with the most recent physician schedule seeing cuts to some areas in an attempt to meet the goals of the statutory sustainable growth rate formula, aimed at controlling Medicare costs.

POCTs are included in the practice cost calculations and are procured by physician practices through contract from providers. These prices are not publicly available. Clinical laboratory services are billed to Medicare separately using the Clinical Laboratory Fee Schedule. Although laboratory fees are not reimbursed through physician payments, the physician is often responsible for ordering the test (for outpatient services), making her an important determinant of uptake for new technologies, as discussed previously.

Acute inpatient payment services

Through Medicare part A hospital providers are paid by Medicare fiscal intermediaries and A/B MACs using prospectively determined payment rates that include all clinical and physician services, as well as other medical items, supplies and services. Laboratory services associated with inpatient visits are also bundled into these payments, which means that hospitals procure laboratory services by contracting processes, either through competitive tenders or negotiation. The prices at which these are procured are not publicly available. Discussion of the role of group purchasing organizations (GPOs) provides more insight into this aspect (see section 10.3). This system of hospital payment is referred to as the Inpatient Prospective Payment System (IPPS). Payments are made up of two national base-payment rates (covering operating and capital expenditure), and a number of adjusted factors including (a) the patient's condition and related treatment strategy and (b) the market conditions in the provider's region.

On discharge the patient is assigned to one of 751 severity-adjusted diagnostic related groups (MS-DRGs). Which group the patient is assigned to will be determined by (a) the principal diagnosis, and (b) up to eight secondary diagnoses indicating either comorbidities or complications. Each of these DRGs has an associated payment that contributes to the overall prospective payment amount. The MS-DRG associated payment is designed to cover the costs that "reasonably efficient providers would incur in furnishing high quality care" within that care package.³⁰

Private health plans have a variety of payment and billing methods for hospital inpatient care, including fixed per diem payments and fee-for-service approaches that are beginning to approximate prospective DRG payments for complete packages of care. Stakeholders suggest that the DRG approach will become increasingly common in the future as a method for controlling costs. The new Health Insurance Marketplace will also have DRG reimbursement, adding to the volume of members covered with this kind of payment mechanism.

With IPPS and DRG style payments, the hospital provider faces fixed payment rates. The broad incentives for hospital providers are, therefore, to minimize the cost of treatment and maximize patient throughput. By keeping costs within the boundaries of the payment rate the provider accrues savings/profits and avoids losses. By increasing the volume of patients treated the provider ensures increased opportunities for profit.

In an effort to reduce inappropriately early discharges, Medicare has implemented financial penalties for readmissions across many hospitals. The maximum penalty will increase to 2% of regular payment starting in October 2013, and increase to 3% the year following. This method is paired with a new policy reducing

payment for any excess LOS associated with hospital acquired infections (HAIs; discussed in section 9.3). For a hospital to consider procuring a diagnostic technology, this technology will need to be able to demonstrate how it increases efficiency for savings in variable costs, or changes the patient care pathway to reduce LOS appropriately, enabling the hospital to increase volumes without facing penalties for readmissions.

In addition to the MS-DRG payment there is the possibility of securing “new technology payments”. For this, a developer must apply to CMS and the technology is evaluated based on the criteria of: newness, substantial clinical improvement and costliness of the technology beyond the level of the current MS-DRG payment amount. These payments are rare in the field of diagnostics because of the difficulty evidencing substantial clinical improvement (Interview).

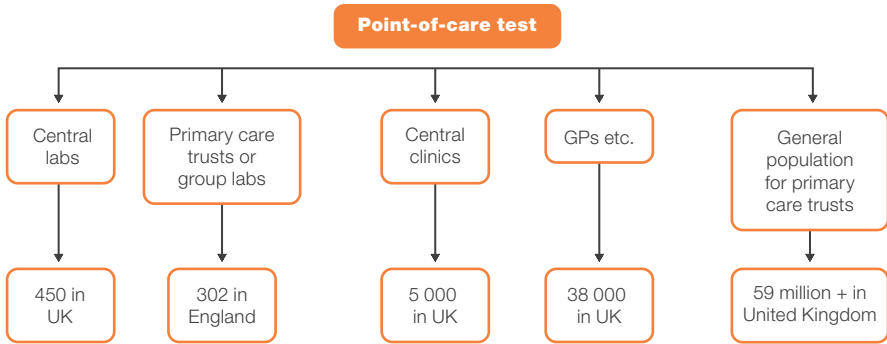
Outpatient hospital services

Medicare outpatient ambulatory services are billed using an Outpatient Prospective Payment System (OPPS). These predetermined payment rates are based on Ambulatory Payment Classification (APC) codes, which group services according to cost and clinical similarity. Units of service within the APC codes are identified by Healthcare Common Procedure Coding System codes. Each APC is a package of critical services, determined in communication with hospitals, hospital suppliers and experts. Some aspects, including physician services, clinical laboratory services and many pharmaceutical products, are billed separately using the appropriate fee schedules. Additionally “pass-through” payments allow new technologies (including devices) to be purchased by outpatient providers when the technology is too new to be appropriately represented in data that CMS uses to set the OPPS payment rates. Pass-through payments are thus based on individual hospital costs, using a cost-to-charge ratio. This ratio presents the relationship between the cost incurred by the provider, and the gross revenue gained. These payments can only be up to 2% of total OPPS payment.

5.4 Background: overview of reimbursement of diagnostics in the United Kingdom and Europe

The NHS is tax-funded public health care system providing care free at the point of access to the patient throughout the United Kingdom (for its structure, see Fig. 5.3).³¹ Collectively the publicly run bodies act as both the provider and the payer of the health service (there is no external third-party payer). Seventy-five per cent of health care provided in the United Kingdom is delivered through the NHS.³²

Fig. 5.3 Health care structures in United Kingdom³³



The NHS does not act as a single purchasing unit. Rather it is a large and complex organization, and this is reflected in its procurement processes. For example, procurement decisions for medical devices may be based on numerous factors such as device complexity, innovation and risk, and price/volume. The organizational level at which procurement-related decisions are made can vary from the national level in some cases and in other cases at the level of NHS Trust, hospital, department or even clinician.³⁴

Examples of the five main purchasing routes currently used by English NHS trusts:^{35, 36}

- national framework contracts – trusts purchasing directly from suppliers but negotiated by the NHS Purchasing and Supply Agency;
- national framework agreements – managed and negotiated by NHS Supply Chain;
- individual trusts’ local contracts;
- consortium contracts or collaborative procurement hubs/confederations – involving a group of trusts (normally regional) working together to negotiate contracts; and
- pan-government National Framework contracts.

There is free pricing by diagnostic manufacturers in the United Kingdom, except in the case of diagnostic substances such as reagents that are considered pharmaceutical products and therefore are subject to indirect price controls from the Pharmaceutical Pricing Regulation Scheme. Laboratory services are funded through a combination of capital spending and operational spending. Capital spending (laboratory equipment and infrastructure) is for the most part centrally funded. However, due to significant expense of the capital equipment involved

in diagnosis, only around 30% of equipment is sold, with the bulk being lent to facilities which are tied into minimum volume contracts, for example on the required assays or reagents.³⁷ It is thus currently the various hospital foundation trusts, acute trusts, strategic health authorities and clinical commissioning groups that control most of the funding and make the important purchasing decisions that are relevant for IVD manufacturers. Major hospitals tend to have their own in-house laboratories, although smaller facilities may share pathology services with other hospitals within the same trust.

If a diagnostics developer wants to sell to the NHS they need to take into account the organization surrounding decentralized testing, the intricate reimbursement architecture, and how device procurement is organized.³⁸ Understanding the operation of local tariffs for pathology is also critical for market entry. Reimbursement for devices used in hospitals is for the most part included within inpatient and day case tariffs. For reimbursement of POCTs in outpatient settings separate tariffs are used.^{39, 40, 41, 42, 43} Pathology services for primary care are costed largely using the system of payment by results. Health-related groups (HRGs) form the backbone of hospital case reimbursement within the NHS and are founded in a traditional DRG model: under the HRG system hospitals are generally reimbursed by indication rather than by procedure, meaning there is no explicit reimbursement for the use of diagnostics throughout a patient care pathway. Some 60% of pathology in the United Kingdom is covered by HRGs, with the remaining 40% reimbursed outside of HRG structures, of which community pathology forms a large proportion. There are some exceptions to this under HRG4, which introduced unbundled HRGs for a small number of specific areas and which allows individual treatment components to be recorded and remunerated separately, including diagnostic imaging and critical care. However, in the case of diagnostic imaging, for reimbursement purposes the activity is re-bundled into a core HRG with the unbundled tariff simply acting as a metric for recording activity levels. Unbundled HRGs for critical care, on the other hand, are excluded from core tariffs and are instead subject to local pricing negotiated between commissioners and providers, as underlying data to date has proved insufficiently robust to form a basis for tariff levels.⁴⁴ There is a drive to bring this area under tariffs in the future, with the first step of “currencies” for critical care having been created in 2012. These currencies act as a non-mandatory price guideline for local units to use in procurement negotiations, although they may be a rather blunt tool as they may not adequately reflect the diversity and complexity of tests used. Another driver of unbundling, where used, is to support the ability to offer certain services outside of the hospital setting without the need for outpatient attendance, with greater transparency on explicit pathology costs being required by primary care practitioners in order to efficiently engage with

pathology providers. The Department of Health document on payment by results highlights that, in general, excessive unbundling is undesirable in that it potentially leads to a “fee-for-service” system, with associated incentives for lack of cost control and overuse. Such issues and negative incentives associated with fee-for-service reimbursement structures means the bulk of indications addressed in hospital settings are covered by pathway tariffs as opposed to unbundled ones. While the majority of tariffs are based on the national average of reference costs, for a small number of indications^a “best-practice” tariffs have been introduced with the aim of promoting care that is both of high quality, and cost-effective. Rather than being based at national average costs, reimbursement for these indications is based on delivering best-practice care, the cost of which may be above (or below) national average costs. These best-practice tariffs are supported by guidance on specific clinical actions or pathways. For example, the best-practice tariff for stroke care consists of a base tariff, with additional payments for admitting patients directly into an acute stroke unit, and their undergoing initial brain imaging within an appropriate time frame.⁴⁵ The Department of Health has aimed to bring some flexibility into the tariff system through the introduction of “innovation payments”, which give commissioners the scope to make additional payments for new (and more expensive) drugs and diagnostics that improve care but would not be covered by the existing tariff. Commissioning for Quality and Innovation (CQUIN) schemes are developed by commissioners at local rather than national level, with payment thresholds set to incentivize local priorities, with their structure guided by national CQUIN guidance.⁴⁶

5.4.1 Previously proposed changes

A 2006 review of pathology services in the NHS suggested the creation of a tariff for pathology services that appropriately recognizes both the cost, and value of diagnostics in the patient care pathway.⁴⁷ In theory the suggested tariff would allow for a better reflection of developer investments in new innovative tests.^{48, 49, 50} This, however, requires an assessment of the clinical and economic benefits of such an investment.^{51, 52} Evidence-based purchasing provides the basis of all procurement decisions in the NHS. On 31 March 2010, the Centre for Evidence-based Purchasing and the NHS Purchasing and Supply Agency were absorbed by the National Institute for Health and Clinical Excellence’s (NICE) Medical Technologies Evaluation Programme^b (although they are only beginning to assess diagnostics).^{53, 54} However, one issue is a lack of standardization

a Cataracts, cholecystectomy (gall bladder removal), hip fracture, stroke, adult renal dialysis, day case procedures, interventional radiology, paediatric diabetes, primary total hip/knee replacements, transient ischaemic attack (mini-stroke).

b Formerly the new Evaluation Pathway Programme for Medical Technologies.

or guidelines as to exactly what cost–effectiveness data is required or how it is presented. This presents a challenge to developers, who may have to present evidence in different formats to different hospitals or procurement agencies, leading to a higher burden on them in terms of evidence generation, and often a lack of clarity on what is expected from them across different settings. Furthermore, with no formal national approved list of cost–effective diagnostics, manufacturers must repeat the process for each purchaser.

A 2006 report by the Department of Trade and Industry into the health care equipment market highlighted⁵⁵ that the United Kingdom procurement environment was particularly challenging for SMEs. The costs and time involved in navigating the NHS procurement landscape were sufficient to drive some SMEs to focus primarily on exports, placing them at a potential disadvantage to both larger firms that have the capacity to interface with complex organizations more effectively, and also, potentially, to peers outside of the United Kingdom that may find the procurement environment in their respective domestic markets more straightforward to engage with. The requirements for new SMEs entering the tender process were also highlighted as a barrier by the same report to such firms winning NHS contracts. A further criticism of the NHS procurement approach was that the focus on cost–effectiveness in reality restricts purchasing decisions to proven technologies, with more complex or innovative products potentially struggling to demonstrate the required evidence base. In particular, the report highlighted the risk that should companies in the United Kingdom focus unduly on the restrictive NHS cost–effectiveness criteria, this may detract from developing more sophisticated evidence and marketing pitches for markets with more advanced demands.

5.5 Implications of being tied to indication

Across the majority of European Member States, diagnostics are not explicitly reimbursed: from a hospital perspective, the cost of their use will form part of the reimbursement for the relevant DRG (or HRG in the United Kingdom). This brings with it a number of challenges that can more generally be applied to the use of DRGs, such as how comprehensive their inclusion of care pathway costs is; how frequently the DRGs are updated; whether they are linked to best-performing or average facilities, to name a few. These factors, by setting overall reimbursement levels, will have a significant impact on hospitals' decisions to invest in technology. Despite some of the associated challenges that arise from being linked to DRGs however, the vast majority of diagnostics companies that participated in our study considered being tied to indication in this manner a superior reimbursement landscape compared to having specific pathology tariffs for the reimbursement of diagnostics, for a number of reasons:

- Explicit tariffs for diagnostics are seen as more likely to exert downward pressure on reimbursement, particularly for innovative diagnostics, which may be grouped with or benchmarked against cheaper but potentially inferior alternatives.
- Building a tariff system with sufficient flexibility to recognize and reward innovation, particularly in a rapidly changing marketplace such as that for diagnostics, is considered by many manufacturers to be difficult to achieve in practice.
- The inflexibility of existing tariff systems for diagnostics, such as in Belgium, and France (for private labs) has been highlighted by manufacturers as a case-in-point of the issues of having specific diagnostic tariffs. One manufacturer of a particularly innovative infectious disease POC platform highlighted the issue of the impossibility of getting the relevant authorities to generate new codes for innovative products, meaning that in these markets reimbursement levels will not capture any premium for degree of innovation, lowering the incentive to develop new products.

In general, this study found widespread acceptance among manufacturers of being tied to indication as a realistic landscape for hospital procurement of diagnostics, with few suggestions of an improved model, outside of the aspirational vision of a value-based approach to diagnostics pricing. What was of more relevance to manufacturers was rather criticism about how hospital procurement is often managed rather than the negatives of conceptually being tied to indication. Criticisms in particular include a lack of strategic vision within hospitals for diagnostic procurement; and pricing negotiations heavily skewed towards cost, with (from manufacturer's point of view) too little emphasis placed on patient outcomes unless improvements are also associated with lower financial expenditure. This in part is likely to be a result of the severe pressure on health budgets across many key western markets for diagnostics, with managers under pressure to secure immediate cost savings. There have been attempts in the United Kingdom to address the former point regarding strategic planning of diagnostics usage through the strategic *Pathology Commissioning Toolkit*,⁵⁶ however there has been some criticism that this document is more a procurement handbook than a strategic blueprint of how diagnostics should be effectively commissioned across the health service. This links to a separate issue, namely that while there is general acceptance from manufacturers of the DRG system for in-hospital diagnostics, the reimbursement of diagnostics outside of hospital settings presents a more significant challenge, as in this market segment the incentives for uptake are much weaker. In large part this is due to a lack of integration between primary care and hospital budgets: for example, from an overall health system perspective, it may

be rational and cost-effective to conduct more effective diagnostics for infectious disease in a primary care setting, to allow earlier and more appropriate prescribing of antibiotics, which in turn may lower hospital admissions. However, if the primary care physician does not bear the financial burden of higher emergency admissions, or more acute illness of patients upon hospital admission, then they may be reluctant to bear the cost of buying potentially expensive POC diagnostic technology. In England, funding for community-based pathology follows a number of different methodologies depending on the trust involved, and can include fee-for-service, capitation, and block contracts (i.e. fixed budgets) or capped costs per diagnostics period.⁵⁷ While fee-for-service reimbursement may encourage diagnostic use, the other methods are likely to act as an incentive to contain costs through rationalizing pathology usage. Furthermore, the fragmentation and different approaches of different trusts makes navigating the market significantly more challenging for manufacturers.

In England, the 2006 NHS pathology review, led by Lord Carter of Coles, recommended, among other things, the development of a tariff-based reimbursement mechanism for diagnostics, either for specific tests or groups of tests.⁵⁸ The aim was that said tariff would be designed with incentivizing the uptake of new technology where appropriate, although the report did not offer granular detail as to potential tariff design that would achieve this objective. The concept of a pathology tariff met with resistance from manufacturers in the United Kingdom, and this proposal has somewhat been kicked into the long grass, particularly given the distraction of other major current NHS reforms. The major finding of the Carter review was the need for consolidation of pathology services in the NHS, driven by the rationale that the resulting efficiencies and cost savings would allow re-investment into services and, among other things, support investment and rapid uptake of cost-effective, innovative diagnostic technologies.⁵⁹

The call for consolidation has been heeded and many hospital trusts have adopted the recommendation to form “pathology networks”. The result, in some cases of anticipated service consolidation, was something of an “arms-race” in pathology services; that is, labs building up capabilities and adding technology in order to position themselves as a consolidator, rather than a facility that might be subsumed by others. Given the razor-razorblade business model of many diagnostic firms, whereby otherwise unaffordable equipment is leased to labs but tied to commitment to purchase accompanying assays or reagents for either specified volumes or time periods, this rush by many labs to acquire new technology in order to achieve scale perhaps provided a short-term boost for diagnostics manufacturers in terms of demand levels, but may come at the cost of medium-term uptake issues for new technology if facilities are already tied into long-term contracts with diagnostic providers, limiting their ability to acquire more innovative technology as it becomes available (because the cost of

terminating or switching contracts may be high, therefore limiting the potential cost–effectiveness of shifting to new technology).

5.6 Variation across countries

Across the majority of public health systems in Europe, hospitals are largely reimbursed for their diagnostic usage through their implicit inclusion in the case-mix funding of DRG codes. From the manufacturers’ perspective, this means that while their approach in terms of pricing negotiations with individual hospitals or groups of hospitals is largely similar, pricing outcomes may vary widely, depending on context, given the decentralized nature of much decision-making across Europe. Even across England, there is significant variation in costs of pathology services across trusts: while some of this may be explained by staffing levels and wage differentials, wide differentials in the prices paid for consumable elements of diagnostic tests, and reagents have been noted (Table 5.4).⁶⁰ There is little uniformity even in how tests are counted and how workload is calculated. In some hospitals urea and electrolytes is one test, and in others it is five, six or seven tests!⁶¹

Table 5.4 *Variation in direct core pathology test costs across trusts in England 2009*⁶²

Discipline	Minimum cost of test	Maximum cost of test	Median cost of test
Biochemistry	£0.50	£2.80	£1.00
Microbiology	£4.00	£9.40	£6.10
Haematology	£1.50	£3.70	£2.40
Histopathology	£21.40	£73.40	£48.10

Beyond variations in the value that different hospitals may place on a given product, the macro backdrop in different countries can be expected to play a significant role in influencing pricing or volume of sales; this is most pronounced in recent estimates by EDMA on the shrinkage of the IVD markets in countries such as Greece and Portugal,⁶³ which have been under particular fiscal pressure. Notable exceptions from the DRG model in Europe with regards to pathology reimbursement are Belgium and France, with both countries having elements of a pathology tariff depending on setting, and Switzerland where, until 2010, a fee-for-service reimbursement model for in-hospital pathology was in place in all but two cantons. Switzerland has, however, been in the process of shifting to a case-mix system for reimbursement.⁶⁴ Note that in primary care settings,

reimbursement of diagnostics through a fee-for-service model is more common, although in some countries a mix of approaches may be used: in England, for example, some primary care trusts (recently replaced by clinical commissioning groups) have been reimbursed through block funding, which covers all pathology services for a set time period.⁶⁵ Fee-for-service is also more common for reimbursement of pathology services for privately insured patients, as is the case in Germany: here rates are benchmarked through the Regulatory Framework of Services (Gebühren Ordnung der Ärzte), although multipliers can be applied to test values depending on both pathologist seniority and complexity of test relative to the benchmark.⁶⁶

Some countries have implemented specific cost-control measures: the creation of managed pathology networks across England is one such example of a broad policy aiming to limit costs by reducing excess capacity in the system. Germany has in place more specific measures to contain outpatient pathology costs,^a including explicit limits on the volume of tests, and amount of hours a pathologist may work.⁶⁷

- *France.* Private labs performing public health work face rigid reimbursement structures that give them little flexibility regarding the choice of diagnostic they may use. From a manufacturer's perspective, after gaining a CE mark they need to apply for inclusion for reimbursement via the Nomenclature des Actes de Biologie (biological tests), or Nomenclature Générale des Actes Professionnels (anatomopathological tests), which grant coverage based on testing cost (including physician time). However obtaining registration and a coding under these systems has been described as complex,⁶⁸ presenting a barrier to diagnostic manufacturers in securing reimbursement for their products. France has faced issues particularly in the reimbursement of companion diagnostics: for example, the use of Vectibix for metastatic colorectal cancer was recommended for use by the Haute Autorité de Santé in wild-type KRAS patients only, but no guidance was released as to uptake and reimbursement of KRAS testing. This is in part due to the fact that, unlike for drugs, pricing for diagnostics is not negotiated at a national level but directly between physician and social security unions,⁶⁹ meaning there is less scope or incentive for the Haute Autorité to get involved in pricing and reimbursement negotiations. Issues with the system have led to the French Cancer Institute (Institut National du Cancer) to allocate specific resources to facilitate uptake of KRAS testing, in acknowledgement of the value

a In this context "outpatient" includes both tests performed on patients visiting hospitals on an outpatient basis, but also diagnostics performed in clinics and other primary care settings.

of the companion diagnostic. Such experiences have led to proposed reforms in diagnostic coding policy, with the Nomenclature Générale des Actes Professionnels system to be replaced by a new coding system, Classification Commune des Actes Médicaux, which may also be supported by national-level technology evaluation of diagnostics by the Commission Nationale d'Évaluation des Dispositifs Médicaux et des Technologies de Santé feeding into coverage decisions.⁷⁰

- *Belgium.* There is a tariff system in place for elements of pathology, which includes specific tariffs for each assay. This has been criticized by manufacturers as being inflexible, particularly in terms of adding new products to the reimbursement/tariff list.
- *England.* While proposals to introduce a national pathology tariff have stalled, the Department of Health does publish a list of indicative tariffs for pathology services, which is based on actual costs incurred across a range of hospital trusts⁷¹ and is aimed at assisting hospitals both in their negotiations with diagnostic providers and in managing overall pathology costs.
- *Germany.* Outpatient diagnostics (which includes both day-case hospital patients plus testing in clinics and primary care facilities) are reimbursed by a weighted funding system. Under this system, reimbursement of a pathologist is linked to their relative activity levels as compared to all pathologists in the same specialty, meaning each pathologist or facility may receive variable funding, within the constraints of a fixed global government pathology budget.⁷² For pathologists, this system introduces uncertainty as to their reimbursement levels, as their funding will depend not only on their own usage of testing but also that of their peers, which is only known retrospectively (information submitted on a three-monthly basis). This may act as a disincentive to perform tests or employ expensive technology. In general, some manufacturers have highlighted Germany as a particularly difficult reimbursement market, with recent policy moved to recentralize pathology services being described by one as a “backward step”.

5.7 Reimbursement case study

The case of Herceptin (trastuzumab) and its companion diagnostic test HER-2/neu, which detects which patients are most likely responders to treatment based on detection of the Her-2/neu amplification, and over-expression of protein,⁷³ is a prime example of the reimbursement challenges facing companion diagnostics. In particular, the variability in reimbursement decisions across jurisdictions may

present barriers to diagnostic development due to the uncertainty it presents (Table 5.5). In Europe, the companion diagnostic is publicly funded in the United Kingdom, France, Germany and Italy (although even in these markets there may have been a lag between reimbursement of the drug and the diagnostic: for example, in France, the companion diagnostic for Herceptin, HER-2 has only been reimbursed from 2007 onwards, despite gaining market approval in 2000). In Spain, however, there is no public reimbursement of the diagnostic test, and where used it is largely funded directly by the pharmaceutical manufacturer.⁷⁴

Table 5.5 *Reimbursement of trastuzumab companion diagnostics HER-2/neu and K-RAS in selected European countries*⁷⁵

Country	Examples of reimbursement
UK	HER-2 and KRAS tests are publicly funded but because the treatments associated with them are so expensive, few tests are performed.
France	HER-2 test was authorized in 2000 but has only been reimbursed since 2007.
Germany	Innovative tests are introduced as LDTs. The HER-2 and KRAS tests are performed using LDTs leveraging assembled research-use-only reagents and are reimbursed by a CPT code like a procedure.
Italy	HER-2 and KRAS tests are publicly funded and available from a network of public hospital laboratories.
Spain	HER-2 and KRAS tests are often paid for by the pharmaceutical companies whose drugs they indicate.

Chapter 6

Regulation

6.1 Introduction

Device developers, policy-makers and regulators all share a desire to see safe, effective diagnostic devices on the market. However, the rapid technological innovation that characterizes this industry is outpacing current regulatory frameworks. Reforms are under way in both the United States and the EU, with regulators on both sides of the Atlantic seeking to reduce bureaucratic roadblocks to developers while still ensuring patient safety.

This chapter provides a comparative overview of the regulatory pathways that developers embark on to gain access to the United States and European markets. Much like the reimbursement process, the regulatory processes in the EU and United States are littered with quirks, foibles and inconsistencies that increase uncertainties, creating hurdles to bringing new devices to market. This chapter provides no silver bullet solutions, but rather provides description of the changing regulatory landscape and the current challenges faced by diagnostic developers. Greater transparency in the process, harmonization between regulators, and more open lines of communication with developers about evidence requirements are needed to help bring truly innovative devices to the market.

6.2 History of medical device regulation

Regulation came relatively late to the medical device world and was largely stimulated by a number of public health scares in the 1960s and 1970s. Those that led the way in regulatory strengthening in the 1970s were notably Australia, Canada, the EU countries, Japan and the United States, which together account for close to 85% of the device market share today.¹ In the United States, 1976 saw a regulatory overhaul which covered “food, drugs and cosmetics (and medical devices)”. In Europe, too, the regulatory environment became more stringent, although mainly to enhance the cohesion of a single internal European market. Beginning in 1990, the EU introduced in all its Member States an approach to medical device regulation based on mandatory “essential requirements” of safety,

performance, and quality.² In the United States, the early 2000s saw an increase in data requirements in response to the increasing number of tests with more specific intended use (as opposed to broad tools) and requirements surrounding analytic performance have increased in complexity due to adverse events and other pitfalls.

6.3 Evolving needs for medical device regulation

Over the last 50 years the technical advances in diagnostic development (supply side) have been rapid, leading to a bolus in availability and variety of IVD devices based on an increasingly diverse array of underlying technologies across the disease spectrum. When the 1988 CLIA guidelines were issued there were seven “waived” tests compared to hundreds today. Additionally, on the demand side we have not only seen an increase in the prevalence of many diseases for which diagnostic tools are available, notably cardiovascular, oncological and infectious diseases, but also an increase in outpatient care and shorter inpatient stays make them an increasingly valuable addition to the physician’s toolbox. Additionally, as the underlying technologies become more sophisticated (yet simple in presentation and use) the tests are increasingly moving out of the laboratory and are available to a broader number of less specialized health care professionals, for whom the more limited diagnostic knowledge facilitates both a greater use of, and at the same time greater dependence on, the information these tools provide to aid clinical decision-making. Increasingly, diagnostics are no longer about a single test for a single disease but a single sample being used to measure multiple parameters and provide a cumulative risk score. Additionally, anecdotal evidence also suggests that financial incentives (through reimbursement policy) favour physicians using a greater number of more sophisticated tests particularly in the United States. This additionally raises questions about the point at which a physician’s office should be considered (for regulatory purposes) a laboratory (and therefore requiring regulatory oversight), a challenge which has recently been acknowledged by CMS.^a Given this context and the relatively short time period, the challenge faced by regulators of this small but very dynamic health technology sector is to safeguard patient safety while remaining sufficiently nimble regarding the needs of developers.

6.4 Overview of regulatory processes for market entry in Europe and the United States

In comparison to Europe, and indeed most of the rest of the world, where a relatively “light touch” approach is favoured, the United States adopts a more

a See: <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5413a1.htm>

holistic or “health system” approach to the regulation of IVD devices, which are often quoted as being the most highly regulated medical devices on the United States market and perhaps also globally. However, when looking beyond history and ideology, we actually see greater similarities between the United States and EU than we might expect, notably that stringency in regulation has been increasing the world over for a number of decades, and this is a trend that is also foreseen to increase in the medical device field. Another similarity is the challenge that regulatory agencies the world over have in adapting and updating their systems in a timely manner in response to an evolving external environment (i.e. health systems) and a small, dynamic, sector (i.e. rapid technological evolution). Global harmonization efforts have been active in the IVD space since 1992 and, while the approach to risk was largely based on the Canadian model, it was the Europeans who were initially more responsive and engaged with these efforts than the United States (which has recently been empowered for deeper participation in these forums). The 2013 announcement of the opening of bilateral trade deal^a negotiations will likely give fresh impetus to these long-standing efforts to streamline and globalize the regulatory dialogue, and to remove more peripheral administrative barriers in areas such as general controls (i.e. labelling and post-market surveillance).

Both the United States and EU are in the process of, or have recently completed, a period of regulatory reform in the area. In the United States a number of recent reforms became effective in 2012 and address issues in the areas of: Resourcing (the FDA Safety and Innovation Act [FDASIA Part II]/ Medical Device User Fee Amendments [MDUFA]), Regulatory Improvements (FDASIA Part VI) and Registration and Device Listing (CFR21-807). The MODDERN (Modernizing Our Drug and Diagnostics Evaluation and Regulatory Network) Cures Act has been referred to committee. With bipartisan support the senate version of the bill is expected to be introduced in the second half of 2013. In the EU, reform to the Medical Device Directives has been a longer time coming as it has been nearly a decade since the *In Vitro* Diagnostic Medical Devices Directive (IVDD) came into effect and it has not been revised in this time; as a result reform is expected to have a more revolutionary impact when it is signed into law^b when IVD devices are likely to become directly regulated for the first time. The nature of and response to these reforms again reveal some common focus areas in current regulatory evolution and indicate some shared challenges to be resolved moving forward. As regulation becomes more stringent in the EU, stakeholders have raised concerns regarding the

a Transatlantic Trade and Investment Partnership (TTIP).

b The previous target of 2014 is looking increasingly optimistic.

effective resourcing of the agencies to manage review times. While in the United States “time to market” (particularly for high-risk devices) is longer than in the EU, reflecting their more robust approach, “time to patient” tends to be similar due to the longer duration of reimbursement decisions in the EU than the United States. Developing effective communication pathways between regulator and developer is also a long-standing issue where we see improvements but also a need for ongoing attention. These areas have significant possibilities to affect the efficiency of regulatory processes. Some of the main technical challenges are also priorities on both sides of the Atlantic. For example:

- How should “investigational” devices be regulated so as to acknowledge their pivotal role in development innovation, while preventing regulations from undermining commercial incentives in the market?
- How is device “novelty” translated into a risk classification and therefore regulatory stringency?
- What is the minimum level of clinical evidence required to ensure safety and efficacy? Can performance ever really be determined without testing occurring in the same environment where the device is intended to be used?

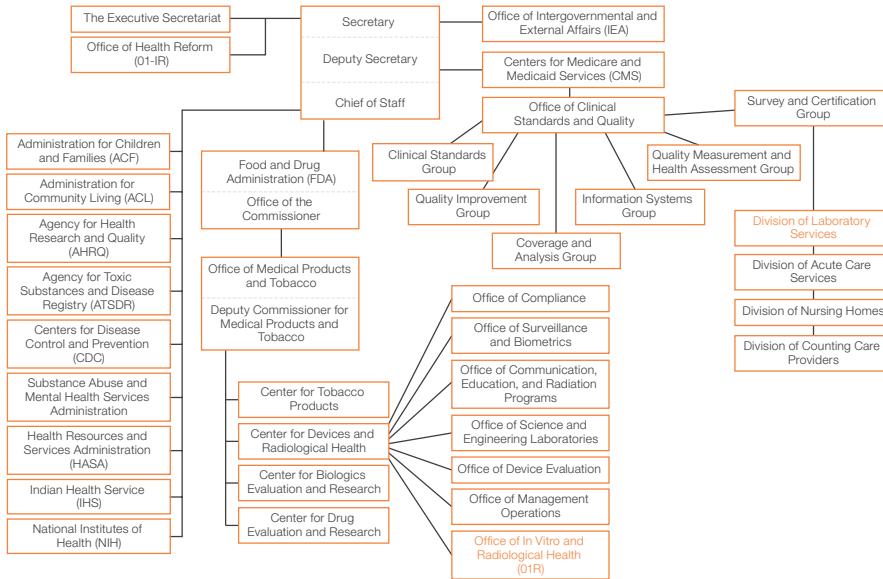
Regarding the latter, the United States currently has far more stringent – but clear – requirements; the EU, however, seems also to be moving in the direction of both greater clarity and stringency. Although both the United States and EU regulatory systems are perceived by developers as being less than perfect, with further room for improvement and efficiency gains, it seems the remaining challenges no longer present a significant barrier to market access for the developers of innovative new POC diagnostics for bacterial infections.

6.5 United States current regulatory structures/frameworks

6.5.1 Framework/oversight

The United States DHHS has overall responsibility for ensuring safe and efficacious medical interventions are available in the United States market. The responsibility for IVD devices is shared between the CMS and the FDA (see Fig. 6.1). This shared responsibility is because two pathways oversee IVD regulation in the United States. The location where the test is performed is regulated through CMS via the CLIA regulations, while market entry of the device is regulated by the FDA.

Fig. 6.1 DHHS organizational chart showing medical device regulatory oversight in the United States (adapted from^{3, 4, 5, 6, 7})



CLIA (Public Law 100-578) was first instituted in 1967 to establish quality standards for laboratory^a testing, where CMS reimbursement was being sought and was to ensure the accuracy, reliability and timeliness of patient test results regardless of where the test was performed, at the time CDC performed the categorizations (for CMS). The 1998 CLIA regulations were expanded to include all laboratories in response to the concerns about laboratory testing errors.⁸ At the same time the FDA became responsible for complexity categorization⁹ (for which CMS pays FDA). While overseen by the CMS, CLIA is implemented through the Division of Laboratory Services, within the Survey and Certification Group, under the Office of Clinical Standards and Quality; CLIA is user-fee funded.¹⁰

In addition to being subject to the CLIA regulations, IVD devices are additionally subject to pre-market and post-market controls as defined by the FDA's Office of In Vitro Diagnostics and Radiological Health^b at the Center for Devices and Radiological Health. The Center also has the responsibility for regulating firms that manufacture, repackage, re-label and/or import medical devices sold in the United States.¹¹

a FDA defines a laboratory as "any facility that does laboratory testing on specimens derived from humans to give information for the diagnosis, prevention, treatment of disease, or impairment of, or assessment of health".

b Formerly *In Vitro* Diagnostic Device Evaluation and Safety until February 2013.

6.5.2 Broad approach and classification

For POC devices that obtain a CLIA-waiver, CLIA regulation of laboratories and FDA regulation of tests are complementary for diagnostic testing. While the trials required for the submissions and separate applications generally occur in parallel, the FDA prefers that reviews occur simultaneously (concomitant review is perceived as too risky), with CLIA review following after the initial FDA decision. Developers prefer to reduce the time lag between the two processes as much as possible. IVD tests are perceived to be the most highly regulated diagnostics in the United States.¹²

Taking the FDA pathway first, all medical devices, of whatever class, require general controls to obtain FDA clearance to market. In addition, IVD devices are subject to pre-market and post-market controls. At present, as the level of technological advancement (underlying the diagnosis) increases, so too does the complexity of the device, and therefore the stringency of the regulatory pathway for approval.

For IVD devices, the FDA takes risks of a new technology into account (particularly if there is no predicate and is therefore “novel”) but focuses predominantly on the risk of the information provided (established through an “intended use” statement). In the United States, the FDA has established classifications for approximately 1700 different generic types of devices and grouped them into 16 medical specialties referred to as panels. Each of these generic types is assigned to one of three regulatory classes (Class I–III) based on the level of control necessary to assure the safety and effectiveness of the device (see Table 6.1). “A device should be placed in the lowest class whose level of control will provide reasonable assurance of safety and effectiveness.” Class I devices are subject only to general controls, with “special controls” being required in addition for Class II devices, Class III devices require general controls plus PMA.

Table 6.1 FDA regulatory classes for IVD devices

UNITED STATES		
Approach: Classification is determined based on complexity of testing (for the analyst to run the test) and intended use.		
Class I	Low-risk devices General controls	“Safe and Effective” Substantial equivalence: 510(k) submission
Class II	Moderate-risk devices General and special controls	90-day review FDA “Cleared”
Class III	Higher-risk devices Pre-market approval	General controls and pre-market approval to mitigate risks = increased “stringency” PMA submission 180-day review FDA “Approved”

CLIA categorizations are differentiated on the basis of complexity, mainly with regard to the technical competence required by the user (number of technical steps, system maintenance and troubleshooting requiring more qualified staff, level of automation). Categorization is determined for each laboratory test system, assay and examination by assigning scores of 1, 2 or 3 for each of seven criteria associated with appropriate usage.¹³ Currently, a POC diagnostic that would provide timely results – about a bacterial infection – at patients’ bedside, is most likely to receive a CLIA-waiver. Because this status assumes least competence from the user, this is the hardest and most challenging (compared to CLIA moderate and high complexity) for manufacturers to meet; that is, more data is required to prove simplicity of use (see Table 6.2).

Table 6.2 *Relative proportions of CLIA designated laboratories*

Total number of laboratories	229 815
Total non-exempt	222 899
	Compliance 19 387
	Accredited 15 697
	Waived 150 256
	Provider performed microscopy 37 559

As the subsequent regulatory pathways can vary in duration and costs by a factor of >2 and 200 respectively, this initial classification decision can be crucial for developers. However the FDA itself acknowledges that classification is “not always intuitive” and that “reasonable people may disagree on the appropriate class”.¹⁴ Reclassification (up and down) can occur but, until recently, has been uncommon and administratively complex.

Overall, the vast majority of microbial non-molecular medical devices are approved through the PMA (510k) route of the FDA first and then, most likely, a CLIA moderate certification by CMS (Table 6.3). This requires studies to confirm performance of the product (510k) and analytical studies, that is, comparison studies performed at the testing site (CLIA). The likelihood of the FDA assigning a microbial molecular POC device to Class I is a far more remote possibility and, indeed, the best developers of microbial molecular POC devices can hope for at present is a Class II designation. In fact, most (74%)^a Class I products are exempt from the FDA’s pre-market review. Furthermore, while many non-molecular anti-microbial IVD devices have been CLIA-waived, to date no molecular test has yet received a CLIA waiver, although anecdotal evidence suggests this is not far off.^b

a Approximately 572 of the Class I devices.

b Cepheid was the first company to receive a “moderate complexity” categorization for a nucleic acid test and January 2013’s sexually transmitted disease test (Xpert CT/NG, *Chlamydia trachomatis* [CT] and *Neisseria gonorrhoeae* [NG]) is the twelfth Cepheid test to be categorized as such.

Most still fall under the “high complexity” categorization: developers are being encouraged to pursue “moderate” complexity categorization to expand the size of their possible, eventual market.

Table 6.3 *Complementarity of the United States system for regulating IVD devices¹⁵*

	CLIA/CMS	FDA
Registration/listing	Registration and certification of lab List of tests maintained by CMS	Registration of establishment Public list of marketed tests
Analytical validation	Post-hoc sampling	Pre-market review
Clinical validation	No	Pre-/post-market review
Research phase	No	Yes
Quality system	Laboratory quality system assessed by inspection	cGMPs, Quality System Regulations assessed by inspection
Design controls	Not required. Software not addressed by CLIA	Required for Class II and III tests and all other devices with software
Report adverse events	No requirement; no system	Yes
Post-market surveillance	No	Yes
Recalls	No	Yes

cGMPs – current Good Manufacturing Practice

6.5.3 General controls

General controls (Fig. 6.2) occur at three levels: those aimed at the facility where the device is manufactured, those pertaining specifically to the device and those governing any clinical trials required for device approval. As regards the former, the intention is that the devices must be manufactured under a recognized quality assurance programme. The key requirements are¹⁶ “establishment registration” and establishing certificated and ongoing compliance with the FDA’s Quality System Regulations (QSR) which replaced, but largely mirror, Good Manufacturing Practices standards.^a As QSR is specific for the United States market, global developers may also choose to also obtain ISO (ISO 13485) certification – the globally acknowledged equivalent. While not harmonized with QSR, ISO has some specific procedures, but in general the requirements are overlapping. Additionally, as ISO issues certification documents, this can be helpful for manufacturers wanting to demonstrate compliance. As could have been anticipated, mutual recognition of ISO 13485 is the top of the list of items industry is pushing for as part of the Transatlantic Trade and Investment Partnership (TTIP).

^a This happened approximately 15 years ago and QSR is seen as current Good Manufacturing Practices plus design controls.

Regarding the device itself, general controls state that the device must be suitable for its intended use, be adequately packaged, properly labelled, and have FDA Medical Device Listing. In addition, post-market surveillance and record keeping systems known as Medical Device Reporting must be in place.¹⁷ General controls are one area that saw fairly extensive revisions in the latest FDASIA.

Fig. 6.2 *General controls*



Additionally where clinical trials are required, Good Laboratory Practices and an Investigations Device Exemption (IDE) will be required. Some products are also exempted from some of the general controls mentioned above, for example general purpose reagents.

6.5.4 510(k) regulatory pathway

A 510(k) is a pre-marketing submission made to the FDA to demonstrate that the device to be marketed is as safe and effective, that is, substantially equivalent, to a legally marketed device that is not subject to PMA. Pre-market notification/review of a 510(k) is the least stringent of the two main FDA regulatory pathways for IVD medical devices and the majority of devices approved under this system are Class II products which require additional study and control (Fig. 6.3).¹⁸

PMA (Fig. 6.4) is the most stringent type of device marketing application required by the FDA prior to receiving approval for market. It is predominantly for Class III medical devices where there is no substantially equivalent product to compare to, or if the device is a type of product that FDA considers too high a risk to down-classify and for which special controls alone are insufficient to ensure safety and effectiveness. Unlike pre-market notification, PMA is to be based on a determination by the FDA that the PMA contains sufficient valid scientific evidence that provides reasonable assurance that the device is safe and effective for its intended use or uses.¹⁹ The FDA has established methods of early collaboration with the sponsor allowing PMA devices to be brought to market expediently; that is, modular and streamlined product development protocols.

Fig. 6.3 510(k) pathway

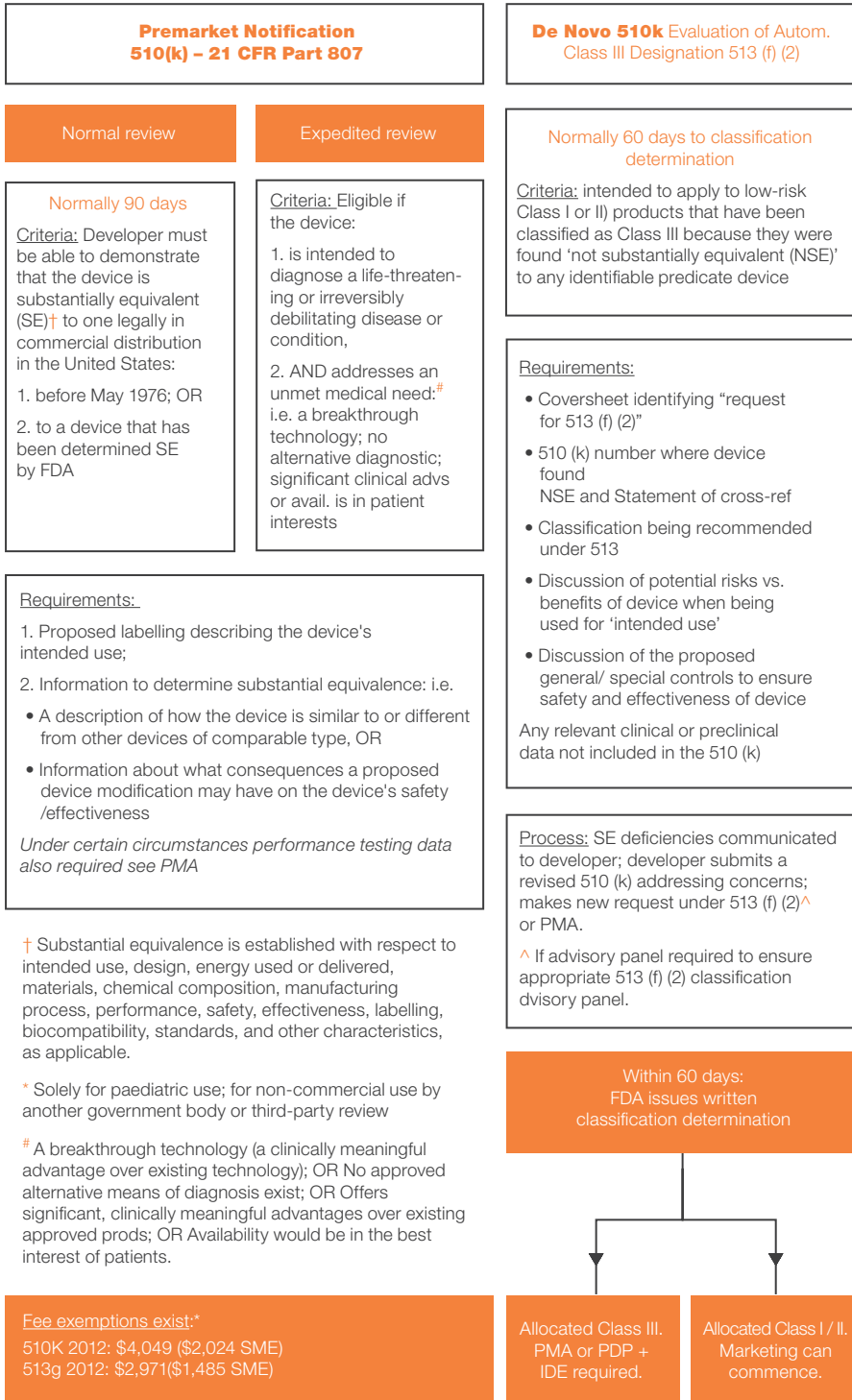


Fig. 6.4 Pre-market approval

PMA – 21 CFR Part 814 (section 515)		IDE† – 21 CFR Part 812
Traditional PMA review	Expedited review	Considered approved 30 days after receipt Criteria: An investigational device exemption (IDE) allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data required to support a PMA application or [infrequently] a Premarket Notification 510(k) 1. Devices with significant risk: need FDA and Institutional Review Board (IRB) approval 2. Devices with non-significant risk: IRB only approval prior to trial commencement
> 180 days to make a determination Criteria: Class III devices are: 1. high-risk devices that pose a significant risk of illness or injury, OR 2. devices found not substantially equivalent (SE) to Class I and II predicate through the 510 (k) process.	Criteria: Eligible if the device: 1. is intended to diagnose a life-threatening or irreversibly debilitating disease or condition, 2. AND addresses an unmet medical need: i.e. a breakthrough technology; no alternative diagnostic; significant clinical advs or avail. is in patient interests	
Requirements: Technical Sections split into two: 1. Non-clinical laboratory studies section i.e. microbiology, toxicology, immunology, biocompatibility, stress, wear, shelf life, etc. 2. Clinical investigations section i.e. study protocols, safety and effectiveness data, adverse reactions and complications, device failures and replacements, patient information, patient complaints, tabulations of data from all individual subjects, results of statistical analyses, etc.		Fee exemptions:* PMA 2012: \$220 050 \$55,013 SME – waived completely for 1st submission)
Process: FDA advisory committee may review the PMA at a public meeting and provide FDA with a recommendation; FDA notifies the applicant that the PMA has been approved or denied; public (internet) notice is posted with the decision and evidence providing opportunity for petition.		Requirements: Abbreviated IDE requirements: Labelling; IRB Approval; Informed Consent; Monitoring Records and Report; Investigator Records and Report; Prohibitions 1. Devices with significant risk: Submit an IDE application and obtain FDA approval, submit investigational plan to the IRB at each participating institution, obtain signed investigator agreements. <i>Sponsor can respond to deficiencies or request a regulatory hearing if IDE disapproved.</i> 2. Devices with non-significant risk: Submissions made directly to the IRB of each participating institution. Sponsors should present an explanation to the IRB where the study will occur of why the device does not pose a significant risk. <i>If IRB disagrees sponsor must inform FDA within 5 days</i>

* This method is generally used if the device has already undergone clinical testing and has been approved in a country with established medical device regulations. Non-traditional methods can be found in the Exceptions section.

† Exempted studies include: a legally marketed device used as per its labelling; the same but also if the testing is non-invasive, requires no invasive sampling, does not introduce energy into the subject, when used in accordance with its labelling, a device intended solely for veterinary use; a device shipped solely for research with laboratory animals (includes specific labelling).

6.5.5 Exceptions

In addition to the “standard” regulatory pathways highlighted previously, which are the route through which the vast majority of devices come to the United States market, there are “exceptions” where, for certain products, manufacturers or circumstances, flexibility has been introduced into these procedures that often serve to prioritize health needs and provide more timely routes to patient access.

Exceptions from General Controls (21CFR-866). Class I medical devices are products that the FDA believes present a very low risk to the consumer and are substantially equivalent to other products already on the market. The majority of medical devices are subject only to general controls. For the >100 generic categories the FDA lists for immunologic or microbiologic devices approximately five are additionally exempt even from some of general controls such as many of the QSR requirements, although these exemptions are unlikely to apply to a POC device targeting a bacterial infection.

Exceptions for SMEs and biotechnology companies. In October 2002 the FDA introduced fees through Medical Device User Fee and Modernization Act (MDUFMA); however, companies with total annual gross sales/revenues of <US\$ 100 million (including those of their affiliates) qualify for lower fees. The submission of a MDUFMA Small Business Qualification Certification (Form FDA 3602) and previous year’s income tax return are required for eligibility. For the 510K and De Novo pathways, the reduction is approximately 50% of the standard fee and 25% for a PMA submission – with the first PMA submission having a 100% fee waiver (see Fig. 6.4).

Exceptions for truly innovative devices which have the potential to meet an important and unmet medical need. This has been in place since 1994, and is currently in its fifth iteration²⁰ since the latest – 2008 version – incorporating the FDA Amendments Act 2007 revisions. The FDA has an expedited review system which is open to developers of products whose device is (a) intended to diagnose a life-threatening or irreversibly debilitating disease and (b) addresses an unmet medical need. Identifying eligible products can be proposed by either the FDA or the developer themselves, and can only be authorized by the Division Director. Although successful receipt of expedited review status does not guarantee the device will receive FDA marketing authorization in a more timely manner, it is placed at the beginning of the appropriate review queue and receives additional review resources as needed.^a

a If multiple applications for the same type of device offering comparable advantage over existing approved alternatives have been granted expedited review, they are reviewed with priority assigned on a first-in-first-reviewed basis.

*Exceptions for products with no substantially equivalent predecessor.*²¹ An adapted pathway was more recently (1997)^a instituted to prevent the most stringent regulatory pathway being automatically instituted (PMA via a Class III designation), for a low- or medium-risk product, solely because of the absence of a pre-amendment^b or substantially equivalent predicate device. Through this De Novo provision, following a 510k submission (assuming the device has not previously been classified), a developer can apply for a risk-based classification determination within 30 days of receiving a “no substantial equivalent” determination, assuming this was for a reason other than failure of performance data, that is, new intended use or different technological characteristics that raise safety and efficacy questions.

In July 2012, the FDASIA signed into law an amended section 513 (f) which included a Pre-De Novo submission, a newly instituted step to make the De Novo process more transparent and predictable by essentially encouraging earlier communication with the FDA. It results in a “suitability letter” and a positive response enables concurrent 510K and De Novo submission.

Exceptions for products that are perceived to be misclassified in eyes of developer. A manufacturer who wishes to have a device reclassified to a lower class must convince the FDA that the less stringent class requirements will be sufficient to provide reasonable assurance of safety and effectiveness. The FDA publish guidelines on appeals and complaints for medical devices,²² which aim to assist manufacturers to navigate the dispute resolution process.

Exceptions for devices intended to benefit people with rare conditions. This is essentially the orphan drug legislation of the device world. The Humanitarian Use Device provision applies to a device that is intended to benefit patients by diagnosing a disease or condition that affects fewer than 4000 individuals in the United States per year. The Humanitarian Use Device application is similar in both form and content to a PMA application, but is exempt from the effectiveness requirements of a PMA; that is, it is not required to contain the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose. However, an applicant must demonstrate that no comparable devices are available, and that they could not otherwise bring the device to market. The Humanitarian Use Device provision also has specific labelling requirements and may only be used in facilities that have established a local institutional review board (IRB) to supervise clinical testing of devices which they have approved. Anecdotal feedback from diagnostic developers suggests that while this exception may prove a useful incentive, the process in its current form is somewhat cumbersome and complex.

a In 1997 a new legislative addition to the FDA Amendments Act (Section 513 [f][2]) was the Evaluation of Automatic Class III Designation provision (also known as “De Novo” or “risk-based” classification).

b On the market prior to the passage of the medical device amendments in 1976, or substantially equivalent to such a device.

Exceptions to support regulatory flexibility in response to public health crises. In certain situations, such as where chemical, biological, radiological, nuclear or emerging infectious disease threats cause diseases or conditions, the *Emergency Use Authorization* (EUA) authority empowers the FDA to respond quickly to critical public health challenges without being constrained by the requirement of the full FDA approval process. The FDA Commissioner may allow unapproved medical products to be used in such an emergency, or unapproved uses of approved medical products, when there are no adequate, approved or available alternatives.

One such example involved the FDA response to the 2009 H1N1 influenza pandemic. Faced with a public health crisis, with no appropriate rapid diagnostic on the market, in May 2009 an initial molecular-based diagnostic device was granted EUA, followed by a number of other tests and assays (18 in total) over the following months.²³ In June the following year, once the health threat had subsided, the EUAs were rescinded. To date, only a small number of the devices granted temporary EUAs have been subsequently approved by the FDA (four, as of 2014),²⁴ highlighting that EUAs are certainly not a short cut to full FDA approval.

Flexibility to fast-track products to meet an unmet clinical need. Where a diagnostic device is intended to diagnose a life-threatening or irreversibly debilitating condition *and* addresses a current unmet need (such as being innovative technology which is clinically superior to current options, or that no alternative diagnostic is available, or, more broadly, where the availability of the diagnostic can be demonstrated to be in the best interest of patients),²⁵ then an application may be granted “*expedited review*” status. This mechanism is relevant for devices subject to PMA and, if granted, the status grants the device priority in the review queue and, where needed, additional review resources from the FDA to speed up the process. However, there is no specific expedited review pathway for rapid POC diagnostics subject to the 510k process and, more broadly, industry experts have commented that granting of expedited review status does not truly speed up the approval process, and rather only acts as an acknowledgement that the product is important.

6.6 EU current regulatory structures/framework

6.6.1 Framework/oversight

The key EU institution for the regulation of medical devices is the EC, which proposes, adopts and steers legislation through the primary EU legislative process involving the European Parliament and European Council. The EC has 33

departments or Directorates-General (DGs) with medical device regulation falling under DG SANCO (Health and Consumers). The Scientific Committee on Medicinal Products and Medical Devices provides technical and scientific support to the EC and additionally there are 12 Medical Devices working groups/task forces providing issue-specific technical support.²⁶ The implementation of EU device legislation occurs at the level of the 27 Member States plus three European Economic Area (EEA) states: Norway, Iceland and Liechtenstein.²⁷ The states' Competent Authorities (CAs) designate Notified Bodies (NBs) as independent third parties that carry out pre- and post-market conformity assessment and certification of medical devices based on the requirements of the EU Directives. DG SANCO also issues regulatory guidance documents which, while not legally binding, aim to ensure uniform application of relevant Directive provisions. A medical device can be sold in any EU Member State once the product holds a CE mark from any other EU Member State.

Collectively known as the Medical Device Directives, this core legal framework consists of three directives that regulate the safety and marketing of medical devices in Europe and came into effect in the 1990s.²⁸ Each Directive establishes essential requirements for their respective products and requires manufacturers to carry out an appropriate conformity assessment procedure to demonstrate compliance with those requirements. Of the three, Directive 98/79/EC (IVDD) governs IVD medical devices and will be the focus of this study. All three Directives are currently undergoing a fundamental overhaul that will be addressed in greater detail in a later section.

6.6.2 Broad approach and classification

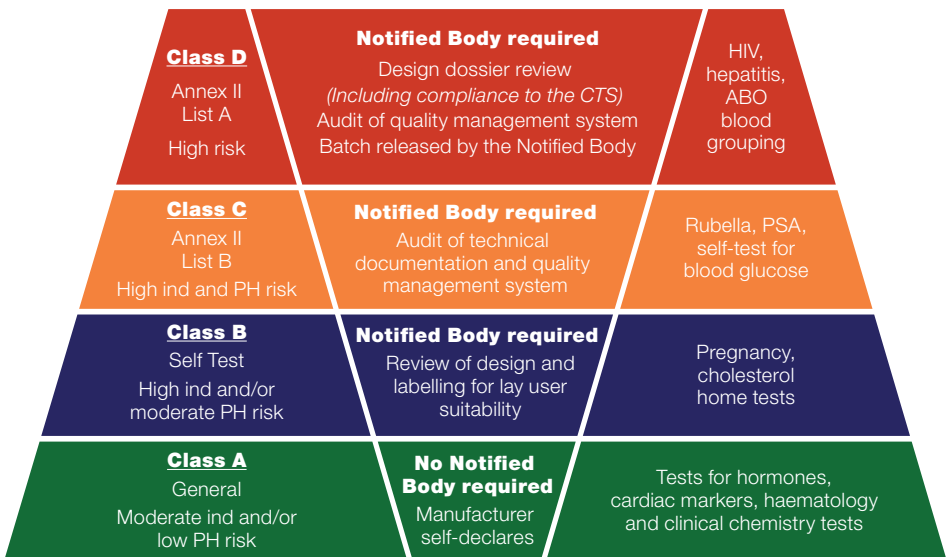
The EU regulatory system for medical devices is seen to be a “tools-based pathway” as opposed to the more holistic “systems” approach of the United States system. The focus is primarily on ensuring the safety of the test. Any IVD medical device manufacturer wishing to place a product on the market or put the product into service must first classify the IVD medical device in accordance with certain predefined risk categories contained in the IVDD (Class A–D; Fig. 6.5). Having determined the category for the IVD medical device, the manufacturer must ensure that the device meets the essential requirements of the IVDD by following the appropriate conformity assessment procedure(s) for that device, seeking NBs' input if appropriate. A core component of proposed reforms to the current IVDD is that this current “list-based” approach should be replaced with a risk-based approach, as recommended by the Global Harmonization Task Force (GHTF). It is widely accepted that the current list (Annex II List B) lacks intellectual coherence in its assessment of risk and this is largely due to how it was developed by Member States. A

move to a list based on a coherent assessment of risk would provide greater flexibility to respond to emerging health threats and diseases more rapidly, although there remain question marks as to how the new rules will be applied and implemented across Europe.

Registration of the manufacturer and device on the market is mandatory prior to market launch and serves to inform the relevant national medical device regulators which medical devices are being marketed in their jurisdiction. This process, while not onerous, will be streamlined when EUDAMED – the European Database on Medical Devices – comes into full operation (part of this will involve transitioning the current registration and coding system to the Global Medical Devices Nomenclature System).²⁹ Owing to the coming into force of the EC decision concerning the implementation of the European databank EUDAMED, the Medicines and Healthcare products Regulatory Agency (MHRA) no longer accepts these notifications nor will it acknowledge notifications submitted under the legislation quoted.

This decision mandates each Member State to forward to the European databank certain medical devices information collected in each country where the manufacturer or the authorized representative is located. Therefore the implementation of EUDAMED, the transitional provision in Article 12 of IVDD 98/79/EC which obliges IVD manufacturers to give notification to every Member State concerned by the placing on the market of IVD devices, ceases to apply.

Fig. 6.5 Categorization of medical devices according to the EC's IVDD^{30, 31}



Ind – individual; PH – public health

6.6.3 Procedures and requirements

Procedures. The IVDD 98/79/EC clearly states that each IVD device must be accompanied by the information needed to use it safely and properly taking into account the training and the knowledge of the potential user.

Annex I – Essential requirements. The essential requirements are listed in Annex I to the IVDD and they are very broad and general, for example “the devices must be designed and manufactured in such a way that”:

- When used under the conditions and for the purposes intended, they will not compromise, directly or indirectly, the clinical condition or the safety of the patients, the safety or health of users or, where applicable, other persons, or the safety of property. Any risks which may be associated with their use must be acceptable when weighed against the benefits to the patient and be compatible with a high level of protection of health and safety.
- The devices must be designed and manufactured in such a way that they are suitable for the purposes referred to in the definition of an IVD device, as specified by the manufacturer, taking account of the generally acknowledged state of the art. They must perform, where appropriate, in terms of analytical sensitivity, diagnostic sensitivity, analytical specificity, diagnostic specificity, accuracy, repeatability, reproducibility, including control of known relevant interference, and limits of detection, stated by the manufacturer.
- The essential requirements also provide details of the labelling requirements for IVD medical devices and general requirements for information that must accompany these products.

In addition, and as with the United States’ “general controls”, manufacturers may choose to apply harmonized standards to the design and quality assurance processes for their products. Although compliance is not mandatory, it does raise a presumption of conformity with the essential requirements (conformity can be demonstrated through other means). European harmonized standards are requested by the EC and are developed by European Standards Organizations (ESOs), such as the European Committee for Standardization (CEN) and the European Committee for Electrotechnical Standardization (CENELEC).^a In many cases the EU standards incorporate international norms such as ISO 13485 and bear the designation “ISO EN”. There are three general classes of standards:

^a In the EU, only standards developed by CEN, CENELEC and ETSI (European Telecommunications Standards Institute) (all of which are ESOs) are recognized as “European Standards”. CEN, CENELEC, ETSI are the regional mirror bodies to their international counterparts, such as ISO.

- *horizontal standards* governing common requirements, for example, sterilization and safety of medical electrical equipment;
- *product standards* for specific types of device; and
- *quality standards* to ensure the quality of design and manufacturing processes.

Annex II – List of higher risk devices. This Annex provides a list of products that help determine a product’s categorization. The products listed in Annex II are subdivided as either high-risk (List A) or moderate-risk (List B) products, and all of them require the involvement of an NB before the product can be placed on the market. As highlighted earlier, this is perceived to be one of the main weak points in the European system. Examples of products listed in Annex II can be found in Fig. 6.5.

Annexes III–IV – Conformity assessment procedures. For IVD medical devices in Classes B–D, the manufacturer may choose from a variety of conformity assessment procedures (see Fig. 6.5) and some combine two or more. The procedures are listed in Annexes III, IV, V, VI and VII of the IVDD, all of which involve some interaction with an NB, with some being more product-focused than others. Exactly which route a manufacturer chooses will depend on the circumstances, and selection has been described as an “art”.³²

- *Annex III* – Product design examination
- *Annex IV* – Full quality assurance (ISO 13485) audit by NB; that is, the NB verifies that every product/batch conforms with requirements of the Directive.
- *Annex V* – Production quality assurance by NB; that is, the NB assesses and monitors manufacturers’ quality systems
- *Annex VI* – Product quality assurance (Product examination) by NB; that is, the NB assesses and monitors manufacturers’ quality system, which must undertake to examine each product or representative batch
- *Annex VII* – Production quality assurance (ISO 13485) audit by NB.

Once the manufacturer has received all the appropriate certificates of conformity, it must make a declaration of conformity in accordance with the requirements of Annex III. It may then apply the CE mark and place the product on the EEA market.

6.6.4 Exceptions

For general IVD medical devices (Class A). The manufacturer self-assesses conformity with the essential requirements and prepares a declaration of conformity in accordance with Annex III of the Directive. The manufacturer can then apply the CE mark and place the product on the EEA market without the involvement of a NB.

For high-risk devices (Class D). An EC expert group has drawn up Common Technical Specifications³³ that establish performance evaluation and re-evaluation criteria, batch release criteria and both reference methods and materials for use in the conformity assessments of IVD medical devices. As with harmonized standards, compliance with the Common Technical Specifications is not mandatory but it does result in a presumption of compliance with the essential requirements.

For laboratory developed tests. “In-house” tests are currently exempt from regulation under Article 1(5) of Directive 98/79 EC, which covers tests that are both manufactured and used in the same health institution, either on the same premises or in the immediate vicinity of manufacture without transfer to another legal entity. This exemption is currently being reviewed as part of broader reforms to the IVDD, in part to ensure the safety standard of such in-house tests, but also to prevent potentially unfair competition between such tests and those that have been through the CE marking process.

For circumstances of public health crises. Similar flexibility exists in Europe, where currently, “Article 9(12) of Directive 98/79/EC makes provision that Member States can accept *in vitro* diagnostic devices in their respective territories without proper conformity assessment procedure if this is justified in the interest of public health protection.” Proposals under the new IVDD are for potential “conditional CE marking” in place of the existing guidelines, which would have the benefit of offering a European-wide, versus national-level, solution for flexibility in response to urgent public health need. In the current form, proposals are for a one-year conditional CE mark. Industry associations such as EDMA and BIVDA (the British In Vitro Diagnostics Association) are supportive of this proposal, but EDMA did highlight the need to clarify what happens when the conditional CE mark expires (should the full CE mark not be in place for the product by that point), and how users of the product could best be made aware of the conditionality of the CE approval, with associated risks. BIVDA also believes such flexibility may be useful in other situations, for example to allow the use of new biomarkers while clinical utility evidence is being generated.

6.7 Reform under way in the United States

Recent regulatory reforms surrounding medical devices affect three main areas of regulation: Reimbursement (MODDERN Cures Act), Resourcing (FDASIA Part II/MDUFA), Regulatory Improvements (FDASIA Part VI) and Registration and Device Listing (CFR21-807). We provide an overview of the latter three in this section, which were part of the same Congressional Bill: the FDA Safety and Innovation Act (FDASIA)³⁴ signed into law July 2012 and effective from the fiscal year 2013, which begins on 1 October 2012.^a The Bill passed with bipartisan support and one interviewee, following the signing, said that “Congress on both sides of the aisle seems intent on further FDA reform, including the Device Centre.”³⁵ FDASIA includes 11 titles, including the fifth reauthorization of the Prescription Drug User Fee Act (PDUFA V), first enacted in 1992, the first iteration of the Generating Antibiotic Incentives Now Act (FDASIA VIII), as well as the third reauthorization of the Medical Device User Fee Amendments of 2012 (MDUFA III). The MODDERN Cures Act, which predominantly focused on further discovery and innovation in diagnostics, more timely access for those in need by streamlining the inclusion of new diagnostics in Medicare, and ensuring appropriate reimbursement for diagnostic tests, is discussed in Chapter 5.

As regards FDASIA, MDUFA was first enacted in 2002 in order to:

provide the FDA with the resources necessary to better review medical devices, to enact needed regulatory reforms so that medical device manufacturers can bring their safe and effective devices to market earlier, and to ensure that reprocessed medical devices are as safe and effective as original devices.

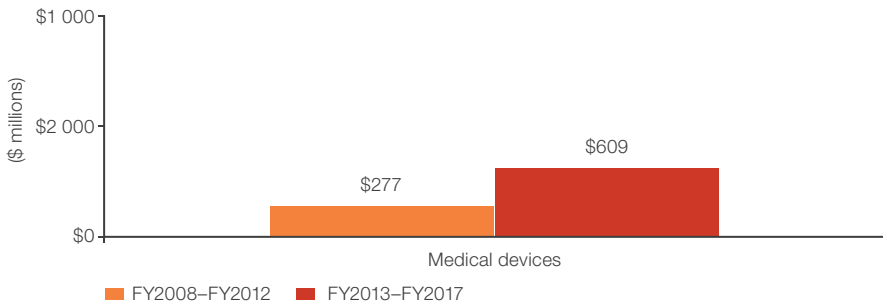
The challenges of sufficient regulatory resourcing – more broadly than medical devices – continues with the FDA commissioner stating in 2010: “the FDA’s resources are outstripped by our responsibilities ... there is a continuing need for expansion of investment”.³⁶

MDUFA III is the result of more than a year of public input, negotiations with industry representatives, and discussions, and will automatically end in five years (October 2017). MDUFA is seen as having made significant progress towards meeting some of its objectives, such as expanding its review capabilities and expertise, defining and meeting a number of its performance goals, expanding the availability of innovative (expedited) review processes, developing electronic tracking systems etc. The latest boost to funding is seen as a significant step in mobilizing the necessary resources to facilitate manufacturers getting products to

^a FDASIA, Pub. L. No. 112-144, 126 Stat. 993 (2012), primarily amends both the FDC Act and the Public Health Service Act (PHS Act). Available from: <http://www.govtrack.us/Congress/bills/112/s3187/text>

market sooner. User fees are expected to more than double from US\$ 277 million in 2008–2012 to US\$ 609 million in 2013–2017, the equivalent of 200 new full-time staff involved in device approvals by 2017.³⁷ Despite this triumph, some consternation has been expressed that the user fee framework under MDUFA has created uncertainty for industry and the FDA regarding the annual increase in fees and the amount of funds that would be collected by the agency in any given year (Fig. 6.6).³⁸ This was recently compounded when the new fees being paid by developers to the agency were sequestered making US\$ 2.9 million (in fiscal year 2013) of medical device user fees unavailable for use by the FDA – a situation that has now been rectified. Additionally, some manufacturers have short-term concerns about the impact on “review consistency” of a rapid influx of new regulatory reviewers.

Fig. 6.6 *Impact of MDUFA reforms on FDA fee revenues for medical devices*



Note: FY – fiscal year

Thirty-three provisions were included in the Medical Device Regulatory Improvements part of the Bill (FDASIA Part VI), with the most significant highlighted in Table 6.4. It seems that manufacturers perceive the Bill as increasing overall regulation.³⁹ However, it also provides some advantages to industry, such as changes in the accepted data standards (the FDA can now only request the “minimum necessary”) and shorter time commitments from the FDA, particularly during the appeals process, will particularly assist SMEs. The fact that the agency is now able to use data from outside the United States for approvals will reduce the information requirements for global manufacturers and increase the FDA’s ability to change the risk classification of a device (where it now has more autonomy). The re-introduction of a third-party review process^a and the more efficient granting of De Novo classification help expedite some previously cumbersome parts of the process, the latter particularly for truly innovative devices.

a A pilot system was trialled in the 1990s with little success and resulted in delayed review times while dossiers were reviewed by the FDA.

Table 6.4 A selection of the 33 provisions, signed into law in July 2012, in the FDASIA relating to medical device regulatory improvements⁴⁰

Regulatory area*	Implication	Need for revision
Investigational device exemptions[†]	An IDE approval is needed to initiate a clinical study of significant risk devices.	It has been a concern in industry that a recent FDA draft guidance might result in IDE disapprovals for studies not viewed by the FDA as likely to support ultimate 510(k) clearance or PMA.
Clarification of least burdensome standard	To prevent FDA reviewers from requesting information that is scientifically or medically interesting but not essential to clearance or approval.	The existing “least burdensome” provisions limit the FDA to requesting only “necessary” clinical data for clearance or approval. FDASIA now defines “necessary” as “the minimum required information”; an ongoing challenge may be that “minimum required” is no less subjective than “necessary”.
Agency documentation and review of decisions	Requires the FDA to document the scientific and regulatory rationale for “significant decisions” regarding IDE, 510(k) and PMA applications.	Will provide greater transparency and clarity to the FDA’s decisions and requires the FDA to provide an appeal decision in a commercially reasonable time frame – both areas that have caused developer concern in the past.
Device modifications requiring pre-market notification	Original guidance (1997) on the issue of “when a device modification will require new clearance” likely to remain in place for some time to come.	Requires the FDA to withdraw the (contentious) draft guidance (2011), and within 18 months report directly to Congress on the approach that should be taken to clarify when a modification to a cleared device requires a new submission.
Modification of De Novo application process	A sponsor who finds there is no available predicate device may now directly request De Novo classification. The sponsor also must include an initial draft proposal for the special controls that would apply, thus potentially easing the FDA’s burden in identifying such controls. The FDA now has 120 days to issue a decision vs 60 days before.	To remove what is considered a superfluous obstacle to efficient granting of the De Novo classification but placing the burden more on the developer than the FDA. In 1997, Food and Drug Modernization Act authorized the FDA to place Class I or II risk devices without a predicate device into the De Novo pathway, with the prerequisite being that the device had to first undergo 510(k) review and receive a “not substantially equivalent” decision.
Reclassification procedures	FDASIA would allow the FDA, based on new information, to change the classification of a device by administrative order instead of by regulation.	A number of existing procedures allow device reclassification by regulation, but have proven so cumbersome they are rarely used. The intention is that this new authority will greatly improve the FDA’s ability to adjust its regulatory classifications based upon new information and post-market experience.
Reauthorization of third-party review and inspection	FDASIA reauthorizes the third-party review programme until 1 October 2017. The programme enables a company to submit a 510(k) directly to an FDA-Accredited Person, who then reviews the 510(k) and forwards this and their recommendation to the FDA, which must make a final determination within 30 days following receipt.	Despite an unsuccessful pilot (many of the reviews had to be repeated by the FDA) of a similar programme in the 1990s, this new, voluntary, programme is intended to speed the FDA 510(k) process by providing third-party assistance for more routine reviews, [†] maximize its inspection resources, provide manufacturers with greater control over the timing of their inspections and reduce the total number of inspections required.

A number of provisions impacting post-marketing phase

Programme to Improve the Device Recall System. For both mandatory and voluntary removals, the FDA is required to clarify procedures for device recall audit checks, and develop criteria for assessing correction or removal actions.

Unique Device Identifier. FDASIA requires the FDA to issue a proposed rule establishing a Unique Device Identifier (UDI) system by 31 December 2012. The mandate is intended to make devices easier to identify for adverse event and recall tracking. For manufacturers this could require serialization not only of finished products but also constituent components, with implications for companies' sourcing and supplier monitoring processes.

Post-market Surveillance. The FDA already has authority to order post-market surveillance for four types of Class II and III devices, but FDASIA addresses the timing of a post-market surveillance order; that is, the manufacturer must submit their surveillance plan within 30 days of receipt of the order and begin the surveillance within 15 months.

Sentinel. FDASIA expands the established (2008) drug "Sentinel" post-market risk analysis and identification system, where it develops safety standards, methods for tracking safety and continuous device safety monitoring. The FDA will be able to monitor passively collected data (commercial and insurance data) and no longer need rely on adverse event reporting from physicians.

Note:

* For new provisions impacting regulatory harmonization efforts please see the Harmonization section

† Certain types of devices (higher risk) are exempted from this programme.

‡ FDASIA also amends the FDC Act § 520(k) by adding language authorizing the FDA to issue an "IDE clinical hold" if it determines a device represents an unreasonable risk to the subjects' safety or for other reasons.

Finally, on 1 August 2012 the FDA published the revised version of Part 807 to reflect the statutory amendments to the device registration and listing provisions of the Federal Food, Drug, and Cosmetic Act (FDC Act) and accommodate new requirements of the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (Bioterrorism Act) and the FDA Amendments Act of 2007. Essentially these provisions make electronic submission mandatory,^a raise the fees and remove previous fee exceptions. They also facilitate collection of additional registration and listing information from foreign establishments and initial importers, and attempt to improve the quality of registration and listing information available to the FDA.

CMS-CLIA

In 2008 a new guidance document was released for CLIA-waiver, which placed greater emphasis on scientifically based flex studies and validation/verification studies, use of quality control procedures, intended users during studies testing the device, use of patient specimens (in an intended use environment over

a Via the FDA Unified Registration and Listing System (FURLS) Device Registration and Listing Module (DRLM).

time), and a recognition that reference methods may not be available for every device type. Unlike the FDA device review pathway, however, there are no reforms to the system currently on the table. Developer concerns around the current system remain and have been voiced in the following areas: expansion of the parameters of responsibility beyond the laboratory setting and its staff; difficulty in conducting tests in POC testing locations whose focus is patient care,⁴¹ and the high standard of performance requirements particularly for infectious disease products.

Efforts by CMS to improve the quality of testing and reporting in recent years have brought a greater regulatory burden to the realm of POCTs and added to the expense of such testing.⁴² CMS has, for example, recently tightened regulations surrounding operator competence for POCTs. Nichols explains that where previously there had been six criteria or categories used to evaluate operator competence (and the lab directors could choose which six were relevant to test the methodology of their programme), recent reforms have meant that now device operators have to be evaluated on all six elements each year for moderate- and high-complexity testing. The evaluation is not just direct observation but also requires that operators can report results and do maintenance.⁴³ Nichols notes that one of requirements that is catching people is the requirement to do a blind sample or a sample of known concentration as part of annual competence testing. Nichols adds that these requirements can also be complicated with POCTs because some samples are not stable. “You’re not collecting a lot of blood if it’s finger stick, so to do a duplicate test just to prove that someone is competent is a challenge.”

CMS has also made changes to the interpretation of quality control for single-use devices such as the cartridges used in blood gas analysers. In the past, it was possible to run quality control on a subset of the devices within an institution. So while a hospital could have 20–50 fifty blood gas analysers in use, the monthly control would only have to be done on a subset of those and rotate each month to a different subset. Nichols explains that today CMS looks at quality control not by cartridge lot but rather by analyte. He explains that now, for example, one might be forced to run sodium quality control once a month on each and every device that is in use. Also, use of the Clinical and Laboratory Studies Institute EP23 guideline will allow lab directors to determine the frequency of quality control and choose the most appropriate control processes for their devices using a risk-based model (which factors in risk of error, risk of wrong result or harm to a patient from incorrect test result and treatment based on the incorrect result).

President's National Action Plan to Combat Antibiotic-Resistant Bacteria

In March 2015 the White House issued a National Action Plan to Combat Antibiotic-Resistant Bacteria.⁴⁴ Among several priorities, the plan details current efforts under way between the FDA and CMS to foster innovation in the diagnostic device industry. Relevant initiatives mentioned include the FDA-CMS Parallel Review pilot programme, permitting simultaneous (as opposed to sequential) product reviews by the FDA and CMS. The Medical Device Reimbursement Task Force, which brings together companies with third-party payers to discuss reimbursement issues before or during the FDA approval process, is also included.⁴⁵ The Entrepreneur in Residence programme to provide technical guidance to SMEs that may lack the necessary expertise to successfully navigate the approval process is also highlighted.⁴⁶ While these initiatives will take time to bear fruit, they are a signal that the current government is attempting to ease some of the friction currently slowing the supply of new diagnostics.

Laboratory-developed tests

Regulation of LDTs is certainly the most contentious area of diagnostic regulatory reform in the United States. As LDTs^a have evolved from being “relatively simple, low-risk tests performed on a few patients being evaluated by physicians at the same facility as the lab” to “more sophisticated and complex [tests whose] results are rapidly becoming a staple of medical decision-making”,^b compounded by the proliferation of commercial laboratories, there has been a growing belief, also within the FDA, that the current distinction in oversight system (no pre-market review requirements under CLIA) is not appropriate given that – as one commentator describes – these devices are “distinct only in the business model used for their creation”^c (a fact vociferously rejected by American Clinical Laboratory Association). While these devices are arguably not in commercial distribution, they are increasingly used in geographically distant commercial laboratories. The implications for this current “war over regulatory ownership of *in vitro* diagnostic devices” are foremost at the level of patient safety. For example, there are reports of problems with laboratory tests that have not had FDA oversight: women were erroneously told they were negative for a mutation conferring a very high risk of breast cancer; an ovarian cancer test, marketed before the completion of an NIH-funded study, gave false readings

a Which may be a whole test or components such as analytic specific reagents.

b http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2013/06/fda-commissioner-calls-for-more-active-fda-regulation-of-laboratory-developed-tests-and-acla-promptl.html Accessed 22 July 2013

c <http://myraqa.com/blog> Accessed 22 July 2013

that reportedly led to the unnecessary removal of women's ovaries; and flawed, mishandled data underlying a test for Down syndrome were discovered only days before the test was to go on the market. For developers, however, the lack of regulation of LDTs creates an "un-level" playing field for developers of devices within the same sector, while many manufacturers are exploiting this pathway as an "alternative" and more rapid route to market for their IVD products. The support of industry association AdvaMed for regulation of LDTs shows that the industry would prefer this discrepancy to be addressed.

Starting in the 1990s there have been a number of attempts – by the FDA and others – to put forward solutions to address the challenges of regulating LDTs. The tally, from the FDA alone, currently stands at three draft guidelines having been issued to date (the latest being in 2011). Most recently, the FDA announced in June 2010 that it was revisiting its years-long policy of exercising enforcement discretion over LDTs and held a public workshop to discuss the issue in July 2010 with another scheduled for July 2013. This announcement was publicly reiterated in June 2013, with the current FDA commissioner confirming that a risk-based framework is under development but without providing details as to what the risk-based framework would entail or when it would be issued (publication was expected in 2013 alongside the long-awaited guidance to the regulation of companion diagnostics). Although it remains unclear how this perceived "regulatory loophole" will be addressed, by whom^a and when, it seems clear that there is a commitment to put the issue on the legislative agenda. Until any reform is enacted, however, the FDA currently regulates under a loose policy of "enforced discretion".

Industry-initiated proposals

In recent years several industry-led proposals for regulatory reform have been presented to the FDA. Most recently a proposal has been under discussion – known as the "Risk Based Approach to Regulation of Diagnostics" – and is being put forward by AdvaMed. The essence of the proposal and associated triage model is to modernize the regulation of all diagnostics to support public health and innovation. In a positive development, the FDA adopted a formal diagnostics triage programme in spring 2013 to aid and speed device reviews, which has been supported by industry. AdvaMed also continues to engage with the FDA on a transitional approach for emerging diagnostics. The proposal aims to create a progressive review pathway to promote the development of new emerging diagnostics. While discussions are still under way with the FDA, this reflects a science-based approach to support analytical performance and clinical significance for new emerging assays to best support public health needs. While the

a The FDA believes this is already under its mandate; Congress, however, may have other ideas.

FDA has indicated an interest in exploring a transitional approach, discussions are ongoing and any major timely changes in this regard will take time and be subject to further discussion with the FDA.

Overall it is clear that the FDA and CMS are trying to adapt regulations to a fast-changing diagnostics market and to respond to developer concerns. However, the flip side of adapting is that there appears to be a “moving target” regarding what is required for approval.

6.8 Reforms under way in Europe

Some experts suggest that the regulatory changes currently under way in the EU are “far more significant” than those under way in the United States. The EU IVDD (98/79/EC), written in 1998, came into full force in 2003 and has not been substantially amended since its adoption.⁴⁷ In 2008, the EC held a public consultation concerning the recasting of the medical devices directives. This started a process that will lead to a fundamental revision of the existing directives in order to simplify and strengthen the current framework.⁴⁸ This public consultation was complemented in 2010 by a similar consultation regarding the technical aspects of the revision of the IVDD; this is also undergoing a “fundamental revision” to keep pace with technological advancements and keep IVDD “fit for purpose”.⁴⁹ The consultation invited comments from a broad range of stakeholders on 19 questions and comments received through the public consultation highlight that more than 10 years of implementation have revealed weaknesses in the IVDD. These issues were raised as part of a review initiated following widespread acknowledgement that scientific and technological evolutions, as well as new business trends in the IVD field – for example, the emergence of companies offering IVD testing as a service – were ineffectively handled in the IVDD. Other concerns have been raised⁵⁰ around weaknesses related to implementation of the Medical Device Directives, such as challenges in the exchange of information (EU database), the long process to conclude on interpretations/borderlines and the 27 Member States having their respective and at times differing views on implementation.

On 26 September 2012, the EC published the long-awaited proposed regulation (not a Directive),^a which covers medical devices in the broader sense (93/42/EEC) and – for the first time – specific regulation for IVD devices (to replace 98/79/EC). The regulation must receive approval from both the European Parliament and European Council before becoming final. The key areas of discussion prior to its release had focused on: the need to revise the current device classification

a Regulation is stronger than a Directive, the latter giving Member States some discretion as to how they sign it into law.

system which was seen as inadequate; whether or not to include specific requirements for POCTs (which previously had been done only indirectly); the need to clarify the requirements regarding clinical evidence; and the handling of in-house tests and companion diagnostics. The published proposed regulation does include all these issues and was broadly welcomed by the European industry association (EDMA). The key areas of proposed change include:

- stronger supervision of NBs;
- more powers and obligations for assessment bodies to oversee manufacturers;
- clearer rights and responsibilities of manufacturers including more stringent clinical evidence requirements and an increase in the classification;
- harmonization of Member State authorities' approach to regulation and improvements to the exchange and coordination of information, especially in the pre-market phase;
- better supply chain traceability of devices.

One additional area of concern is the implications of the likely absence of a “Grandfather clause”, whereby companies will be required to review their current products (those already approved and on the market) for compliance with any new classification system. This initial bolus in submissions on enactment of the legislation raises questions as to whether the national systems and NBs have the resources to absorb this initial work without significant supply disruptions for existing or – even more importantly – innovative new products needing licensure at the same time. The responses to the public consultation on all of these issues are briefly summarized in Table 6.5, which also includes a focus on developer responses.

The commenting period ended in September 2010 and a summary of the results was published in February 2011. The EC had 12^a “Medical Device working groups”⁵² tasked with exploring various issues in greater depth and facilitating pan-European dialogue, and a proposed regulation was published by the EC (at the same time as an impact assessment) in September 2012. The regulation has been approved by both the European Parliament and the European Council before becoming EU law. However a number of Members of the European Parliament have proposed revisions to the regulation, most notably in April 2013 Dagmar Roth-Behrendt called for medical devices marketed in the EU to be subject to a pre-market assessment system in which high-risk devices would need to undergo

a NB-MED, EUDAMED, New & Emerging Technologies, Electronic Labelling, Clinical Investigation and Evaluation, IVD Technical Group, Notified Body Operations Group, Compliance and Enforcement Group, Classification and Borderline, Vigilance, Competent Authorities meetings, Medical Devices Expert Group.

Table 6.5 Summary of the response to the public consultation of the IVDD revisions⁵¹

Question	Total	Summary of developer feedback	Summary of aggregate feedback
Q1. Would you consider the adoption of a risk-based classification for IVDD medical devices as an improvement of the current European regulatory framework?	116 93% stakeholder support	Industry (BVDA and EDMA) also supportive. Concerns voiced over the significance of “changing the nature” of the classification system, particularly additional costs; and need to allow sufficient transition time (esp. for SMEs, those with B&C devices) or a “grandfather” clause. The need for a “conflict resolution board” (borderline device classification disputes).	Almost unanimous support – across stakeholders – for the movement to a risk-based classification system based on the GHF model. Advantages were seen to be: the better protection of public health, timely access to the market for new tests, increased alignment with other regulatory systems and a system more robust to technological progress (list systems need constant updating).
Q14. Do you see a need to add specific requirements for “point of care” or “near-patient” IVDD medical devices? If yes, regarding which aspects (e.g. information supplied by the manufacturer)?	93 65% agreed with the need	Developers disagreed (BVDA and EDMA) with the need for additional, specific requirements here, citing the adequacy of the existing risk management systems. One alternative proposal was that “instructions for use” should indicate the intended user and that defining “health care professional” would facilitate developers to state this more clearly.	Most respondents felt that current requirements were insufficient and that the clinical validity of the test must be demonstrated in the same conditions as those in which the test will be used (i.e. manufacturer needs to demonstrate the same level of clinical sensitivity or specificity as the test performed in a clinical laboratory). The issue regarding appropriate communication (on device handling) was also raised. As was the fact that genetic tests should not be performed in the POC environment.
Q15. Do you see a need to further clarify the requirements regarding clinical evidence for IVDD medical devices?	110 90% agreed with the need for clarity	Given almost unanimous support there was reluctant agreement from developers, some specifying only higher-risk devices. Concerns over the “radical nature” of this new proposal. Particularly because of shifting the burden of responsibility (in proving value) from physician to manufacturer. Propose focusing on “means of implementation” but awaiting a more concrete proposal from GHF or applying STARO criteria.	Respondents agreed that the requirements regarding the clinical evidence should be more detailed in the Directive, specific for the different classes and that the Directive should include some requirements on how to demonstrate the clinical evidence.
Q16. Clinical Validity. On the basis of the above, do you see a need to extend the requirements regarding the demonstration of clinical validity[†] in Directive 98/79/EC?	106 81% agree there is a need to extend	Among manufacturers there was little support for this proposition (-ve/+ve predictive). Particular concern was voiced around the additional regulatory barriers this would mean for novel markers that there is under the current system. Either meaning significantly greater pre-market investment or a device remaining for a longer time outside the scope of the Directive (as they would remain “research use only” devices or “in-house developed assays”).	The stakeholders agreed quasi-unanimously on the fact that the requirements on the demonstration of clinical validity should be extended at least to the demonstration of Negative Predictive Value and Positive Predictive Value (not currently included in the IVDD). Requirements on clinical validity should be proportionate to the risk linked to the use of the IVDD medical device and then adapted to the risk-based classification.
Q17. Clinical Utility. In the context of the above, do you see a need to require the demonstration of the clinical utility[†] of the parameter in Directive 98/79/EC? If yes, how should the clinical utility be demonstrated?	115 67% disagreed with the need for the demonstration of clinical utility by the manufacturer	It was underlined that, for new parameters, it will be impossible to demonstrate the clinical utility and therefore it will limit market access for innovative IVDD medical devices. See also comments under Q16.	Concept of clinical utility being a “moving concept” difficult to capture in a regulatory framework. Many felt the concept of clinical utility should remain outside of the pre-market assessment process. In addition, it was underlined that the clinical utility should not be demonstrated by the manufacturer, but should be assessed by the user. However, some of the answers underlined that the demonstration of clinical utility might have an interest for direct-to-consumers testing or genetic testing.

Note:

* <http://www.stard-statement.org/>

† Clinical validity was defined within the public consultation as the demonstration of the performance characteristics supporting the intended use of the *in vitro* diagnostic medical devices and includes diagnostic sensitivity, diagnostic specificity based on the true disease status of the patient, and negative and positive predictive values based on the prevalence of the disease. *Latter two not included in current IVD.*

‡ Clinical utility was defined as the demonstration of the potential usefulness and added value to patient management decision-making.

a full review – as in the United States, while devices of lesser risk would undergo an expedited assessment procedure overseen by NBs. Lack of agreement on what the final proposal should look like, plus the fact that the recast of the Medical Devices, Implantable Medical Devices and IVD Directives will be occurring in parallel means 2014 will be the earliest point at which agreement will be reached.^a There is likely to be a minimum of a three-year transition period to the new legislation, therefore implementation may not now occur until 2017–2018.

6.9 Industry stakeholder involvement in European regulatory reforms

As part of the ongoing efforts to update the IVDD, a consultation with key stakeholders was held in June 2010 on the proposed revisions to Directive 98/79/EC on In Vitro Diagnostic Medical Devices. Among others, IVD manufacturers have had an opportunity to express their views, particularly on a number of critical or potentially contentious aspects of the proposed legislative changes. Both the reforms and, more specifically, IVD manufacturers' response to the public consultation, have been addressed in section 6.7. An assessment as to whether or not industry input into the process will have shaped the outcome will need to be revisited once the changes to IVDD have been finalized, and thus an analysis of the effectiveness of this communication pathway, and regulator flexibility to industry demands, will be saved until such time as the evidence is available.

6.10 Evaluation of communication pathways between regulator and industry

In the past there have been frustrations from both developers and the regulator regarding communication deficiencies that have added to review times and exacerbated tensions. Additionally a number of recent studies continue to criticize regulatory agencies for limited transparency.⁵³ However, it seems things are slowly changing, especially in the United States, with a number of developers citing an improved “flexibility” on the side of the FDA and willingness/openness to interact with those making submissions and to engage in public meetings.⁵⁴

^a This is looking increasingly optimistic.

In June 2009, the FDA launched its “transparency initiative”.⁵⁵ This had three phases, which started in January 2010 with the launch of a web-based resource for public access called “FDA basics”. Phases 2 and 3 in – in May 2010 and January 2011 respectively – were the release of two transparency reports, the first for the public and the second for regulated industry. Most recently, in January 2012, the FDA released a new report⁵⁶ presenting eight initiatives adopted by the Commissioner to explore avenues for making FDA’s compliance and enforcement data more accessible and user-friendly (this followed a two-year period of development that included a public consultation). The eight initiatives include items such as the exploration of different ways to: improve data quality, facilitate more timely data disclosure by expediting data entry, expedite inspection review and classification, update the data more frequently, explore tools that may facilitate more expedient error reporting, and better integrate presentation (including through mobile apps) of its compliance and enforcement data, etc.

Aside from more administrative commitments of the FDA, however, recent regulatory reforms highlight how the FDA is making great strides in improving the communication during the core processes and dealings with industry. This is best illustrated through the expedited regulatory pathways and some of the newer more flexible regulatory pathways (see section 6.5.5 on Exceptions). The FDA comments that “a PMA will be assessed against the MDUFMA II expedited performance goals without a pre-filing meeting, however FDA strongly recommends to industry to have such a meeting”.⁵⁷ In order to reap a benefit from the expedited review process, the commitment on behalf of the applicant to resolve all scientific and regulatory issues should match that of the FDA. It will only be through effective communication (i.e. interactive review) and a total commitment to fulfilling all regulatory and scientific requirements that the FDA and the applicant can speed market authorization for safe and effective products. Also, the newer pathway processes, such as the Pre-De Novo, pre-SUB^a product development protocols, modular and streamlined PMAs are all underlain by an earlier, more flexible and interactive communication between the developer and regulator (see section 6.5.5 Exceptions). Here the FDA states that establishing a solid working relationship with the FDA during development can facilitate the pre-market submission review and set expectations with regard to data requirements for the submission.

In order to facilitate dialogue and approval, particularly for innovative devices, the FDA has established a “pre-submission” (pre-SUB) process, whereby manufacturers of particularly cutting-edge technology (which may include many molecular diagnostics) are invited to submit to an informal pre-SUB process

a Pre-submission (pre-SUB), prior to MDUFA III was “pre-Investigational Device Exemption (IDE)”.

to open dialogue on appropriate analytical or clinical protocols and discussing requirements for the appropriate regulatory pathway. This is entirely voluntary for device manufacturers, although arguably FDA familiarity with the product may facilitate speed of approval once the relevant formal FDA approval is sought. In reality, however, this mechanism applies to all FDA applications rather than being restricted to particularly innovative devices, with the majority of applicants taking advantage of pre-submission communication to facilitate the approval process once the formal application has been submitted.

One such example of a positive and open communication process between the FDA and industry is the current application by Curetis for their Unyvero platform. Curetis' Unyvero platform is a rapid molecular diagnostic that has the capability to extract DNA from a range of microorganisms, including bacteria and fungi. It is the first platform to market in Europe which can handle detection of both bacteria and fungi from any native clinical samples, including many antibiotic resistance markers, and is currently going through a trial aimed at the FDA approval process, with Curetis announcing the launch of United States multi-site clinical trials in December 2012. Given the innovative nature of the platform, the regulatory pathway in the United States was uncharted, and while the product is still in the early stages of the approval process with United States clinical trials having begun in late 2012, to date it provides a strong positive example of the flexible, interactive communication between regulator and developer outlined above. Throughout the process thus far, Curetis has indicated there has been a genuine partnership between manufacturer and regulator regarding forming an appropriate regulatory pathway for the product, including evidence expectations and trial design. While the outcome of the application is yet to be determined, feedback from Curetis thus far is that there has been demonstrable effort from the regulator to actively engage with the manufacturer to ensure the process is product-appropriate.

More generally, the FDA appears to have been making efforts to bring closer coordination between their drug and diagnostic arms, which is potentially supportive for co-development candidates: they now hold joint meetings between their drug side (Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research), and diagnostics side (Center for Devices and Radiological Health).⁵⁸ Industry feedback about the FDA approach in this regard has been positive: a recent comment piece by the College of American Pathologists regarding co-development more generally cited Dr Walk (Ventana) as saying "The FDA's been very good about working with industry, both diagnostics and pharma", and Dr Hampton (Senior Director, oncology biomarker development and companion diagnostics, Genentech): "They're genuinely interested in enabling the use of diagnostics to identify patients who will or won't gain benefit from drugs. There's no question about that."⁵⁹

6.11 FDA flexibility in antibiotic approval/trial design which may influence uptake of diagnostics

Limited Population Antibacterial Drug approval

Arising from frustrations in the approval pathway for new antibiotics, a broad coalition of stakeholders, including industry and clinicians have agitated for a more flexible approach by the FDA to balancing the risk–benefit equation in approving new antibiotics, in particular those intended to treat the most serious of infections. The result has been proposals for a Limited Population Antibacterial Drug (LPAD) approval mechanism, aimed at enabling smaller, more rapid and consequently less costly trials for antibiotics intended to treat those indications by which relatively small patient populations are affected (not dissimilar to allowances made for orphan drugs).⁶⁰ This pressure from a broad coalition of stakeholders appears to have gained traction within the FDA, who appear to be moving forward on this issue in response. Should LPAD come into being, the potential implication for antibiotic manufacturers may be more rapid approval of a relevant antibiotic therapy, albeit for a limited population. Similar to orphan drugs, this mechanism will likely mean antibiotic manufacturers are able to achieve premium pricing for their products approved under this mechanism. For the diagnostics industry, this may have important ramifications for the use of diagnostics in identifying the relevant stratified population for whom therapeutic may be more rapidly approved. In particular, should pricing of the drug therapy be relatively high under LPAD, payers will have an additional incentive to limit use strictly to the target population, supporting uptake of a rapid diagnostic where available. Dr Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research, has indicated that two antibiotic manufacturers have already expressed interest in this mechanism should it be available, with the IDSA identifying seven companies whose products may fit under these proposals. The time-line and likelihood of these proposals being introduced is as yet unclear, as legislative action is yet to be taken on the proposals.

6.12 Flexibility in clinical trial requirements for antibiotic development

The challenges of enrolling patients in antibiotic trials have been well documented elsewhere in the literature (see 2010 European Observatory book *Policies and incentives for promoting innovation in antibiotic research*), with strict regulations on patient enrolment attracting much criticism from industry, who argue that antibiotic trials for critical indications are exceptionally difficult, hampering R&D in infectious disease at a time when new antimicrobial therapies are needed. Signals from the FDA indicate some agreement with this view, most notably

comments from Janet Woodcock, Director of the Center for Drug Evaluation and Research at the FDA, regarding a “reboot” for antibiotic trials, at a presentation in May 2012 to the Brookings Institution.⁶¹ Reportedly Dr Woodcock mentioned a number of areas up for discussion in regard to trial design, such as pathogen- rather than indication-specific studies (which may facilitate greater partnering with diagnostic firms, given their scientific objective tends to be pathogen identification). The use of Bayesian methods was also mentioned,⁶² a topic which has most prominently been championed by John Rex of Astrazeneca. This could involve using Bayesian statistical methods to inform how non-trial data, for example from natural history studies, could be incorporated into trial design, such as in the calculation of non-inferiority margins or non-inferiority analysis, although there are a number of issues with such approaches, not least that the strength of the prior evidence is critical. Discussions at the conference indicated that areas of priority for potential trial flexibility would be targeted at areas of unmet clinical need, and that ideally labelling would limit the usage of such approvals to restricted patient populations.

A further change which key antibiotic stakeholders have indicated is under discussion at the FDA is the potential for new regulations regarding the enrolment of patients in clinical trials: changes discussed may enable the enrolment of patients who are culture negative if they fit a number of other criteria, including positive diagnosis from a PCR diagnostic. This should significantly support the role of PCR diagnostics in trial settings.

6.13 Regulatory comparison United States/EU

When comparing the United States with the EU system of IVD device regulation, an active debate continues – on both sides of the Atlantic – around the robustness, advantages and disadvantages of both systems. As discussed earlier in this chapter the United States system, specifically for IVD devices, is characterized by a dual regulatory system that is not just about the device itself but also takes into account the environment in which the testing is performed,^a previous devices that have gone before, the intended use, etc. This creates a more holistic or “health system” approach to regulation but also attracts accusations of being “complex” and “cumbersome” for developers to navigate compared the “light-touch”, single or “tools-based” or self-certification pathway presently favoured by the EU, which allows the manufacturer to self-declare compliance with the IVDD and notify respective countries of their intention to market. Conversely, the EU system’s harshest critics tend to be the public health community, who voice concerns for patients on the grounds that it potentially allows

a This is also the case in some EU countries when considering “quality system regulation” but is not standardized across Member States.

“ineffective” devices onto the market and, due to the absence of post-market surveillance,^a the downstream impacts on patients are largely unknown. While ongoing reforms limit meaningful comparison of the two regulatory systems, important fundamental differences can be highlighted, including in the areas of IVD device regulation that remain the most contentious, or challenging, on both sides of the Atlantic.

For example, the issue of how to regulate research use only (RUO) or “for investigational use only (IUO)” products (products that a manufacturer provides to laboratories to do research/investigation). Frequently RUO instruments and reagents are used in LDTs. This can create a situation whereby rapid development and innovation maybe stifled if these tests “leak” onto the commercial market, either providing a “back door” route to market or undercutting those regulated more stringently through commercial regulatory pathways. In the EU these tests are referred to as “in-house” tests whereas in the United States they are LDTs or “home-brews”. We have seen that this is perhaps the single most pressing issue to be addressed in the United States market but also that this was the area that received most responses from the public consultation in the EU. While in both regions the issue of LDT definition, terminology and scope are similar, in the United States the current focus seems to be as much around the reality of how and who should enforce the existing provisions whereby in the EU, despite a guidance document being issued in February 2004 to clarify its situation,⁶³ the question remains one of the need to clarify or limit the scope of these exemptions. While the device industry (through AdvaMed) is strongly in favour of the FDA regulating the LDTs, there remains significant opposition from many of the (larger) laboratory associations (notably the American Clinical Laboratory Association), which favour^b keeping these provisions, citing the need (in patients’ interest) for a rapid route to market in certain circumstances. The “un-level” playing field this creates in the United States between different sections of the same industry is seen as a significant market distortion, negatively impacting the current incentives to IVD development and exacerbating a perceived laboratory monopoly.

“Optimum source and quantity” of clinical evidence in order to determine safety and performance is another area to highlight. The EU focus is “clinical evaluation” (assessment and analysis of clinical data),^c while the United States focuses on assessing safety and performance, and accepting only *clinical* data (from a variety of settings). In the EU data can also be accepted from broader, non-clinical sources and include post-market data but United States data requirements are seen as much more stringent and resource intensive than those

a The FDA has always assessed risk across the total product life-cycle.

b 86% of the 144 responses to the question in the EU public consultation on the issue.

c A term coined by the GHTF.

currently required in the EU, where there is currently seen to be “little emphasis on clinical evidence – the focus is on analytical performance”.⁶⁴ However this was a key area of debate in the IVDD review, and it seems the EU is likely to increase the requirements of clinical evidence when the legislation is enacted. The EU discussions focused on three components: clinical evidence, clinical validity and clinical utility. Despite developer concerns over the “radical” implications for IVD manufacturers, 90% of respondents agreed with the need of the Directive to provide “more detailed requirements regarding what clinical evidence is required and how to demonstrate it, while making these specific for different device classes”. Most respondents felt that current requirements were insufficient and that the clinical validity of the test must be demonstrated in the same conditions than those in which the test will be used (i.e. manufacturer needs to demonstrate the same level of clinical sensitivity or specificity as the test performed in a clinical laboratory). As the EU increases its stringency in this area, it is also possible that the United States will soften a little (at least informally) its requirements, having the overall effect of some level of convergence between the two regions. In the past, regulatory authorities would not approve devices that were inferior to the performance of predicate devices. Signs are beginning to show of a convergence towards an understanding that, while POC devices may have comparatively inferior performance, they can prove beneficial through significantly increasing access to testing.

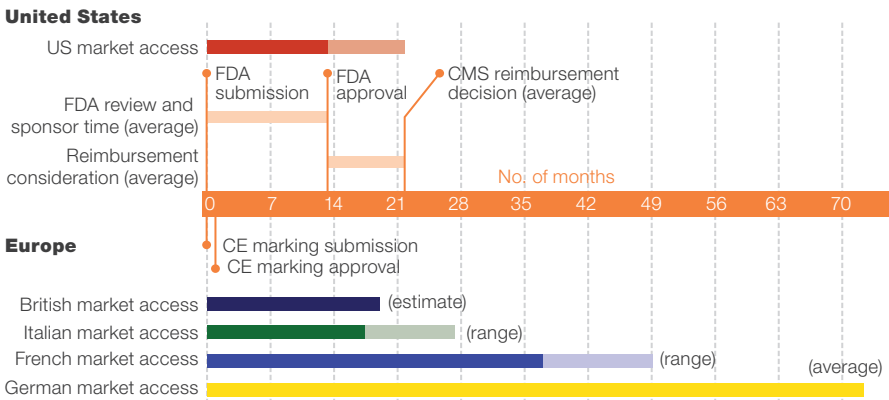
Finally, the third area of note is that of risk-based device classification and how risk is determined and categorization occurs. As outlined earlier, the class designation decision directly determines the stringency of the regulatory pathway to be pursued by the developer and therefore has significant implications for the speed and cost of getting that product to market. However, we have also seen how the designation decision itself is not always straightforward, as acknowledged directly by the regulatory agencies themselves. The commonality between the two systems here is in the shared challenge of finding the optimum (or at least a satisfactory) approach to the issue of class reassignment in the situation of designation disputes. The principal distinction between the two systems is in how the classes are determined in the first place: in the United States they have classes I–III and in the EU also a fourth (Class A–D), with regulatory controls increasing as the class number rises. Both systems currently utilize a categorization based on risk, but the method for defining risk differs.^a In the EU it is widely acknowledged that the classes listed in Fig. 6.5 do not resemble an intellectually coherent list based on risk assessment, while in the United States the three main areas used to define risk (underlying technology, intended use and possibility for misuse) inevitably introduce a component of interpretation or subjectivity. As we have

a The other key US considerations being “intended use” and complexity of testing, whereas in the EU the system is “list-based”, that is, based on a list compiled at the time the IVDD was instituted.

seen, in the EU there appears to be broad, cross-stakeholder, support for moving^a to a pure “risk-based” categorization – in line with International Harmonization proposals. However, developers again highlighted the significance of the impact of such a move, particularly in terms of additional costs (especially for Class C products) and advocated for a sufficient “transition time”. More timely access to market, better protection of public health and more robustness to technological progress were also cited as advantages.

As the FDA takes pains to point out, the reality of what its more robust system means in terms of impact on developers and ultimately patients is less than is often cited or claimed by developers. Although focusing more on high-risk devices a 2012 study in the *New England Journal of Medicine* concluded that although “time to market is quicker in the EU”, “time to patient” remains faster in the United States once reimbursement decisions are factored in (see Fig. 6.7).⁶⁵

Fig. 6.7 Comparison of time to market in PMA and reimbursement processes between the United States and the EU⁶⁶



6.14 Harmonization of the diagnostics regulatory pathway in the United States and EU

The importance of global regulatory harmonization in the field of medical devices has long been acknowledged. The growing importance of this need was formally acknowledged with the inception in 1992 of the GHTE, whose founding member countries were: United States, United Kingdom, Japan, Australia and Canada. It was convened from a voluntary group of representatives from national medical device regulatory authorities and the regulated industry and had a rotating Chairmanship. Their work to develop and promote a GHTE

a 93% of stakeholders out of 116 who answered the question.

medical device regulatory model was built on interlinking guidance documents and was accomplished through five Study Groups and various Ad Hoc Working Groups under the oversight of the GHTF Steering Committee. GHTF handed over in February 2011 to the International Medical Device Regulators Forum (IMDRF), whose mandate is the “*strategic acceleration of medical device regulatory convergence*”. Officially instituted in March 2011, the new forum has a similar structure and mandate to the GHTF but has a broader country membership (including emerging economy^a regulatory authorities and the possibility to invite “official observers” such as WHO). Its Management Committee now excludes industry^b in order that regulators can truly work on converging internal practices and procedures. During the first meeting of the IMDRF in March 2012 priority areas for moving forward were identified (remaining current as of July 2013) and are summarized in Table 6.6; these demonstrate some overlap with the previous GHTF working groups.

Table 6.6 *Priorities of the new international forum (IMDRF) for facilitating global regulatory harmonization for medical devices*⁶⁷

Work item and notes	Target outcome
<p>A review of the National Competent Authority Report system</p> <p><i>Facilitates the global exchange of relevant post-market safety information.</i></p>	Will review current arrangements and advise on opportunities for possible improvement /expansion of the current system to also include selective pre-market and other post-market actions.
<p>Roadmap for implementation of the UDI system</p>	Seeks to define the path to implementing a globally harmonized approach to a uniform device identification system.
<p>Medical Device Single Audit Programme</p> <p><i>A first step in establishing a single-audit programme – to complement the current ISO 13485 revision process.*</i></p>	Will develop a standard set of requirements for auditing organizations performing regulatory audits of medical device manufacturers’ quality management systems.
<p>Recognized standards</p> <p><i>In the “information-gathering phase” (no assigned working group).</i></p>	To create a list of International Standards used for medical device regulatory purposes that are recognized by IMDRF
<p>Regulated Product submission</p> <p><i>Will utilize existing International project that is under way.</i></p>	To result in a messaging standard that supports the electronic transmission of regulatory submissions. Will define a “table of contents” as a first step in defining a common data set.

Note: * Following a public consultation, the revision of ISO 13485 is projected to be completed in 2015 and may have substantial impact on medical device manufacturers around the world.

- a Brazil, China, Russia, India – membership of the latter three is not yet confirmed. However Russia and China are currently “observers” and have confirmed their “intention” to become members.
- b An industry request for “observer” status was met with an agreement that “representative stakeholder delegations” would be able to attend “nominated sessions” to provide an update at future meetings. Industry will continue to participate in certain work groups and items as well as the stakeholders meetings.

The efforts made in the two decades since GTHF was founded are likely to receive new impetus with the announcement in 2013 of the TTIP whose negotiations are already under way. AdvaMed in the United States made “harmonization” one of seven items on its wish list^a and in April 2013 industry representatives^b from the EU and United States met with the US–EU High Level Regulatory Cooperation Forum to announce its “enthusiastic support” for the TTIP while highlighting four areas that it would be looking for the scope to encompass: (1) mutual recognition of ISO 13485, (2) a single audit process, (3) harmonized format for product registration submission and (4) a common product tracing system using a single UDI process with interoperable databases. These four areas demonstrate significant overlap with the ongoing five focus area of IMDRF efforts (see Table 6.6).

Previously, WHO has also played a pivotal role in the quest for global harmonization of medical devices. These activities were initiated in the early 2000s with two publications,^c including WHO’s 2001 report: *A model regulatory programme for medical devices: An international guide*. The focus of this document was to provide a framework to assist Member States in establishing regulations for medical devices, which has greater relevance for countries yet to enshrine regulatory pathways, rather than to directly influence the regulatory process in key markets such as Europe and the United States. More recently, WHO’s activities have supported harmonization through the hosting of the First Global Forum on Medical Devices, held in Bangkok in September 2010. At the Bangkok meeting it was reported that approximately 30% of countries have a developed framework for regulation of medical devices, approximately 30% of countries only have partial regulation of medical devices, and the remaining countries are either developing a framework or proceeding without any current regulation. WHO has largely encouraged the use of mutual recognition as a key tool in its harmonization objective.

Beyond mutual recognition, a number of other mechanisms are in use supporting harmonization between countries, such as the signing of Memorandums of Understanding on manufacturing protocols such as Good Manufacturing Practices, or similarly Good Laboratory Practices, upon which the OECD has issued guidelines. The EU, for example, has signed Mutual Acceptance Agreements in the area of Good Laboratory Practices with Israel, Switzerland and Japan. More broadly, the liberalization of trade policy can facilitate acceptance of standards from other countries, with recent EU free trade negotiations with Japan actively supported by the key diagnostics industry body, the EDMA.⁶⁸

a Including removal of non-tariff barriers, tariff elimination, procedural fairness and IP protection <http://advamed.org/news/43/enhancements-to-trans-pacific-partnership-agreement-needed>

b AdvaMed, COCIR, Eucomed, EDMA and MITA.

c The second report, *Medical device regulations: Global overview and guiding principles*, was published in 2003.

While an in-depth analysis of industrial policy and trade protectionism in key diagnostic markets is beyond the scope of this study, one SME diagnostic manufacturer did indicate that, in their opinion, the FDA approval process was sometimes used as a barrier to entry for foreign firms, and a more detailed analysis of approval time-lines for foreign versus domestic firms in the United States may be of future interest.

At a regional level, one key player also contributing to the device regulatory harmonization movement is the Asia-Pacific Economic Cooperation (APEC) Harmonization Center launched in Seoul, Korea in June 2009. This grew out of the APEC Life Sciences Innovation Forum (LSIF), founded in 2002, which has since grown to become APEC's leading initiative on health and health sciences innovation. As part of the Center, an LSIF Regulatory Harmonization Steering Committee (RHSC) was created to advance the harmonization agenda. During the first IMDRF meeting in March 2012, the RHSC was invited to become an affiliate organization due to the similarity and complementarity of its mandates.

Outside of these global and regional initiatives and forums, individual national regulatory authorities continue to be active in the dialogue. For example the FDA's Center for Devices and Radiological Health has stated that it intends to release a position paper in on global harmonization. Further, as part of the July 2012 FDASIA regulatory revisions, the FDA has now been freed to greater participation through two new legislative provisions. The first is its new ability to "enter into arrangements with nations regarding methods and approaches to harmonizing regulatory requirements for activities, including inspections and common international labelling symbols", where previously its role was limited to harmonizing Good Manufacturing Practices, that is, the agency may now use data from outside of the United States for device approvals, further reducing the information requirements for global manufacturers.⁶⁹ Although the FDA allowing the incorporation of international symbols in device labelling has been easier and more widespread in IVD devices than other devices, the rapid pace of acceptance here is seen as particularly advantageous to global harmonization efforts. The second is a subtle expansion of the FDA's ability to "Participate in International Fora", which now includes the ability to also provide guidance to organizations running them and involving the United States public.

6.15 Industry perspectives on harmonization

While the diagnostic manufacturers participating in this study indicated that having to face a number of differing regulatory regimes did add to the costs of getting their products to market, it was clear that harmonization in and of itself was not desirable if it meant convergence towards an FDA approach, as the costs

involved in this would be significant for industry versus what are viewed as less stringent regimes in other key markets such as Europe. Further, there appeared to be little sense from industry players that the FDA would be willing to soften its stance to levels similar to those seen in Europe. Many manufacturers indicated a belief that the United States would always forge its own path rather than compromise its position, with one commentator noting that the FDA considered the EU system to be an “honour system” that goes against their philosophy of needing bureaucratic oversight of the regulatory process.

6.16 Stakeholder perception of overall regulatory processes for diagnostics

6.16.1 United States

In contrast to what is often seen as relatively “soft touch” regulation in the EU, the United States regime is considered to be far more stringent in terms of evidence requirements and the approval process. FDA requirements can be off-putting for many European manufacturers, given cost and high evidence requirements (both in number of samples, and multi-site requirements). Some device developers commented that even some United States developers are moving to European launch first, given that it is quicker, easier and may help in terms of providing an evidence base (while manufacturers cannot use European evidence for securing actual FDA approval, it may help guide the FDA process, see below), although this maybe less prevalent within the IVD device sector. The FDA likes to see evidence from Europe, it can assist in dialogue in the FDA process, and having an existing evidence body helps device developers manage FDA expectations regarding the types and levels of evidence trials are likely to yield. While many stakeholders argue this offers superior safety protection for patients, it involves trade-offs, particularly in the speed at which products are appraised and the costs for manufacturers to go through the approval process, which some manufacturers have indicated run into hundreds of thousands of dollars. These dual issues of time and cost are not new, but IVD manufacturers continue to see them as a hurdle to launching their products in what is a critical market for sales. Critically, while larger IVD manufacturers seem better placed to absorb the higher costs and administrative and technical burdens of the United States process, some of the smaller IVD manufacturers involved in our research indicated that the resource requirements needed to seek FDA approval were sufficient to discourage applications in the United States, particularly as they may be less able (due to the higher capital costs involved) to exploit the LDT route to market by setting up their own commercial labs to bypass the FDA route. Despite the FDA presently seeing more applications from SMEs than larger developers, and considering

the important role that SMEs play in innovation in the sector, it is of particular concern that even more of these organizations are potentially prohibited from entering the United States market. Both from the perspective of United States patients, who may therefore suffer a lack of access to cutting-edge technology, and for the manufacturers themselves, who are unable to fully capitalize on their R&D investments, this may lower the returns on R&D and therefore the incentive to invest. The differing evidence requirements in the United States versus Europe can lead to different market access decisions. One example is tumor markers CA 125 and CA 15-3. These had been launched in Europe, but regulators in the United States did not recognize additional medical value as compared to existing markers, although European clinicians had indicated the new markers did offer incremental clinical value. The result was the markers were available in Europe but not the United States, leading to frustrations from the United States clinical community with the FDA for restricting access to technology. Subsequently, the FDA has approved CA 125 as a valid marker for monitoring disease progression in ovarian cancer sufferers, but the issue highlights the additional challenges and delays in gaining market access faced by manufacturers looking to launch in the United States versus Europe.

Beyond the oft-mentioned issues of time and cost, however, a number of other issues have been highlighted by industry experts, including a lack of clarity over regulatory requirements. James Nichols described regulatory requirements for POCTs as a “moving target” while becoming more stringent, particularly in the case of waived tests. For example, according to Nichols, manufacturers don’t always understand what is needed to gain a CLIA waiver for a product, given the variation of approaches between reviewers, and device types. This may lead manufacturers of simple devices, which should in theory get waived status, to classify them as “moderately complex” since they understand the regulatory requirements better. The resulting trade-off is that the diagnostic must remain in the lab rather than be utilized at the point of care.

6.16.2 Europe

Diagnostic industry stakeholders interviewed as part of this research did not highlight any major issues with the current EU process of CE marking overseen by NBs. In general, the current regime is seen as one that contains relatively few barriers for developers in bringing new diagnostic products to market. Further, communication between industry and regulators is said in general to be good, with regulators receptive to the concerns of industry and key trade associations such as BIVDA and EDMA taking a positive role in supporting dialogue. The process in Europe in general is relatively rapid and comes at a much lower cost than the approval process in the United States in particular; one developer

estimated the costs of gaining approval for an incremental assay on an existing diagnostic platform as <€1 million in Europe as compared to €3–5 million in the United States, with the former taking less than a year, but the latter closer to 24 months. Manufacturers in Europe are heavily focused on the upcoming changes to the regulatory environment in the form of the new IVDD revisions currently under way, and actively participated in the stakeholder engagement process as part of the IVDD revisions. Manufacturers have highlighted that there is a risk that the dynamic of good communications and relations between industry and regulator may change under the new IVDD proposals, which brings greater scope for conflict in areas such as device risk classification.

Chapter 7

Intellectual property challenges

7.1 Introduction

Patents for genetic discoveries have been issued to encourage innovation and provide protection for financial investors in genetic research. These patents can claim a composition-of-matter (e.g. genes), methods, platform technology developed for the performed analysis, or a combination of all of these.

For stakeholders in the POC diagnostic device market, the primary areas of concern are those dealing with the rapid advances in molecular microbiology and nucleic acid-based methods, particularly the use of PCR – a technique for amplifying, detecting and cloning DNA sequences.

Today's limitations and challenges in the clinical implementation and development of new diagnostics, in particular POC diagnostics, come from the need to use and apply knowledge from previously issued patents for genes or gene-based methods of analysis.

While patent granting has been a key stimulus for the nascent biotechnology industry over the last few decades, concerns have been raised surrounding licence fees and more generally regarding restrictions imposed by patent owners that may inhibit biomedical research conducted with these foundation tools, limit development and use of new a diagnostic product, or restrict patient access to diagnostic tests.

7.2 History

Gene or genetic patents are a subcategory of biological patents. A patent provides a patent holder the right to prevent others from making, using or selling the claimed invention for a given amount of time. In the United States that time is 20 years after filing of the claim. In 1980 the first patent for a man-made whole-scale microorganism was awarded under Section 101 of the United States Patent Act. The United States Supreme Court, in *Diamond v. Chakrabarty*,¹ upheld the first patent on a newly created living organism, a bacterium for digesting crude oil in

oil spills. This patent included three parts: the method to produce the bacterium, the inoculum composed of carrier material for growth of the bacterium, and the bacterium itself.² The United States Patent and Trademark Office (USPTO) had originally rejected the patent of a living organism, but Chakrabarty appealed, won, and indeed the case has set precedent for subsequent cases. While raw natural material is generally rejected for patent approval by the USPTO, in this case the Court ruled that, as long as the organism was truly man-made, such as through genetic engineering, it is patentable. (Since the DNA of Chakrabarty's organism was modified, it was patentable.) This Supreme Court decision opened the door for the granting of a large number of biotechnology-related patents, which led to the creation of numerous companies and gave a substantial boost to the nascent biotechnology industry.³

The biotechnology patents issued since the ruling on Chakrabarty have covered a very large scope of products and technologies, ranging from drugs and diagnostics to agricultural and environmental products.⁴ A large number of genetically modified organisms have been patented, particularly in the United States. This includes bacteria, viruses, seeds, plants, cells, and even animals. Going even further, some organizations like the University of California have patented entire genomes.⁵

Patents have also been awarded for isolated genes. A gene patent is a patent on a specific isolated gene sequence, its chemical composition, the methods to obtain or use it, or a combination of these. Gene patents may claim the isolated natural sequences of genes, or a natural sequence that has been altered to make it more useful, or the use of a natural sequence for purposes such as diagnostic testing. In the United States, patents on genes have only been granted on isolated gene sequences with known functions, and these patents cannot be applied to the naturally occurring genes in humans or any other naturally occurring organism.⁶

It is important to note that patents can be awarded for methods developed for genetic testing without claiming the genes themselves. Many method patents are used in diagnostic DNA-based research done with microorganisms to either detect number of microorganisms (e.g. PCR) or to identify them (e.g. microarrays). Key foundation methods for biotechnology have been patented by various universities and licensed broadly, earning substantial sums for these research institutions.⁷

Many of the discoveries that stimulated the growth of the biotechnology industry – namely in molecular methods or technical platforms – originated in academic research. Public sector efforts to patent such discoveries (e.g. university and hospital laboratories, federally funded research centres) have been very strong both in Europe and in the United States.⁸ On 12 December 1980, the United States Congress passed the Bayh-Dole Act (P.L. 96-517, Patent and Trademark

Act Amendments of 1980), which created a uniform patent policy among the many federal agencies that funded research, enabling small businesses and non-profit-making organizations, including universities, to obtain title to inventions made under federally funded research programmes. The Bayh-Dole Act is seen as instrumental in the push by universities to participate in technology transfer activities and seek patents for their discoveries.

In a similar way, the European Parliament's 1998 law (Directive 98/44/EC) stimulated gene patenting in Europe and promoted public sector applications for patents on human genetic material. As many as a third of gene patent applications have come from the public sector.⁹

In the United States, patents are regulated by USPTO. In Europe they are issued by the European Patent Office and in Japan by the Japanese Patent Office. Each nation has its own patent law and indeed patentability does differ. A well-known example of such diversity is the case of stem cells derived from humans. While in the United States isolated stem cells are patentable as long as they have been sufficiently transformed, the European Patent Office has ruled against the patenting of stem cell lines derived from the destruction of human embryos.¹⁰

While the awarding of patents was intended to encourage innovation, unintended consequences of the patenting process and licensing practices for genetic material have started to emerge over the last decade and are presenting significant challenges to the discovery and development of new diagnostics: for example, diagnostics that make heavy use of PCR methods to amplify, isolate or identify microorganisms responsible for infection. While there may be limited debate surrounding the idea of patenting genes used in drug manufacturing or in the chemical industry, the patenting of some genes, and in particular human genes involved in diagnostics research, has sparked much controversy.¹¹ Early (and still unresolved) objections were based on the idea of genes being "part of our collective heritage" and thus not justifiably patentable. More recently the debate has concerned the liberal granting of gene and genetic methodology patents.

In Europe, objections were raised as soon as the first patents were issued in 1998 (when isolated genes, nucleotide sequences and methods for genetic testing became patentable). The legitimacy of such patents was quickly challenged by some European clinical-genetics laboratories as they created difficulties for inventing around them, increased test prices and appeared to hinder innovation, in particular for new diagnostics.¹²

In a survey of European genetics-clinical laboratories in 2008, Gaisser and Hopkins interviewed 77 heads of laboratories providing genetics testing to

health care providers across Europe to understand the impact of patent issues on their work. They identified poor awareness of patent licensing conditions across Europe, potentially leading to cases of patent infringement.¹³ They also identified that some laboratories were unaware that the price of the licence was sometimes included as a royalty in a kit they purchased or that a licence might be required to use the test. In other cases, these labs may have developed in-house tests without concern for potential patent infringement. The authors also pointed out that the lower reporting of patent infringement issues may have been due to a lower level of prosecution of patent infringement in Europe than in the United States. Only 4% (3/77) of these public sector laboratories reported having been prevented from offering a test because of a patent-related issue, while in the United States the number was higher 25% (30/122). They suggested that there are fewer patent-infringement lawsuits either because in Europe patent application requires a lengthier process than in the United States, because these patents may not have been submitted in Europe, or because patents owners had not yet taken action against the laboratories at the time of the survey.

Fewer patents are granted in Europe relative to the United States as it is more expensive and the “patentability bar” is higher in Europe.¹⁴ For example, in the United States – but not in Europe – the inventor of a patent has no requirement to actually use or develop the invention.¹⁵ In the United States, this lack of requirement has allowed patent applications for patent rights on genetic sequences that lack intrinsic marketability or definite utility. This has led to concerns that genetic patents in the United States may be granted too broadly and pushed the USPTO to revise its guidelines in 2001. It tightened patent criteria requiring inventors to disclose a clear use to the gene or gene fragment. It required that patent applications provide three new utility criteria: specificity, substantiality and credibility.¹⁶ These new requirements aimed to narrow patent claims as well as reduce the number of unsubstantiated applications.¹⁷

7.3 Patent-related bottlenecks to diagnostic development

In addition to concerns about legality and moral issues surrounding the patenting of genes, particularly human genes, new concerns have been raised about potential harm of gene patenting and licensing practices to biomedical research and public health. While many arguments for the limitation on patentability of genes and genetic methods have been worded in terms of human genes, the same arguments apply to the use of these patents for microorganisms analysis, which use the same methodology and the thus the same patents.

One concern is over the expense of patented diagnostics tests. Because many diagnostics are based on already patented technology or processes, the cost of

licences or royalties add to the basic cost of development of new diagnostics. For example, the discovery of the gene for haemochromatosis at first stimulated research in 119 United States laboratories but, as soon as a patent was issued to one of these laboratories a few months later, a third of the laboratories stopped their related research. The patent holder was asking for an up-front fee of US\$ 25 000 from academic laboratories and US\$ 250 000 from commercial laboratories, plus a fee of US\$ 20 per test.¹⁸

Another concern is linked to the ownership of the patents. A gene patent holder has absolute power for 20 years from the day the patent is filed to control any use of the respective gene. This means that they have the power to prevent others from developing and marketing cheaper public health genetic testing. With regard to infectious diseases,¹⁹ this could have grave consequences for diagnostic development and drug research surrounding antibiotic-resistant strains. Patentability of the methods to do these analyses adds yet another layer of potential obstacles inhibiting discovery and development of new diagnostics.

Licensing approaches may have a negative impact on biomedical research as well as health care accessibility. In the United States, neither patent law nor the USPTO regulates licensing strategies and practices. The owner of a patent gives rights to licensees to use their invention through two major types of licences: exclusive and non-exclusive. The exclusive licence is used in two ways. An exclusive-all-fields-of-use licence, which gives the user exclusive rights but only in a given “field” (which can be a country, a market area, a technology, or another pre-determined meaning).²⁰ The licensee can sublicense the patent within the field and the owner can sublicense to other users outside the defined field. A co-exclusive licence restricts the number of additional licensees the patent owner can grant. The non-exclusive licence does not restrict the number of licences the owner can grant after granting it to a first licensee. Owners of a given patent may give exclusive licence to some research collaborators and refuse entirely the use of their patent to other potential users and thus may prevent the further development of certain new diagnostics that could compete with theirs and be potentially cheaper. Another potential problem with exclusive licensing of patents is visible from the health care delivery aspect, as patients who desire second-opinion testing from an independent laboratory cannot have such a test done if there is a sole licensee/provider controlling where the diagnostic test can be done and who can do it. There is unease that patents granted on DNA testing cannot be easily “invented around” and are thereby limiting options for developing and providing alternate genetic diagnostic tests, in particular when broad patents are granted.²¹

Andrews points out that owners of gene patents often do not let anyone else screen a gene sequence that they have patented and thus prevent the discovery

of other mutations on that same gene that may potentially be associated with a given disease.²² Multiple disease-associated mutations are often found when other laboratories screen for a patented gene. This is the case of the cancer-associated gene BRCA1, for which French researchers found that only 10–20% of potential mutations were detected by the Myriad Genetics test (Myriad Genetics being the owner of the gene and of the methods to detect breast cancer by comparing their gene sequence to that of a patient). Andrews also stresses that there is a common apprehension that gene patents may compromise the scientific method, as researchers and organizations have financial incentives to file for patents and push for use of these genes in diagnostics before there is sufficient data to provide a good evaluation of the predictive accuracy of a new test for a given disease.²³

In response to these concerns, various analyses have been conducted, and discussions and conferences have been held in Europe and the United States to explore the potential of using litigation, legislation, patent pools and compulsory licensing to ensure that genetic patents do not impede the practice of medicine and scientific progress.²⁴ The ultimate goal of these analyses has been to look for and document potential gene patent interference with biomedical research and health care, propose solutions and advise governments and their public health-related branches. Some examples are given below.

7.3.1 Europe

To evaluate the magnitude of the challenges posed by existing patents to the discovery process, Gaisser and Hopkins surveyed European labs and found that they often had little experience in dealing with patents and needed help to understand or be aware of the patent limitations and requirements.²⁵ By comparison with the United States, they found that in Europe patents infringements by testing laboratories were not as systematically prosecuted, sometimes because the patents were not yet granted in Europe or because the testing laboratories ignored, consciously or not, the existence of a patent. They suspected that in Europe public and private health insurers would eventually have to come to terms with the fact that costs could rise as patents became more respected and financial stakes increased.

In 1999 the Human Genetics Commission (HGC) was created in the United Kingdom to give the government advice on human genetics with a focus on social, ethical and legal issues.²⁶ In October 2010 a seminar was held by the HGC to evaluate the impact of DNA patents on diagnostic innovation. It included a wide range of stakeholders and reviewed evidence in order to foster policy deliberation on what would constitute “fair and equitable” positions in the field of IP for diagnostic testing. The recommendations made by this group were published as a report summarized by Stuart Hogarth and Michael Hopkins.²⁷

The recommendations of the HGC to the United Kingdom government were to review all guidelines on patenting and licensing, establish a governmental monitoring of biomarker IP (genes and other biomarkers), designate a government body responsible for policy implementation, continue gathering independent evidence and pursue analysis of the impact of IP and patents on diagnostic innovation (see Appendix D for more details). The HGC and its recommendations played an important role in helping the public and the United Kingdom government to better understand the issues created by developments in human genetics. It was closed and replaced in 2012 by a new committee, the Emerging Science and Bioethics Advisory Committee. The goal was for the Committee to take on the responsibilities of the HGC, while adding a broader overview than human genetics, and to monitor the implementation of recommendations made by the HGC.²⁸

7.3.2 United States

In the United States, advice to the government on policy issues raised by the development and use of genetics technologies is given by the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS), which reports to the Secretary of Health and Human Services. In March 2010, the Committee published a report on the effects of patents policy and licensing practices on basic genetic research, genetic test development, patient access to genetic tests, and genetic testing quality. The report also offered advice on how to deal with identified problems.²⁹

The Committee acknowledged that there was ongoing debate surrounding the evaluation of patent policy and licensing practices, and that indeed more evidence was needed. However their main observations and conclusions validated many of the concerns expressed in Europe. For example, some patents limited rather than promoted availability of testing and some patent owners created difficulties for patients seeking to obtain second opinion since no independent laboratory was allowed to run the test except the sole provider. They also found that scientists, particularly in academia, were not stimulated in their research by the prospect of obtaining a patent. By contrast, in the private investment world patent-seeking was a larger incentive, but more from the therapeutic application point of view than that of diagnostic discovery and development.

The SACGHS committee made six recommendations to the DHHS intended to help address existing concerns and eliminate potential barriers to development of promising technologies or assays in future. The first two recommendations were regulatory. They recommended exemptions from infringement liability when developing or selling a test intended for patient care and promotion of non-exclusive licensing of diagnostic genetic/genomic technologies to ensure

access. The other recommendations were general guidelines to improve existing rules and regulations. They recommended mechanisms to make the licensing process more transparent and the establishment of an advisory body to continue monitoring and advising on the health impact of gene patenting and licensing practices, to provide expert advice to the USPTO regarding scientific and technological developments related to genetic testing and accompanying technology, and to make sure that genetic tests of clinical value were made accessible. (See Appendix E for more details.)

Congress has been reluctant to explore the health system impact of gene patents. In 2002 and 2007 two versions of a bill called the Genome Research and Accessibility Act proposed a new law to exempt health care providers and researchers who carried out genetic testing in diagnostics, prognostics, predictive tests or basic non-commercial genetics research from being sued by holders of the patents. On both occasions the bill died and was referred to committee for further evaluation. Even a bill with the simple goal “To direct the Director of the Office of Science and Technology Policy to conduct a study of the impact of Federal policies on the innovation process for genomic technologies, and for other purposes”³⁰ also died in 2002 and was referred to committee.

Furthermore, until recently, most of the patent litigations revolved around which entity (often a university vs. a biotech or pharmaceutical company) had the right to a specific patent. Neither player was interested in testing whether a gene patent by itself was appropriate because both sides wanted to reap the financial benefit of that patent.³¹ Only very recently has the issue of patentability of human genes come to the fore, not only from a moral or ethical point of view but also from a health care and scientific perspective. This is illustrated by recent lawsuits against the Myriad Genetics patents that challenge the basic tenet of human gene patentability. One of the questions raised in this lawsuit and taken on by the Supreme Court was whether “Human genes are patent-eligible subject matter”.³² In 2013 the Supreme Court ruled unanimously against Myriad Genetics, arguing that the mere isolation of genes found in nature does not justify patentability.³³

Case study: Myriad Genetics and patent for the gene associated with breast cancer

In 1994, the University of Utah and the United States company Myriad Genetics filed a patent for the isolated BRCA1 gene and cancer-promoting mutations, as well as methods to estimate the likelihood of getting breast cancer.³⁴ Then Myriad, in collaboration with various partners including the University of Pennsylvania, isolated and sequenced the BRCA2 gene and filed a patent

for that gene in the United States in 1995.³⁵ Myriad is the exclusive licensee of these patents and has enforced them in the United States against clinical diagnostic laboratories.

In 2001, Myriad Genetics was granted the European patent related to the BRCA1 associated with breast cancer. The patent (EP699754) covers all methods for diagnosing breast cancer by comparing a patient's BRCA1 gene with the BRCA1 gene sequence that Myriad describes in its patent.³⁶ This patent implied that testing should be done through Myriad's laboratories or by a laboratory that has obtained a licence to do the test. Both the breadth of Myriad's BRCA1 patent and the company's refusal, in some cases, to grant licences for BRCA1 mutation detection has led to concerted and international opposition.³⁷ For example, French physicians voiced concern that such a mandate compromises patient care³⁸ and gave evidence that Myriad's test evaluated only a fraction of potential BRCA1 mutations.³⁹

In the United States, objections to the Myriad patents started in 2009. The American College of Medical Genetics and the College of American Pathologists raised a challenge to the Myriad patent complaining that the patents on BRCA1 and BRCA2 and associated methods prevented them from doing their own diagnostic tests and interpreting the results, and were thereby preventing patients from getting a second opinion – an option that is normally considered a basic right of patients. The case of *Association for Molecular Pathology v. Myriad Genetics* challenges the general validity of gene patents in the United States. Myriad's claims for its patents were first supported by a District Court (New York) but were later overturned by the United States Court of Appeals for the Federal Circuit. The Supreme Court was solicited and requested that the Court of Appeal review the case. The Court of Appeal maintained its decision. The United States Supreme Court granted a petition for *certiorari* (meaning that they agreed to hear the plaintiff's appeal) in November 2012 in the case of *Association for Molecular Pathology v. Myriad Genetics Inc.* (United States, No. 12-398, *review granted* 30 November 2012).⁴⁰ On 13 June 2013, Justice Thomas delivered the unanimous opinion of the Court that patents for isolated genomic DNA are invalid under section 101 of the Patent Act (35 U.S.C. § 101).⁴¹ The Court agreed with the petitioners of the lawsuit that Myriad's uncovering the exact location and genetic sequence of the BCRA1 and BCRA2 genes does not render the genes patent eligible as they are not new composition of matter. The Court thus struck down patent claims on genomic DNA that has been simply "isolated" from the body as not meeting the patentable subject matter under section 101 of the Patent Act.

By contrast, the Court let stand that synthetically created DNA (cDNA), which contains only protein encoding regions of a gene (exons) without the natural

non-coding introns regions, is patentable. Also, the Court did not address methods claims or gray areas such as the status of “purified” or altered genomic DNA. It addressed only “isolated” genomic DNA.⁴²

The consequences of this ruling will be global and significant. They will be global because, as described earlier, most national patent offices, including the European Patent Office and the Japanese Patent Office have followed the USPTO initiatives over the last few decades in moving towards greater harmonization. As described earlier, they have also granted many patents for isolated human genes. The United States Supreme Court ruling, which is now going to force the USPTO to change course on the granting of some gene patents, is likely to be followed by these organizations as well.

The immediate consequence of the ruling is that tests for breast and ovarian cancer can now be performed by laboratories outside of Myriad. Dr Harry Ostrer, one of the plaintiffs in the case, will soon offer that test, and suggests that this competitive landscape should drive the test price down.⁴³ However, while many prospective competitors may have already been preparing to enter the BCRA market because the Myriad patents were soon to expire, it will take time for them to develop the technology, go through the regulatory approval process and be accepted by the insurance providers, thus the test price may not drop as quickly as patients may wish.⁴⁴

One of the important and immediate consequences is that patients will now be able to obtain a “second opinion” from another lab for specific diagnostic tests previously done exclusively by a single company, like Myriad.

In a larger context, every patent that, like Myriad’s, claimed an isolated genomic DNA coding for a specific protein is now invalid. By contrast, patent claims that are limited to cDNA versions of genes will continue to pass the acceptance “threshold” test of being a man-made molecule and be patentable.

As discussed earlier, R&D of diagnostics was often hindered by the existence of patents (if and when researchers were aware of these patents). This should cease to be the case for genomic DNA patents.

Where to?

Patents for genes and genetic methodology are at a turning point. The potential negative impacts of these patents on diagnostic development and on health care are starting to be identified and acknowledged. Proposals have been put forward to address them without destroying incentives for the financial rewards provided by new discoveries. The recommendations by various private- and government-sponsored committees were tailored to address the issues pertaining

to diagnostic discovery and patient access to diagnostic tests while maintaining patent-related incentives for therapeutics development and commercialization. It is clear that establishing the negative impact of gene patents is an ongoing and evolving process, and that more data is needed to guide the agencies in charge of regulating patents and patient access to diagnostic tests. Genes straddle the boundaries between patentable and unpatentable substances, and the debate on how to balance business and health care needs must continue. New models will likely be needed.

Chapter 8

Demand-side issues

8.1 Introduction: complexity in demand expression

In the case of some technologies, and indeed diagnostics in particular, true demand – defined here as the technologies most needed or desired to improve patient outcomes – may not be expressed due to a multitude of factors. First, health care is typically provided within a complex organizational structure that influences demand. For example, the governance arrangements for deciding to adopt a new POC diagnostic often include many players. In hospitals, there is typically a team of people involved in decision-making – a mix of clinicians and laboratory staff, with the involvement of experts from the clinical specialties that will make use of the device, for example consultants from emergency medicine and intensive care. Other departments that may be involved include the pharmacy and staff involved in the maintenance of equipment. In some hospitals there is a dedicated POC testing manager who can help guide the decision-making process. These decisions are not made by the patient but rather on his or her behalf via agency relationships. Further, the demand by a clinician, for example, may be expressed by those who are unaware of the price of a particular technology. Additionally, the device is usually ultimately covered by payment by a third-party organization. Demand is also influenced by other factors, such as ethics, altruism or other financial and non-financial incentives in the health system.¹ These complexities are also compounded by the difficulties in building a strong evidence base surrounding the relative merits of these technologies that includes their respective cost–effectiveness for clinical units, for hospitals and for society more broadly given their potential to help slow resistance to antibiotics.

From the perspective of diagnostics developers, these complexities can give them an altered view of demand and the willingness to pay for the technologies that meet it. Fragmented decision-making in many health care markets makes it extremely difficult for companies to understand the requirements of all key stakeholders. To be selected for use, a device might have to be approved by a national or regional authority, selected by a health care provider, specified by a particular clinical team and then chosen by doctors, often in consultation with patients. Finally, it may be the patients' own reactions to the device that define

its success in use.² Ultimately, the basic task of identifying the customer can be complex. Indeed, developers need to understand the needs of the appropriate staff using and interpreting POCTs. Indeed, there are numerous examples of technologies being developed that lack the necessary characteristics for clinical adoption. One interviewee emphasized the over-reliance of the developers of a sepsis-related technology on microbiologists rather than physicians. The lack of understanding of “real-life” clinical decision-making has effectively rendered the device useless in many settings in which it was most needed. Another example of a good technology that failed to fit into the wider clinical context comes from a study into whether carrying out a POC blood test at a patient’s bedside would reduce the LOS in an emergency room setting. The POCT that was used only provided a limited biochemistry profile. While POC testing delivered quicker test results, the researchers found that patients were not leaving the hospital any faster because of the need to wait for additional necessary tests to be analysed by a central laboratory.³

A number of developers and industry consultants have raised the issue of divergent views among the microbiologists’ community as a challenge to gauging the priorities and focus of end-users of their products: even at institutions facing similar challenges, views on both pathology priorities, and desired solutions are often different. This adds another dimension to the fragmentation in the marketplace, and means diagnostic manufacturers need to engage with a wide range of professionals in the microbiology community in order to fully understand the potential demand for a given product.

8.2 Engagement to improve developer understanding of demand

The only way that developers can sufficiently understand true demand in order to produce a diagnostic capable of altering the patient care pathway and improving health outcomes is to work very closely with clinical staff and patients. There is evidence that a significant gap exists between the views of frontline clinicians and industry professionals on what constitutes an ideal POCT. In a recently published study by academics from Johns Hopkins University, diagnostic users and developers were surveyed about perceived barriers to using POCTs for STIs.⁴ The industry representatives identified problems such as complexity, unreliability and difficulty reading test results, whereas the clinicians placed much greater weight on workflow factors, such as the time frame of a test and how well it integrates into existing work processes.

This disparity in perceptions may, in part, explain why there are still POC diagnostics being marketed with characteristics that are potentially major barriers to

adoption in practice. In an online survey of STI experts and professionals, barriers to routine use of POC diagnostics that were cited included tests that could only be undertaken in a laboratory and tests that interrupted work flow⁵. There are also examples of products reaching the market without sufficient preparation being made for their adoption; for example, when the breast cancer drug, Herceptin was initially approved for use in the United Kingdom, consideration had not been given to how the companion diagnostic, which is used to establish clinical eligibility for treatment, would be funded.⁶

At a conference at the University of Oxford in 2011 that brought together industry professionals, clinicians, academics, and regulators, a wide range of benefits were identified that could be achieved through early engagement.⁷ These included supporting prioritization of the development of new tests, increasing understanding of market trends that may influence a test's future uptake and, through confirming unmet needs, improving the evidence base used to justify investment in R&D to investors. Engagement can also facilitate an understanding of how a new test will change existing care pathways and how it will change resource utilization – for example whether it could enable disinvestment in existing processes. As clinical needs and barriers to using a test vary depending on the clinical setting as well as contextual factors, such as the availability of pathology services,⁸ the approach to engagement needs to reflect this heterogeneity.

At present, although there is engagement between industry and clinicians, it is often informal. Carol Cresswell, POCT Manager for Newcastle Hospitals in England, reported that her team's primary engagement channel with industry is visits from industry representatives, particularly from larger companies. This provides an opportunity to offer views on areas of unmet need and make suggestions on enhancements to devices; however, she felt that this was not ideal and was keen to see a move towards a more structured approach. The type of staff that the industry is in routine contact with, for example through providing sales, training and support for their products, are not always the frontline clinicians who will be using tests. Future users of a proposed test are best placed to identify problems with current processes and the potential impact of introducing a new device. Another challenge cited by Doris-Ann Williams MBE, Chief Executive of BIVDA is that compared to the pharmaceutical industry, diagnostic companies tend to have a much smaller sales force and so may have less opportunity for day-to-day contact with clinicians.

Dr Gary Thorpe, Biochemistry Director at the University of Birmingham believed that when industry seeks to work jointly with health professionals, there is sometimes unease among clinicians and suspicion about industry's motives. This is a potential barrier to improving engagement. A physician from the United States interviewed for this study reported that if they experienced a problem with a

diagnostic test, they were more likely to contact a regulatory body than pick up the phone to report the problem to the manufacturer. When questioned further, their view was that they simply did not trust the manufacturer. In the United Kingdom, there has been recognition at the highest levels within the NHS that suspicion such as this can hinder partnership working;⁹ there is a need for both the NHS and industry to work towards a more collaborative culture, for example through improving understanding of the benefits to society of a more joined-up approach.

While patients may not have as good an understanding as clinicians of the complexities of care pathways, they can offer an important insight into the patient experience – for example the impact of delays in receiving test results in outpatient care. To date, there has been limited exploration of patient acceptability of POC testing,¹⁰ but emerging evidence suggests that patient preferences can influence the uptake of a new diagnostic. For example, in a study evaluating the effectiveness of the BioStar Chlamydia OIA POCT, 6.8% of female adolescents tested at a public clinic in Atlanta were unwilling to wait 20 minutes for the results.¹¹ A concern raised by Dr Ron Daniels, Executive Director at Global Sepsis Alliance, was that where engagement is narrow, individual or professional agendas may shift the focus of debate away from patients. He sees involving patient groups as a way to balance this effect and ensure that tests met patient needs.

To improve engagement, a number of national strategic initiatives have been established. In England, NHS organizations are being given the opportunity to bid for funding to host Diagnostic Evidence Co-operatives (DECs), which are designed to facilitate collaborative working between health professionals, the diagnostics industry, providers of NHS pathology services, academia and patient representatives, as well as support the generation of real-world evidence of the clinical utility and cost-effectiveness of devices.^a In the United States, the National Institute of Biomedical Imaging and Bioengineering has supported the development of the POC Technologies Research Network (POCTRN).¹² Institutions that have been designated POCTRN centres offer practical support to industry, such as needs assessment to inform device design and evaluation of the potential clinical impact of prototypes.¹³

8.3 Determinants of and barriers to uptake of new POC diagnostics

In 2001, the United States Institute of Medicine voiced the concern that science and technology are advancing more rapidly than health systems can consistently

a As of July 2013, these hosts had been announced as the universities of Oxford, Leeds, Newcastle and Imperial College.

deliver them.¹⁴ In their ground-breaking report, *Crossing the quality chasm: A new health system for the 21st century*, the Institute identified a range of shortcomings, including constraints in exploiting the revolution in information technology and poorly organized delivery systems, both of which have significance in the context of the introduction and uptake of diagnostics in health care. In 2000, the Center for Health Care Quality at the University of Missouri estimated that the time lag between research identifying more effective treatment options and their adoption in practice was approximately 17 years.¹⁵ In the United Kingdom, the 2002 Wanless Report cited the United Kingdom as a “late and slow adopter of medical technology”¹⁶ and, more recently, in a report into how the adoption of innovation could be accelerated in England, the Department of Health singled out diagnostics as a key area for action.¹⁷

Studies on health technology adoption rates in the NHS in the United Kingdom have illustrated how the diffusion rate is dependent on the nature of the technology. While the cholesterol-lowering drug, simvastatin was adopted very rapidly, it took six years from the launch of coronary stents to rapid diffusion across the United Kingdom and a further two years before they were in widespread use. In the case of MRI scanners, only 70% of hospitals had access to the technology 17 years after it became available.¹⁸ More recently, it has been estimated that it takes around 10 years for widespread adoption of a new diagnostic test within the NHS.¹⁹

8.3.1 Quality control arrangements

Training

By design, POC devices are often simple to operate, but the potential consequences of inadequate training, including delayed or incorrect diagnosis, are significant. Real-life anecdotes shared by laboratory staff²⁰ include POC glucose tests appearing abnormally high where the test strip has been contaminated by the patient or health professional not washing their hands, pregnancy tests being misinterpreted because the faint indicator line was not detected in the poorly lit sluice room where the tests were being interpreted, and the over-referral of patients to a specialist endocrinologist because the device used on wards to monitor patient urine chemistry was changed and staff misinterpreted readings from the new device. A small study across three hospitals in Northern Ireland in 2011 provided evidence to suggest that the quantity of user errors may be significantly higher for POCTs compared to central laboratory testing.²¹ Many of the errors identified in the study could have been avoided through better training or improved adherence to standard operating procedures.

To help ensure that users are competent to use tests, many countries require training either as best practice or as a regulatory obligation. In the United States,

under the CLIA of 1988, all facilities examining human specimens for diagnosis must register with the CMS and obtain CLIA certification. However, the nature of registration and subsequently the training requirements vary according to the nature of the diagnostic device being used.²² In a number of circumstances, the FDA has waived tests from regulatory oversight, including where they are for home use, where the test's simplicity makes it unlikely that erroneous results will be generated and where there is no reasonable risk of harm if tests are incorrectly undertaken. Where a provider is only offering waived tests, they can choose to apply for a "certificate of waiver"; this exempts them from routine inspections but they must adhere to the manufacturer's instructions for performing the test and best practice still applies.²³ In 2005, to support facilities, the CDC and the Division of Laboratory Science and Standards jointly published guidance on "Good laboratory practices for waived testing sites".²⁴ This recommends that careful consideration is given to ensure adequacy of training, including evaluating competence before staff perform training; ensure competence is maintained, particularly where testing volumes are low and making provision for turnover of staff. The guidance also advises that training is documented and suggests key areas that should be covered, including safety and quality control procedures.

Where a facility intends to use tests that have not been waived from regulatory oversight, they need CLIA certification and to comply with a range of regulatory requirements; on training this includes ensuring that, prior to testing, staff have education and experience relevant to the type and complexity of services offered and have demonstrated their competence, and that policies are in place to assure continued competence. For facilities using waived tests, an alternative to applying for a CLIA Certificate of Waiver is establishing an agreement to work under an existing laboratory with CLIA certification.

Training can be a barrier to the diffusion of a new diagnostic. The view of Simon Kimber, project manager of Metro-POCT – a training initiative in the north-west of England – was that the greater the burden involved in organizing training, the less likely it is that a provider will adopt the technology. Typically, training is provided by device manufacturers; Carol Cresswell, POCT Manager for Newcastle Hospitals in England reported that their contract with manufacturers will often include provision for training "cascade trainers", who can train colleagues within the hospital, as well as periodic top-up training during the term of the contract. However, a risk of relying solely on manufacturers as trainers is that the quality of training may not be adequate and they may omit critical information, such as device limitations and contraindications. Lynda Petley, Manager of the POC Testing Team at Frimley Park Hospital in England, witnessed a trainer employed by a manufacturer informing users that their device was so simple users can never make a mistake. This led staff to believe inappropriately that the system was foolproof. In her view, there is a case for training being

independent of manufacturers and, where training is manufacturer provided, service commissioners should be prepared to mitigate the risk by monitoring the delivery of training.

Access to adequate training in primary care was a particular concern highlighted by interviewees. In secondary care, because of proximity to the lab, laboratory staff are more likely to be aware of the introduction of a new diagnostic and are in a position to offer support; in primary care, however, a GP practice will often procure a device without the lab's knowledge.

Based at Manchester Metropolitan University, Metro-POCT is a two-year proof-of-concept project to improve access to training on POC devices in the north-west of England. Their philosophy is to complement rather than duplicate the training provided by manufacturers and, as one part of their deliverable, they are aiming to work with manufacturers to offer a comprehensive "one-stop" training solution that is simple for users to arrange. Only about 20% of the training that Metro-POCT provides relates to practical device use, the remainder of the curriculum covers device storage (including expiry date checking of consumables and cold chain requirements), sample handling, interpretation of results, clinical waste disposal, health and safety, quality control arrangements, standard operating procedures, and how to integrate use of the device into normal clinical practice. A challenge that project manager Simon Kimber identified as an independent training provider was coping with the variation in device design between different manufacturers.

Some hospitals also offer training to primary care facilities as a commercial offering. Frimley Park Hospital has a team of POC device trainers and offers training and competence testing on request to GP practices. Lynda Petley, from Frimley Park Hospital, viewed offering training in this way as a valuable aspect of a quality-managed POC testing service; not all hospitals will have the resources to provide this service, however, and where it is not mandatory there are problems encouraging GP practices to arrange adequate training, particularly where they need to independently fund it.

A significant proportion of the cost of delivering face-to-face training is the time for a trainer to physically attend a site; both initially, when new staff members join and then for periodic refresher training to support re-certification. One approach, piloted in 2008 by the United States Department of Veterans Affairs (VA), was to deliver training on use of an HIV POCT over the internet to a remote primary care facility using a range of tools, including a webcam.²⁵ Participants in the pilot were satisfied with the approach, which proved to be a practical solution to the challenge of delivering training to the VA's geographically remote facilities and was more cost-effective than in-person training. The researchers also found that, in the six months after the training was delivered, there was a

significant increase in the number of tests being undertaken at the facility. Five years on, Dr Herschel Knapp, one of the researchers behind the original study, reported that online training was still being delivered where appropriate, both for initial training and re-certification, and the benefits reported in the original study appeared to be sustainable. Rather than being the default option, online training has become one of a menu of training methods that the VA uses to meet the needs of either POCT operatives or their trainers. In organizing training, a lesson shared by Dr Knapp was the importance of scheduling training, ensuring that it is organized for a dedicated training time slot when all staff are available or alternatively organized in shifts to ensure that all staff members have the opportunity to attend.

The task of ensuring that all users have received appropriate training can be considerable; Lynda Petley, Manager of the POC Testing Team at Frimley Park Hospital, said her team is responsible for 27 different devices across four hospitals, with training requirements specific to the nature of an individual device. Over 4000 staff are trained annually, with update training and competence checking dependent on the complexity of the device and the frequency of use. In the event of clinical mismanagement of a patient based on a POCT result, the hospital needs a full audit trail to investigate the incident; this could include every aspect of the test, including who undertook the test, when they were trained, who trained them, trainer competence and who maintained the device. In England, each hospital has a different approach to how they manage assuring user competence; in some hospitals, records of training and competence assessment are stored as part of a staff members' employment record. To support governance, Lynda Petley was keen to see POCTs including secure login functionality to ensure that only centrally authorized users who had proved their competence could access devices.²⁶

As mentioned earlier, overall QC requirements for devices are becoming more burdensome²⁷ and could increasingly serve as a bottleneck in the market for devices requiring extensive QC measures. James Nichols illustrates the extent of the newer requirements.

Traditionally we have bottles of reagents in our chemistry analysers in the laboratory, and we do testing out of those bottles of reagents periodically to make sure that those reagents are still good.²⁸ We do two levels of liquid quality control once a day, and that would tell us if that bottle is still good on our analyser until that bottle runs out, and then we'd run quality control on the next bottle when we opened it up, and periodically until we finished that bottle.²⁹ But now that we have single-use cassettes, we're running quality control on that cassette. It uses up the whole test and you don't know that the next cartridge is actually going to behave the

same as the cartridge you ran the quality check on. How do you perform quality control on those cartridges?³⁰ You don't. You quality-control the lot. You insert internal control processes from the manufacturer with each and every test. So this is a different strategy for running quality control that I think is going to challenge the regulatory process in terms of approval. The question becomes, 'Is this safe and effective when we put it in the hands of general users that don't have a lot of laboratory experience?'³¹

The greater quality control also extends to multiplex assays.

Consider the DNA chip that may contain 500 different tests. Do you have to run two levels of quality control on each and every one of those 500 spots on that array? Or, is it sufficient to run a couple of process controls on this card and say that the card is working appropriately? That question is open, and it's still being debated. But of course there are certain processes for which it is physically impossible to test every aspect of a card, and this is going to come down to risk management.

More and more it will be the laboratory directors determining what is effective in their settings for the way that they are using those test results, and the specific control processes for that device, as factors for how they will manage quality control. The balance between internal engineered control processes on the device and the liquid quality control that the laboratory is analysing, plus the frequency of that quality control, is going to be the responsibility of the lab director more as this risk-based quality control gets implemented.³²

Finally, related to the issue of training is the idea that the expertise of clinical staff is only maintained if there is sufficient frequency of use of the device. So while there may be demand for a particular technology, and indeed the use of it could really improve patient care, ongoing training costs may not be justified unless a critical mass of relevant cases exists.

8.3.2 Reconfiguration of pathology services

POC diagnostics are considered to be "disruptive technologies", or technologies able to have a significant impact on the systems into which they will be introduced. Where the introduction of POC diagnostics is not properly managed, it can leave technicians working in central laboratories concerned about how it will impact on their roles and impact on the quality of patient care, for example through clinicians misinterpreting test results because of insufficient training or out-of-date tests being used due to inadequate quality assurance procedures.³³

While some interviewees reported good communication and engagement between laboratory and clinical staff, others felt that engagement was inadequate. Among concerns cited by numerous interviewees were instances of representatives from device manufacturers providing equipment to clinicians directly without the relevant POC testing manager in the laboratory being aware. In the United Kingdom, to prevent this problem from occurring, the industry organization, BIVDA, has issued guidance to its members to “develop and rigorously enforce a policy of involving POCT Managers in the initial stages of marketing POCT products in secondary care, primary care and the community”.³⁴ A particular frustration of one laboratory representative interviewed was that there had been occasions where the laboratory could have offered the same turn-around times as a POC diagnostic, but clinicians had never raised turn-around times for that particular test as a problem before becoming aware of a POCT.

One clinical staff member, who had sought to get laboratory “buy-in” to introducing a POCT across multiple hospitals, felt that a key challenge was securing the trust of laboratory staff, who may take ultimate responsibility for use of the device in their hospital. Clinical staff reported that, in the early days, when there was limited awareness of POC testing, gaining laboratory support could be difficult; now, as long as there is good evidence to support adoption, they didn’t expect many problems. They did, however, report experiencing exceptional cases where they perceived laboratory staff to be blocking the uptake of a diagnostic, regardless of how strong the evidence base to support adoption; they attributed this to “human factors of ego, power and control”, influenced by the attitude of the laboratory director, for example whether the latter was progressive or a traditionalist.

One approach tried at the St. Alexius Medical Center, Bismarck, North Dakota, involves bringing laboratory and nursing personnel together to jointly direct the hospital’s POC testing programme.³⁵ This delivered a range of benefits. By involving nurses in the evaluation of new tests, potential problems were identified before instruments were purchased. For example, there were instances of nursing staff finding devices difficult to use that laboratory staff, with a different type of experience, considered simple. Working jointly also helped facilitate nursing staff’s acceptance of new devices with the view that “nurses were more willing listen to nurses”.

One industry representative interviewed for this study believed that industry has historically taken the approach of marketing POC testing as an alternative to laboratory testing when the more appropriate approach is as part of a unified pathology service with laboratory staff and clinicians working hand-in-hand.

A wide range of resource and organizational considerations must be taken into account in implementing POC testing. These include changes in staff roles and responsibilities, training and competency assurance, putting in place new processes (for example, for ordering and storing test consumables), results handling, quality assurance, ensuring appropriate arrangements to dispose of clinical waste, and equipment storage (for example, if the test is bulky or requires cold chain storage).

While POC testing has the potential to empower clinical staff, it can also be viewed as a burden, an additional duty that is introduced without staffing being increased.³⁶ In a review of the introduction of a POC blood analyser in a rural hospital in New Zealand, respondents reported increased workload. However, views were conflicted: while there was an argument that wards were busier because staff were managing patients who previously would have been transferred, this was balanced by patients being discharged more quickly because staff had direct access to the POC device.³⁷ One interviewee cited personal experience of concerns being raised by a nursing union that the introduction of POCT was overburdening staff. A related point emphasized by another interviewee suggested that, in giving nurses a greater number of duties surrounding diagnosis, POC testing can become an unwanted distraction from proper patient care.

In the United Kingdom, a 2006 independent review found that POC testing was contributing to the fragmentation of pathology services in England, with testing increasingly being undertaken by clinical staff without any reference to pathology practitioners.³⁸ Recommendations made in the associated report included reviewing the role of the pathology workforce, for example pathology staff providing advice on the use of POC diagnostics and taking responsibility for quality assuring decentralized services. Six years on from the report being published, the NHS is continuing to work towards implementing these recommendations.

8.4 Diagnostic and clinical guidelines

Beyond regulatory and reimbursement challenges, clinical awareness of effective diagnostic technology is critical for diffusion of appropriate technologies. Clinical guidelines, or the use of “best-practice tariffs”, which may incorporate appropriate diagnostic use into the accepted care pathway, are potentially important tools for supporting the uptake of new and effective technologies, given the ability of good guidelines to impact clinical behaviour.³⁹ An Audit Commission report on best-practice tariffs, however, found that a detailed knowledge of these tariffs was “not the norm” among clinicians they engaged with for their report, with differing views as to whether educating junior clinicians on them was useful or not, given their decision-making was more likely to be driven by medical evidence than the financial incentives associated with best-practice tariffs. Only

one foundation trust had made achievement of best-practice tariffs a component of the medical director's objectives.⁴⁰

In addition to guidelines on the appropriate use of diagnostic technology, advice on discontinuation of old/less effective technologies is also seen by many industry developers, and funders, as critical for uptake of new technology: guidelines should look to incorporate direction on this side as well as addressing uptake of new technology. Cost-effectiveness of new platforms is reduced if it is not possible to decommission existing diagnostics, for example due to contractual commitments with suppliers. This may particularly be the case where hospitals have either been loaned, or leased, diagnostic capital equipment at favourable rates by the manufacturer. The placement of equipment within facilities is then linked to contractual agreements to perform a minimum level of tests or volume of consumables such as reagents. This "razor-razorblade" model is frequently employed by manufacturers where the analytical platform is particularly expensive and/or complex, for example as may be the case for many molecular diagnostics. As these agreements tend to be used where the primary platform is of prohibitively high cost for hospitals or labs to purchase outright, the relevance of this issue to POC testing will also likely depend on how expensive the testing device is, particularly relative to the cost of the consumable element. A number of studies have attempted to address the impact of clinical guidelines on medical practice. A recent Cochrane review⁴¹ found that the majority of 27 studies evaluating the use of clinical pathway maps showed they had an impact on reducing LOS and hospital costs. There has been little systematic analysis, however, of the impact of guidelines on procurement of diagnostics in the medical field, and this is an area that may warrant further investigation.

Guidelines are one tool that can be used to support bridging the gap between evidence and practice. They are an imperfect tool, however, with evidence of the ability of guidelines to change behaviour considered to be limited.⁴²

In the United States in 2010, 377 children were born with syphilis, a disease that can cause fetal or neonatal death.⁴³ Although the CDC recommends that all women are screened for syphilis during pregnancy,⁴⁴ this does not always happen in practice. In Florida, where state law requires a minimum of two syphilis tests as part of routine prenatal care and, in some circumstances, a third test at delivery, researchers found that screening guidelines were rarely being followed, with the majority of patients being screened only once and in some cases not at all.⁴⁵ The reasons for this included poor understanding of guidelines and a lack of awareness that syphilis was a problem, possibly linked to physicians not having encountered cases in practice. A similar picture has been seen with chlamydia screening; despite clear guidance from the CDC, in the United States, less than half of eligible women were screened for chlamydia in 2007.⁴⁶

In a study involving semi-structured interviews of 20 GPs from Sweden, researchers found variation in perceptions of the link between treatment for UTIs and antibiotic resistance; while some GPs recognized the need to be careful to avoid unnecessary antibiotic prescribing, other views captured by the study were that resistance was, “no problem, I have never seen resistance” or that “the problem is bigger somewhere else”.⁴⁷ Importantly, only those GPs who did recognize the risk of resistance indicated that they followed all relevant prescribing guidelines.

A variety of reasons have been cited for poor adherence to clinical guidelines; Cabana et al. identified seven key overlapping themes: lack of awareness, lack of familiarity, lack of capacity to comply, disagreement with the guideline’s approach, lack of confidence that the guideline will deliver the relevant outcomes, inertia regarding previous practice as well as external factors, which were divided into three classes: guideline-related, patient-related and environmental.⁴⁸

Once routine practices are in place, behavioural inertia can make it difficult to bring about change.⁴⁹ Routine practice can slow the pace of replacing older technology, even when better technologies exist.

In the United Kingdom, a frustration of some industry observers is that there has been no substantive sanction if health care organizations do not follow guidelines from NICE on new technologies that are cost-effective. To address this, the Department of Health has recently committed to introducing a compliance review, which will include publishing an “Innovation Scorecard” to improve transparency of the extent to which local organizations are adopting NICE-approved technologies. While the initiative holds promise, it is still in the process of being implemented.⁵⁰

8.4.1 Clinical guideline development in the United States

Many guidelines in the United States context are informed, or commissioned, by the AHRQ. At a national level, the AHRQ manages the EPCs programme, awarding five-year contracts to institutions in both Canada and the United States to serve as EPCs. These centres conduct systematic literature reviews on topics of interest to AHRQ, and produce evidence reports or technology assessments. These assessments and reports help inform coverage decisions, as well as guidelines and quality measures for public and private health care payers and providers. The inclusion and exclusion criteria for the reviews are found on most of the EPCs’ web sites and usually frameworks adopt a hierarchy of evidence, where data from RCTs are weighted most heavily.

The AHRQ also hosts the National Guidelines Clearinghouse, a public resource point for evidence-based clinical practice guidelines created or issued by clinical

specialty groups or organization. Rather than presenting a definitive guide, the clearinghouse facilitates greater evidence-based comparison between guidelines and identifies areas of conflicting guidance, as well as differences in methodologies. A search for guidelines pertaining to bacterial infections retrieves 170 guides, including guides from United Kingdom-based clinical groups. These guidelines can then be presented in a way that facilitates comparison. For example, the guideline on diagnosis and management of lower UTIs compares and contrasts guidelines from three different clinical groups: the American College of Obstetricians and Gynecologists, the Infectious Diseases Society of America, European Society for Microbiology and Infectious Diseases, and the Society of Obstetricians and Gynaecologists of Canada.

Additionally, within the AHRQ the Effective Health Care Program creates summaries about the risks and benefits of alternative treatments for health conditions, based on comparative effectiveness research (CER). Topics are suggested by the public. Summaries are aimed at consumers, clinicians and policy-makers, yet the disclaimer that the research summaries are not clinical recommendations or guidelines seems to undermine their purpose.

The United States Preventative Services Task Force (USPSTF) is a national body formed of experts in prevention and evidence-based medicine. Guidelines are available online, along with the date of issue and the “status” of the guidelines.⁵¹ Guidelines rated A or B are likely to lead to NCDs by federal payers, as well as more likely to achieve coverage with private payers. Screenings for most sexually transmitted diseases are recommended for high-risk populations, along with specific recommendations for molecular testing methods.⁵² A white paper by UnitedHealth⁵³ shows high volumes of molecular tests for infectious diseases within the Medicaid health maintenance organizations’ beneficiary population. Interviews with UnitedHealthcare representatives confirmed that clear guidelines and coverage contribute to high volumes of these relatively cheap and simple “bread-and-butter” molecular tests being used by providers.

The AMA also hosts guidelines on their web site. For example, in response to the many guidelines for acute respiratory tract infections, the California Medical Association Foundation’s Alliance Working for Antibiotic Resistance Education (AWARE) produced summary guidelines for adults, and paediatrics by synthesizing the available evidence and incorporating the opinions of medical experts and professional organizations. The AMA collaborated with AWARE to host these guidelines on their web site.⁵⁴

The CDC is a particularly important source of guidelines pertaining to infectious diseases. A report by expert consultants from the CDC explores the use of rapid molecular testing to detect drug-resistant TB and extensively drug-resistant TB (MDR/XDR TB) as a matter for public health concern.⁵⁵ This report suggests

that the CDC should engage with existing laboratory contracts to allow molecular tests to be included for at-risk patients, including those already very ill, or suffering from comorbidities. The management of drug-resistant TB begins with identifying the bacteria reliably, as well as its drug susceptibility. Traditional measures can take up to six weeks, while molecular methods can be as quick as one day. The study also identifies funding challenges associated with rolling out molecular testing, including accurately projecting the volume of tests demanded and associated costs. They suggest that establishing high-volume regional laboratory capacity would improve the viability of this service, but that more research into the costs and benefits is needed. Additionally, they note that there is no evidence of any one test's superiority and that procurement choices would depend on cost, throughput, turn-around time and validation of the test. This report was sent directly to physician stakeholders, with whom much demand-influence resides, and is accompanied by an analysis of the use of molecular detection of drug resistance, including pros and cons.⁵⁶

Health care providers are usually governed by the coverage decisions issued by the medical directors of health plans and Medicare contractors. These are nationally determined, locally determined, or determined on a case-by-case basis. Even with a large insurer like BCBS, there may be some coordination of guidelines across regions but each is separately licensed and therefore able to make independent guideline decisions. Clinical specialty groups, advocacy groups and patients can motivate for a specific treatment process to be adopted within their spheres of influence, and many coverage decisions come down to individual decisions about individual patients. These specialty organizations and advocacy groups were mentioned as important stakeholders in determining how and which guidelines are adopted.

Health plans are responsible for defining what medically necessary and reasonable care includes, without curtailing the autonomy of clinical providers. Respondents from health plans and research bodies suggested that this can sometimes be a difficult balancing act and highlighted the variability that exists in how health care is delivered across regions. It was suggested that providers in the medical research “meccas” are often quicker to adopt innovative products and new treatment guidelines, while isolated areas are often left behind, highlighting the need for improved information diffusion and continuing medical education.

8.4.2 Clinical guideline development in the United Kingdom

In the United Kingdom, a number of different organizations are involved in writing and publishing clinical guidelines. The main national-level bodies are NICE in England and Wales, the Scottish Intercollegiate Guidelines Network and the Guidelines and Audit Implementation Network in Northern Ireland.

NICE tends to act in a coordination role with relevant clinical bodies in the development of national guidelines, rather than produce them directly themselves given the importance of engaging the relevant clinical stakeholders in the process. In addition to the aforementioned bodies, a number of professional organizations and royal colleges produce guidelines on their respective areas of expertise. NICE has engaged in several pieces of work that include appropriate use of diagnostics largely in the field of cardiology, although little to date in the field of infectious disease. In 2009, NICE established the Diagnostics Assessment Programme (DAP), which is a sister programme to their existing medicines and devices health technology assessment processes. This has been relatively limited in scope thus far. Table 8.1 shows completed assessments and those which are in progress. While the primary output from the DAP is not to write specific clinical guidelines on the use of the evaluated diagnostic technology, the evidence assessment process may be used to contribute to guidelines on diagnostic uptake and use formulated either by NICE or other relevant bodies.

An important tool supporting the appropriate use of diagnostics within the NHS are the “Map of Medicine” pathways that have been developed for a number of indications, with over 1400 local care maps in place across the NHS.⁵⁸ While the majority of these maps are locally designed, they draw on best-practice clinical advice from professional bodies and NICE clinical guidelines. The assessment of the benefits of introducing these maps in particular settings may encourage evidence sharing across local NHS bodies, and for some indications national care pathway maps have been developed, including for *C. difficile* and community acquired pneumonia in the field of infectious disease. These process maps set out for the relevant indication at what stage examinations, diagnostics, treatment and referrals should be employed. Therefore an integral part of these maps will be to inform clinicians when it is appropriate to employ a diagnostic to support the patient evaluation and clinical decision-making process. In most cases, however, the maps do not offer specific direction on accessing or conducting the test,⁵⁹ meaning the guidelines may support the use of some form of diagnostic, but will not necessarily support the use of innovative products per se. A recently announced collaboration between the Royal College of Pathologists and Map of Medicine⁶⁰ may in time address more specifically the issues around guidance on diagnostic use in the published patient care maps.

In some cases, where there is consensus on best practice, international guidelines may also be used by clinicians. For example, the campaign Surviving Sepsis has actively promoted use of its guidelines on the management of sepsis, and these are used by some hospitals as a benchmark which actual treatment actions are audited against, although not necessarily with any associated rewards or penalties or rewards for (non-) adherence.

Table 8.1 NICE DAP diagnostics guidance to date (published and in progress)⁵⁷

PUBLISHED DIAGNOSTICS GUIDANCE		
Ref.	Title	Date issued
DG1	EOS 2D/3D imaging system	Oct. 2011
DG2	Elucigene FH20 and LIPOchip for the diagnosis of familial hypercholesterolaemia	Dec. 2011
DG3	Computed tomography (CT) scanners for cardiac imaging – Somatom Definition Flash, Aquilion One, Brilliance iCT and Discovery CT750	Jan. 2012
DG4	Adjunctive colposcopy technologies for examination of uterine cervix – DySIS and the Niris Imaging System	Aug. 2012
DG5	SonoVue (sulphur hexafluoride microbubbles) – contrast agent for contrast-enhanced ultrasound imaging of the liver	Aug. 2012
DG6	Depth of anaesthesia monitors (E-Entropy, BIS and Narcotrend)	Nov. 2012
DG7	SeHCAT (Tauroursodeoxycholic [75Selenium] acid) for the investigation of bile acid malabsorption (BAM) and measurement of bile acid pool loss	Nov. 2012
DIAGNOSTICS GUIDANCE IN DEVELOPMENT		
Title	Anticipated publication date	
Epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation testing in adults with locally advanced or metastatic non-small-cell lung cancer.	Sep. 2013	
Faecal calprotectin diagnostic tests to differentiate inflammatory bowel disease from irritable bowel syndrome	Oct. 2013	
Gene expression profiling and expanded immunohistochemistry tests to guide the use of adjuvant chemotherapy in early breast cancer management: MammaPrint, Oncotype DX, IHC4 and Mammostrat	Jan. 2010	
Intraoperative tests (RD-100i OSNA system and Metasin test) for detecting sentinel lymph node metastases in breast cancer	Jul 2013	
KRAS mutation testing of tumours in adults with metastatic colorectal cancer	TBC	
NIOX MINO for the measurement of exhaled nitric oxide concentration for inflammatory airway disease	Apr. 2014	
Xpert MTB/RIF assay (and alternative technologies identified during scoping)	TBC	

While guidelines may support or steer clinical decision-making, in the United Kingdom the NHS executive states that guidelines are not to be used to mandate, authorize or outlaw treatment.⁶¹ In some jurisdictions, guidelines hold more legal sway; for example, in France, guidelines published by l'Agence Nationale pour le Développement de l'Evaluation Médicale constitute an enforceable code of conduct for doctors working under the social security system.⁶²

8.5 Prescribing culture

In the absence of rapid POCTs, it takes approximately 36 to 48 hours to undertake a culture and sensitivity analysis using current methods.^{a, 63} This can leave

a It is important to note that in many lower-income countries it often takes up to five days to obtain what amounts to a questionable result.

physicians with no choice but to blindly treat a patient, increasing the risk that antibiotics are prescribed unnecessarily. For example, studies have shown that uncertainty in distinguishing between acute bronchitis and pneumonia has resulted in overuse of antibiotics in primary care.⁶⁴ Similarly, difficulty differentiating between viral and bacterial causes of conditions such as acute sinusitis⁶⁵ and otitis media⁶⁶ has led to inappropriate prescribing.

From the patient perspective, there is significant evidence of misconceptions about the value of antibiotics in treating conditions such as viral infections. In a large population-based telephone survey across seven states in the United States in 1998–1999, over a quarter of respondents erroneously perceived that antibiotics could help cure a common cold.⁶⁷ In a study from England in 1997 involving 1000 patients with acute lower respiratory tract illness, the majority of patients believed that they had an infection, that antibiotics would be of benefit, and they expected a prescription.⁶⁸ In this study, no relationship was found between the severity of symptoms and the patient demand for antibiotics.

Where prescribers perceive that patients expect antibiotics, numerous studies have shown that patients are more likely to receive one.⁶⁹ In an Australian study, patients were 10 times more likely to be prescribed an antibiotic where their GP believed that this was what the patient was expecting.⁷⁰ In a study by the University of California involving 10 physicians and 306 patients between the ages of 2 and 10, where physicians perceived that a parent expected an antibiotic, antibiotics were prescribed 62% of the time compared to 7% of the time when the physician did not believe an antibiotic was expected.⁷¹

This phenomenon may in part be explained by the results of a study in general practice in Wales, which found that despite prescribers being aware that antibiotics may offer limited clinical benefit for sore throats or upper respiratory tract infections, GPs knowingly prioritized the possible immediate benefit to their individual patients above the theoretical longer-term risk to the community of increased resistance.⁷² In addition to the potential clinical benefits, the act of prescribing may itself help parents with sick children by reassuring them that their concerns have been taken seriously by the prescriber.⁷³

Another factor that has been found to influence prescribing is a prescriber's level of risk aversion; for example, researchers from Belgium have provided evidence of a link between the degree to which an individual prescriber copes with uncertainty and antibiotic prescribing rates.⁷⁴ In addition to personal traits, a defensive attitude can be engendered during medical training⁷⁵ and may be influenced by the structure of the health system. In a multi-country European survey of risk-taking attitudes in 1990, 60% of physicians in Belgium reported that they sought to avoid risks compared to only 24% in The Netherlands, a difference that researchers attributed to greater patient choice of physician in

Belgium at that time.⁷⁶ Where physicians are financially incentivized to ensure patient satisfaction, they may factor in the risk that the patient may switch physician if their expectations aren't met when making prescribing decisions.⁷⁷

An approach that has been found to be successful in improving prescribing practice is jointly targeting both patient and prescriber education, for example a community-wide educational intervention in 2002 directed at both health professionals and the public in Tennessee led to a reduction in antibiotic prescribing for children.⁷⁸ As well as reducing uncertainty in diagnosis, POC diagnostics can also play a role in managing patient expectations. In a multi-country European study on physicians' and patients' views on POCTs for lower respiratory tract infection, the most commonly cited advantage of testing was that it could help the physician in managing patient expectations.⁷⁹ Some of the physicians interviewed also believed that testing could help shift norms and alter patient expectations over time.

A particular concern voiced in the United States market is that socio-cultural factors that encourage defensive prescribing practices have been compounded by the medical-legal environment.⁸⁰ While there are no definitive national statistics on the volume of medical malpractice claims in the United States,⁸¹ it has been estimated that the average physician is affected by an unresolved claim for approximately 11% of their career,⁸² with the risk of facing a claim differing by specialty. Physicians in low-risk specialties have a 75% chance of facing at least one malpractice claim during their career while the probability of facing a claim in high-risk specialties has been estimated at 99%.⁸³

Using data from the National Practitioner Data Bank, medical malpractice insurer Diederich Healthcare estimated that in 2011 approximately US\$ 3.7 billion was paid out to patients.⁸⁴ Taking into consideration additional costs such as indemnity payments and insurer overheads, legal expenses and the cost of physicians practising defensive medicine, researchers from Harvard University have estimated that the total annual cost of the medical liability systems in the United States is US\$ 55.6 billion in 2008 dollars (excluding indirect costs, such as lost clinician work time and the reputational and emotional toll from dealing with cases).⁸⁵ This equates to 2.4% of total health care costs and was significantly lower than an earlier study by PwC, which used a different methodology and estimated that the medical liability system represented 10% of health care costs.⁸⁶

Scenarios that have led to malpractice claims include failure to prescribe antibiotics; failure to monitor patients taking antibiotics; antibiotics being prescribed at a suboptimal dose or for too short a period of time; antibiotics being prescribed alone without additional treatments such as surgical drainage and antibiotics being prescribed without reference to diagnostics tests that could have helped identify the more effective class of antibiotic for that particular infection.⁸⁷

In an online survey in 2012 by the United States health care staffing company Jackson Healthcare, over 1500 physicians were quizzed on their reasons for practising defensively. Reasons cited included “to avoid being named in a potential lawsuit” (78%), because “defensive medicine has become the new standard of care” (61%), because the “patient or family demands that everything humanly possible be done” (59%), “to protect my good name” (48%) and because they believed they were “trained to practice defensively” (19%).⁸⁸

Although difficult to reliably measure, there are indications to suggest that defensive medicine could be a significant problem; in one 2005 survey of hospital physicians in Pennsylvania, published in the *Journal of the American Medical Association*, almost all of the physicians surveyed reported practising some form of defensive medicine and 33% of respondents indicated that they often prescribed more medicines than were medically necessary, including antibiotics.⁸⁹ An independent Gallup poll commissioned by Jackson Healthcare in 2010, found that 73% of respondents practised defensive medicine in the previous year; a practice that Jackson Healthcare has estimated is costing US\$ 650–850 billion per year, equivalent to over a quarter of annual health care costs in the United States.⁹⁰

Where steps have been taken to reduce physicians’ risk exposure, for example limiting the damages that can be claimed for pain and suffering, there is some evidence to suggest that it has been ineffective in reducing defensive practices.⁹¹ In Massachusetts, seven hospitals have recently adopted a “Disclosure, Apology, and Offer” policy, which enables physicians to apologize and offer compensation without the admission of apology being used in court⁹² but, similarly, there is little evidence to suggest that this approach will be effective, with some physicians believing it could increase rather than decrease risk avoidance.⁹³

In recognition of the potential importance of defensive medicine in the fight against antimicrobial resistance, the WHO has identified it as a priority research topic for the future.⁹⁴

Finally, it should be noted that regional differences in the underlying socio-economic and cultural attitudes affecting prescribing (and the adaptation of test results) may also be very important but difficult to assess.⁹⁵ Within Europe itself much variation exists.

8.6 Patient barriers

Patient preferences can also influence the benefits and uptake of POC diagnostics. For example, in a study evaluating the effectiveness of the BioStar Chlamydia OIA POCT, 6.8% of female adolescents tested at a public clinic in Atlanta, were unwilling to wait 20 minutes for the results of the test.^{96, 97}

Chapter 9

Economic evaluation: the limited evidence base affecting both supply and demand for new diagnostics

9.1 Introduction

The entry and uptake of novel POC diagnostic devices is often hampered by an inability to make coherent “business cases” for their use. Unfortunately, diagnostic devices pose unique challenges to economic assessment, in particular to the formulation of informative cost–effectiveness models. This chapter aims to provide a thorough overview of the complexities inherent in analysing the cost–effectiveness of POC diagnostic devices, including the logistic, economic and political backdrop that magnifies some of these complexities.

Comparing the effectiveness of diagnostic devices will require new models that incorporate an in-depth knowledge of how these diagnoses will be used to inform treatment decisions. Appropriate analysis must include a sufficiently long time-line to see the impact of more appropriate prescribing on antibiotic resistance and the incorporation of both societal benefits and cost offsets accrued in that time.

9.2 Background: economic evaluation and cost-effectiveness

Economic evaluation of health interventions is established practice in the United Kingdom and Canada, and is growing in popularity in other countries. It is also subject to controversy in the United States. Cost–effectiveness analysis is one method of economic evaluation and is often confused with other methods, or used loosely to describe any analysis of costs and outcomes. Essentially, those who are involved in paying for, delivering or receiving health services have to work through many questions about what care should go to whom, when and where. In order to make these decisions, we need to be able to have some way of estimating the relative value, or meritorious outcome, of alternative courses of action and uses of resources.

Cost–effectiveness analysis compares the differences in costs and consequences between two interventions, measuring the cost per unit of effect for each intervention (e.g. QALY gained, year without negative health event gained, days without negative health event gained, etc.). If the outcome can be translated into comparable units, for example life-years saved, then the interventions can be compared.

In the United States, many technology assessments are implicitly or explicitly cost-minimization exercises, where alternative technologies are weighed for comparability of efficacy, effectiveness, benefits and harms. After this process, comparable technologies are chosen based on the least costly option. This approach is only really helpful where two options are absolutely comparable in all regards except price,¹ for example choosing between drugs within a pharmacologic class. The perspective most commonly adopted in economic evaluations is that of the payer or health care provider (payer stakeholder interviews). CER is increasing, but explicit cost considerations remain illegal for any federally funded body in the United States, and are tiptoed around in private spheres.

In the United Kingdom, most economic evaluations of health care technologies are actually cost–utility analyses, measuring intervention outcomes in gains or losses in utility. This allows outcomes to be measured in comparable units, usually QALYs, allowing multiple interventions to be compared. QALYs gained through an intervention are quantified by weighting the treatment-affected life years by a utility measure (between 0 and 1) associated with the resulting health state. Interventions are compared using a “cost-per-QALY” approach. There are many methodological concerns about the ways in which these utility measures are elicited, but the approach itself is developing rapidly. In the United Kingdom, NICE already plays a central role in assessing innovative and high-cost technologies with these methods. For diagnostics, most decisions rely on market wisdom about mature tests, and no analysis of new technologies has taken place. NICE has recently established the DAP, and lists a number of tests currently under assessment, including a test for KRAS mutations. Developers undertake some level of technology assessments in motivating uptake, but there exists no established systematic approach to evaluating the benefits and costs of new diagnostic technologies.

Both cost–effectiveness analysis and cost–utility analysis are concerned with arming decision-makers with appropriate evidence for allocating resources within a given budget constraint such that their decisions will maximize health benefits. This means that any decision to allocate resources necessitates an opportunity cost somewhere else in the budget. It is important to consider opportunity cost because this represents the real “price” of an intervention. Rather than cost simply being represented by the accounts attached to an intervention, it is understood

as the value of the benefits linked to an intervention that are forgone by committing resources to an alternative intervention.

9.3 Background: economic evaluation in the United States

There have been a number of attempts at creating methodologies specific to the United States for valuing health outcomes. Additionally, work has been done by research centres aimed at increasing the role of cost–effectiveness analysis and economic evaluations within health and other policy areas. Around 2004, a research body called Resources for the Future hosted a workshop, sponsored by federal agencies (including AHRQ), to explore the implications of both cost–effectiveness analysis and cost–benefit analysis within the context of analysing regulatory impact. The Resources for the Future report, *Valuing health outcomes: Policy choices and technical issues*, is based on the discussions at this conference.²

In 2006, the United States panel on cost–effectiveness in health and medicine recommended that AHRQ fund a study to establish population-based preference values for the EuroQol group EQ-5D™. Preference weights for community-based measures of health-related quality of life were elicited from the general population as well as among Hispanic and non-Hispanic black populations.

The study's aims were to:

- determine preference values for 45 health states using time trade-off exercises;
- compare the health state values for the two minority groups with those of the general United States population;
- impute values for the full set of 243 health states represented in the EQ-5D™ for the general United States population based on the data collected for the 45 health states;
- compare the United States population-based EQ-5D™ health state values with previously derived values for the United Kingdom;
- establish United States population norms for self-reported health status as measured by the EQ-5D™.

The EQ-5D™ Health States, data collection instruments and study data are available online, as is detailed information on the scoring algorithm and index scoring.

AHRQ is working with the Institute of Medicine towards assessing the scientific validity, ethical implications and practical utility of a range of health benefit measures currently used, or proposed for use in cost–effectiveness analysis. The EQ-5D™ outcomes measurement project falls under the Research

Initiative in Clinical Economics. Begun in 2001, the Initiative determines the AHRQ's research agenda and activities linked to cost–effectiveness analysis, cost–benefit analysis and other methods for estimating the value of health care interventions. Within this body, the Center for Outcomes and Evidence emphasizes the role of clinical economics in informing efficient health care resource allocation.

The following four priorities are held by the Research Initiative in Clinical Economics:

1. to facilitate the use and enhance the credibility of economic analysis in decision-making, through to development, research and training;
2. to promote availability of standardized inputs to cost–effectiveness and related studies;
3. to support advances in methods for economic analysis;
4. to provide targeted support for extramural clinical economics studies to inform health care decision-making.

AHRQ has initiated a number of projects to support the development of improved systems and mechanisms for using cost–effectiveness analysis to inform decision-making. As part of this there are database resources. One such is the AHRQ Clinical Economics Research Database, which contains 544 health economic publications funded either partly or entirely by federal agencies, covering the period 1997–2001. These include cost–effectiveness analyses and cost–utility analyses, and articles on health outcome measures.

The Center for the Evaluation of Value and Risk in Health, linked to Tufts, houses a cost–effectiveness analysis registry that contains 534 cost–utility analyses from the period 1976–2001.³ The Center also conducts analyses for government agencies, private foundations and industry groups on the benefits, risks and costs of health interventions, including cost–effectiveness analyses, using the analyses in the registry. Of the data included in the registry, 8.3% comprises analyses of diagnostic technologies, and 41% of the studies are conducted in the United States.

The Academy of Managed Care Pharmacy (AMCP) supplies and updates format guidelines for “submission of clinical and economic evidence of pharmaceuticals in support of formulary consideration”, usually referred to as *Format for formulary submission*, or just *Format*. This document gives suggestions for how to include the use of cost–effectiveness information in decision-making. The guidance refers to the “ACCE” framework, which contains four categories of evidence that manufacturers should provide when making a business case for reimbursement:

1. Analytical and technical validity describes the accuracy of measurement.
2. Clinical validity describes the strength of the association between the test findings and clinical outcomes as well as the predictive power of the test.
3. Clinical utility, in some form of quantitative risk–benefit trade-off. And, finally,
4. Economic or societal efficacy, which would include a measure of incremental cost–effectiveness (AMCP format 2012).

Stakeholders from the academic community estimate that a threshold of around US\$ 50 000/QALY is general considered acceptable cost/QALY in the United States, but that this means very little in practice.⁴ The Patient Protection and Affordable Care Act 2010 created the Patient-Centered Outcomes Research Institute (PCORI) and prohibits the use of dollars per QALY thresholds for both PCORI recommendations and federally funded coverage decisions.

CER is discussed by stakeholders as an implicit method for considering cost and alternative health outcomes. CER is designed to inform health care decisions through evidence-based policy, based on the evidence of the effectiveness and benefits and harms of different treatment options. Suggestions for research can be submitted by anyone but the topics selected for review are usually high-cost ones or those with potential for high volume-costs. Research is either conducted through synthesizing existing clinical literature through a systematic review, or through conducting studies to generate new evidence on effectiveness and comparative effectiveness. With both methods, information is stratified based on different patient populations. EPCs like Tufts conduct the reviews. When insufficient existing data exist, there are two research networks that conduct original research. These are the DEcIDE (Developing Evidence to Inform Decisions about Effectiveness) network, or the Centers for Education and Research on Therapeutics.

The principles guiding research are as follows:

1. Questions that are relevant to patients and health care decision-makers are chosen. Existing literature is examined, with special attention given to studies that use health outcomes as the endpoint rather than intermediate outcomes. Studies adopting longer-term perspectives are considered more useful than those with short-term perspectives.
2. RCTs, observational studies and other research studies are assessed for quality for inclusion.
3. Efficacy studies are assessed for their relevance to patients, clinicians and the setting in which treatments or devices will be used. Data on efficacy and on effectiveness in everyday practice are both considered important.

4. Benefits and harms for different treatments and tests are presented in a consistent way to facilitate decision-making with clarity about trade-offs involved with different treatments or diagnostic strategies.

Benefits are expressed in absolute terms (intervention prevents one negative health event for every 100 treated patients) because this is considered more meaningful than presenting results in relative terms (50% reduction of adverse events). Research aims to present areas where trade-offs, benefits and harms are different for distinct patient groups. This CER approach has been criticized by proponents of cost-effectiveness analysis and succinctly described as a “menu without prices” by Garber (2004).⁵

According to stakeholders, the area with most unexplored potential for cost-effectiveness analysis is in companion diagnostics accompanying expensive drugs. Herceptin is mentioned as a good illustration for this kind of scenario. Warfarin, on the other hand, is cited as an example where it is difficult to show cost-effectiveness of a companion diagnostic because the diagnostic does not actually enable changed patient treatment. If the diagnostic identifies someone at risk, there is no method for stratifying treatment or acting on the information. Medicare had determined the diagnostic for warfarin as not clinically effective – although cost-effectiveness is taboo, stakeholders believe that this decision could be read as an implicit recognition of the lack of both health and economic benefits provided by the diagnostic.

One method suggested for determining the “cost-effectiveness” of a diagnostic that was raised during interviews would be to assess the cost-effectiveness of a drug with and without the diagnostic. The difference is then the “value” of the diagnostic. Because most antibiotics are low-cost, the role of companion diagnostics and innovative POC diagnostics is undervalued in light of the large social cost linked to antimicrobial resistance. The use of cost-effectiveness analysis is discussed further in section 9.7.

9.4 Background: summary of the evidence from economic evaluations of rapid POC diagnostics

While limited in both scale and scope, the published evidence surrounding diagnostics does shed light on important implications of their adoption.

9.4.1 Length of stay

Currently, attempting to reduce high costs associated with inpatient care is the most common focus of diagnostic economic evaluations for infectious

diseases. This is to be expected in the current financial climate, where budgets are squeezed to make every penny count towards improved health outcomes. In the United States, the focus on reducing inpatient costs is driven by the growing popularity of prospective payment by DRG groups. Within the DRG world, reducing cost per episode of care is critical for provider financial viability. Because fixed costs represent the bulk of hospital expenditure, surrogate measures like LOS are often associated with the highest portion of costs in an episode of care.

The most common causes of extended LOS are nosocomial (hospital acquired) infections, bloodstream infections, pneumonia, catheter-associated UTIs, intra-vascular device-related infections, surgical site infections (SSIs), and *C. difficile* diarrhoea related infections.^{6, 7, 8} Many HAIs, if poorly managed, may lead to sepsis and further infections within the hospital. This stands too for infections acquired outside of the hospital (community acquired) and managed within. Diagnostics play a critical role in enabling the swift identification of infected patients to stop contagion of other patients and begin appropriate antibiotic therapy for infected patients.

There has been a concerted effort to quantify the costs associated with extended LOS as attributable to health care acquired infections. These cost analyses use hospital accounting data (not prices or willingness to pay) and adopt a hospital or national system perspective. This means that interpreting “savings” and “costs” is not necessarily straightforward, since reduced LOS will not lead to cash savings, just a redistribution of fixed costs.

Reducing excess LOS does, however, free up resources for new patients and other sources of income-generating activities for the hospital. In the world of DRG reimbursement, where reimbursement is prospectively determined and excess LOS is often not reimbursed, this is particularly important. Increased LOS reduces hospital capacity, including beds and theatres. This reduced capacity can lead to lengthening waiting lists or even contractual failure. The financial risk associated with these aspects usually fall on the provider. Similarly, the risk of reduced value in post-contract assets like reputation are difficult to quantify but would be considered by health care providers.

A study funded by United States federal funding makes a number of estimates of the proportion of HAIs that are reasonably preventable, as well as their related mortality and costs.⁹ Large variability in the infection surveillance data used in their study mean that findings should be treated with caution. Not all HAIs are preventable, and the literature is not yet clear on what proportion may be preventable.¹⁰ There is some evidence to suggest that catheter-associated bloodstream infections are the most preventable HAI, with the highest number of preventable deaths.

Scott¹¹ presents an analysis of the economic burden of HAIs faced by United States hospitals, through synthesizing economic and clinical literature. This report was sponsored by the CDC and is cited widely on their web site. Their main findings suggest that the annual medical costs of HAIs to United States hospitals range from US\$ 28.4 billion to US\$ 33.8 billion (adjusted to 2007 dollars using CPI for inpatient hospital services) and US\$ 35.7 billion to US\$ 45 billion (adjusted to 2007 CPI for inpatient hospital services). Their estimates of financial benefits of prevention measures vary widely, from a low US\$ 5.7–6.8 billion to US\$ 25–31.5 billion using the same two CPI adjustments. Estimates for the costs attributable to the following types of infections were taken from the named studies:

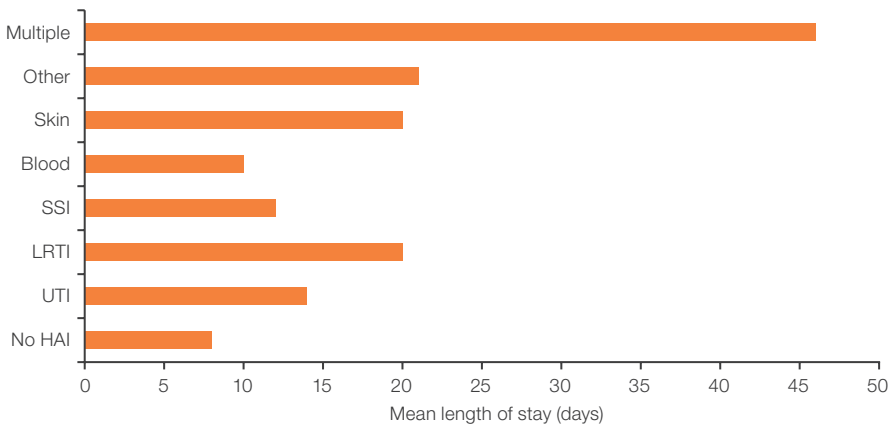
- Surgical site infection: SSI
 - Anderson et al. (2007)¹² estimate an attributable cost of US\$ 10 442 per infection in 2005 dollars, while Stone et al. (2005)¹³ estimate a high US\$ 25 546 per infection in 2002 dollars.
- Central line associated bloodstream infections: CLABSI
 - Hu et al. (2004)¹⁴ estimate costs attributable to CLABSI to range between US\$ 5734 to US\$ 22 939 in 2003 dollars.
- Ventilator-associated pneumonias: VAPs
 - Warren et al. (2003)¹⁵ estimated US\$ 11 897 in 1999 dollars and Anderson et al. (2007)¹⁶ estimate US\$ 25 072 in 2005 dollars.
- Catheter-associated urinary-tract infections: CAUTIs
 - Anderson et al. (2007)¹⁷ estimate US\$ 758 per infection and Tambyah et al. (2002)¹⁸ estimate US\$ 589 in 1998 dollars.
- *Clostridium difficile* associated disease: CDI
 - Dubberke et al. (2008)¹⁹ estimate costs between US\$ 5042 and US\$ 7179 in 2003 dollars.

An earlier study by Kohn et al. (1999)²⁰ estimated HAI costs in the United States to be around US\$ 17–29 billion. Navarrete-Navarro et al. (1999) estimated paediatric HAI to be associated with average cost per infection of almost US\$ 12 000 in intensive care. The 9.6 days of excess hospital stay was deemed the main contributing factor in this cost.²¹

A study completed in the United Kingdom in 1999 by Plowman et al.²² found that adult inpatients who developed HAIs remained in hospital 2.5 times longer (Fig. 9.1) and incurred hospital costs almost three times higher (Fig. 9.2). Their estimate of the national annual cost burden of HAI for hospital inpatient settings is close to £1 billion. Additionally, 19% of patients not diagnosed and 30% of

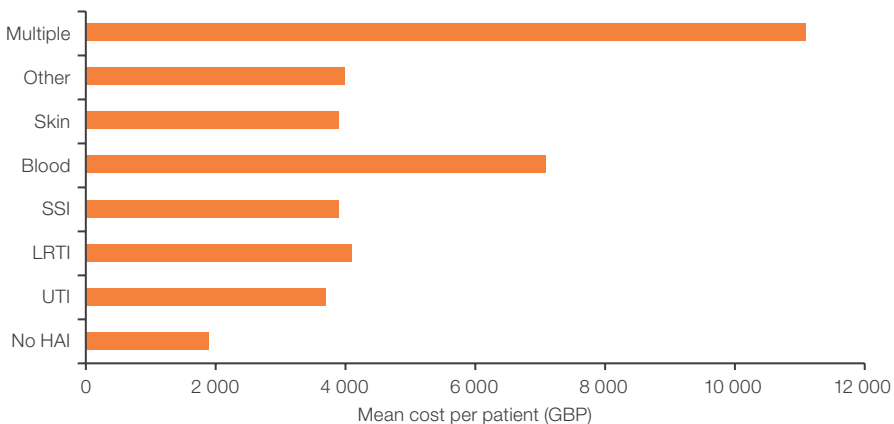
those who were diagnosed showed signs and symptoms of HAI manifesting after discharge and had higher GP, district nurse and hospital costs after discharge. This means that some of the costs associated with inappropriate management of infections within inpatient settings get shifted to other care settings. Reflecting this, national post-discharge costs were estimated at around £56 million, including general practice at £8.4 million, hospital outpatient centres at £27 million, and community nursing services at £21 million.

Fig. 9.1 Mean LOS for non-infected patients and those with HAI at various sites²³



LRTI – lower respiratory tract infection

Fig. 9.2 Mean hospital cost for non-infected patients and those with HAI at various sites²⁴



LRTI – lower respiratory tract infection

9.4.2 Costs associated with specific pathogens, either nosocomial or community acquired

MRSA is one of the pathogens that leads to high levels of HAIs,^{25,26} so it is critical to identify it before it enters the hospital. Murthy et al. (2010)²⁷ evaluate the cost–effectiveness of universal MRSA screening on admission to surgery from a hospital administrator’s perspective. They find that, although universal screening using PCR molecular assay does result in lower MRSA infection rates, it is not cost–effective unless the prevalence of MRSA colonization is above a certain level. They argue that in settings with a higher prevalence of MRSA colonization universal screening might be cost–effective or even cost-saving. These costs are estimated as a function of excess LOS. Their initial analysis suggests that the costs avoided by reduction in MRSA infection (through reduced LOS) did not completely offset the costs of screening on admission. Since screening involves variable costs, and LOS involves fixed costs, the practical impact on the hospital budget would be even less favourable than on paper.

Between 30% and 40% of all bloodstream infections lead to severe sepsis and septic shock, and rapid detection of bloodstream infections, as well as antibiotic susceptibility, can have direct implications for therapeutic management, clinical decision-making and infection control. With sepsis cases, delays in appropriate antimicrobial treatment contribute to high levels of morbidity, mortality and high resource use.^{28, 29, 30, 31, 32, 33, 34, 35, 36} Lehmann et al. (2009)³⁷ demonstrate that a multiplex PCR assay is able to differentially identify sepsis patients who will benefit from a specific antibiotic intervention. They observe that if the care pathway can be adapted in response to findings, 36.4 (22–51) days of inappropriate treatment could be eliminated per 100 PCR tests performed in the ICU.

Following on from this, Lehmann and colleagues (2010)³⁸ attempt to make predictions of cost and mortality impact of PCR testing in sepsis management. They found that 13.1% of PCR tests enabled earlier adequate treatment, with test costs of €300/test recoverable for patients with daily treatment costs above €717, with an incremental cost–effectiveness ratio of €3107 per QALY. Their cost estimates are based on reduced direct hospital costs associated with ventilation and intensive care bed-days, and did not include differential costs for antimicrobial drugs or the costs of potential false positives and gesture towards these aspects for future research.

Alvarez et al. (2012)³⁹ conduct an analysis from the hospital perspective, exploring the cost implications of using PCR diagnostic techniques for patients with severe sepsis and septic shock against the current procedure of empirically prescribed broad-spectrum antibiotics. Costs were included based on resources used in diagnosis and treatment as well as LOS in ICU and general hospital wards.

Antibiotic costs (variable costs) differed, with a mean value of €2812 in the group using PCR diagnostics and €3576 in the control. Total cost per patient also differed: the PCR group cost €42 198 and the control group cost €32 228, resulting in an average net saving of €9970 per patient due mainly to shorter LOS in ICU and largely resulting from shifts in fixed costs.

Variable costs include volumes of laboratory and sometimes imaging investigations, increased infection control costs, epidemiological investigations and staff time. Under Medicare payment plans, these costs will not be reimbursed if they are associated with HAIs, creating even greater financial incentives for the hospital to invest in cost-effective technologies that reduce LOS (see section 9.3 for more detail). Ill-managed infections are also often the subject of litigation, with financial consequences. Most of these variable costs are incorporated into LOS costs in analyses, making it difficult to tease apart fixed and variable components.

UTIs account for roughly 40% of nosocomial infections.^{40, 41} Downs (1999)⁴² presented a decision tree analysis of alternative diagnostic approaches for UTIs with paediatrics. The costs included in the analysis were: cost of diagnostic testing, treatment, complications of treatment, hospitalization for urosepsis, imaging studies, surgery or prophylaxis, and management of hypertension. The most significant costs were, unsurprisingly, linked to potential renal failure and to the development of urosepsis requiring hospitalization. Antibiotic prophylaxis also presents significant variable costs.

Little et al. (2009)⁴³ present a comprehensive analysis of different diagnostic measures for UTIs for adults. Costs included detailed patient resource use, including diagnostic, travel, physician time, number of prescriptions and referrals to secondary care within one month and then within one year. No statistically significant difference in resource use, or savings, was identified.

Because in some cases it is very difficult to identify how or if a specific test will alter patients' outcomes, many studies do not incorporate the costs associated with changed treatment pathways, but only those linked to various diagnostic tests.^{44, 45, 46} This approach is more of a comparative effectiveness, cost-minimization exercise.

Sometimes "savings" are just presented as the unquantified, unnecessary antibiotic treatment avoided through reduced false-positives, reduced laboratory services and reduced health costs to the patient associated with inappropriate antibiotic prescribing.^{47, 48, 49, 50} Standard treatment for UTI varies substantially, making it difficult to quantify what the actual savings or cost-containment from reduced variable costs might be.⁵¹

In an outpatient setting, the financial motivations for reducing inappropriate prescribing are fewer, but will depend on reimbursement systems. Fee-for-service

payments do not place physicians under any considerable financial risk, and incentivize over-expenditure as well as oversupply. Under a capitated payment system, however, the physician or physician groups would face financial pressures to prevent patients from remaining ill for too long.

Pharyngitis in adults accounts for roughly 1–2% of primary care visits. While most cases are caused by a virus, about 10% are caused by bacteria, and only some of these bacterial cases should receive antibiotics. However, physicians are reported to prescribe antibiotics for around 73% of patients.⁵² Inappropriately high antibiotic prescription is known to be influenced by patient expectations as well as cultural factors⁵³ and diagnostics can equip physicians with evidence to guide appropriate prescribing in the face of patient pressure. Appropriate concomitant diagnosis and treatment is important, especially with children, because it can prevent rheumatic fever and subsequent rheumatic heart disease with high associated health care costs.

The use of rapid streptococcal antigen test is presented as a cost-effective approach to diagnosing bacterial pharyngitis, facilitating optimal antibiotic prescribing.^{54,55} Ehrlich et al. (2002)⁵⁶ also identify the use of a rapid POC antigen test with concomitant antibiotic culture as the most cost-effective approach, with savings accrued through avoiding expensive and lengthy culture-based tests. Neuner et al. (2003)⁵⁷ find various diagnostic strategies to be almost equally cost-effective, including rapid testing and culture-based testing, and Tsevat and Kotagal (1999)⁵⁸ find culture-based testing to be the most cost-effective approach, even when including patient costs.

Accurately identifying viral respiratory infections in paediatric patients is also part of managing bacterial infections, since inappropriate antibiotic prescribing in this case leads to the emergence of microbial resistance.⁵⁹ Woo et al. (1997)⁶⁰ estimate a 52% reduction in antibiotic use following improved viral diagnostic turn-around time, as well as a saving of HK\$ 1 299 130 annually in reduced LOS.

Similarly, Barenfanger et al. (2000)⁶¹ assess the benefits of improved rapid diagnostic methods for identifying respiratory viruses, finding a 5.3 day decrease in LOS. Variable costs (supplies used, laboratory or radiological tests etc.) reduced by US\$ 5716 per patient and net savings (after cost of reagents and technological time are subtracted) were estimated at US\$ 144 332 annually. Other studies have also explored the cost-effectiveness of tests with higher specificity of viral diagnosis, leading to reduced inappropriate antibiotic prescribing.⁶² One study finds that improved viral diagnostic techniques might be a more successful approach to curbing inappropriate bacterial prescribing than more refined antibiotic prescribing guidelines.⁶³

9.4.3 Patient cost perspective

Patient morbidity resulting from poorly managed infections has significant health and financial costs. The financial costs that patients face can be reduced by reducing morbidity, allowing minimal trips to the place of care, and minimizing time within health care settings. This is particularly important for infections where concordance is critical to the infection being cleared, as well as reducing contagion in the neighbourhood.

For example, one challenge faced by the new Public Health England is the coordination of testing and treatment for STIs (stakeholder interviews). Whether these patient costs are included in an economic evaluation or not will have implications for the choice of therapy. For example, a slightly more expensive test may eliminate the need for a second consultation, increasing the probability that the patient will receive appropriate treatment and reducing the work time lost to the patient. For infections with high levels of stigma (e.g. STIs), stakeholders also identify the “invisible” cost of losing the patient to follow-up when repeat consultations are required. Rapid HIV, STI and TB tests are particularly important because of the stigma often involved with seeking treatment.⁶⁴

The increase of MDR TB and the twin illnesses of TB and HIV AIDS provide a clear situation where being able to appropriately identify treatment susceptibility will be beneficial to patient outcomes while also reducing the individual and social cost of inappropriate prescribing.⁶⁵ In South Africa, the adoption of GeneXpert means that TB screening can be completed within rural clinics in under two hours, including identification of drug susceptibility.

A whole range of different cost-saving factors come into play when moving beyond high-income settings to countries where the only viable way to conduct testing may be at point of care. Even within high-income countries, low-income areas rely on low-cost diagnostic methods to meet patients’ needs when laboratories are too far away or too expensive.

Finally, the wider social costs of inappropriate antibiotic prescribing must begin to be incorporated explicitly into analyses of new diagnostic interventions. Adopting a hospital-level, budget-driven perspective, or even including individual patient cost-perspectives, is unlikely to adequately capture the costs of antimicrobial resistance.⁶⁶ Although national bodies have begun galvanizing their plans to prevent antimicrobial resistance, successful approaches will also require that the economic and health-related externalities of inappropriate antibiotic use begin to be incorporated explicitly into decision-making.⁶⁷ The challenges of valuing reduced antimicrobial resistance are significant but a wider, social value perspective is essential to accurately capture the cost of antimicrobial resistance.⁶⁸

9.5 Challenges in making the “business case” for new diagnostics

9.5.1 Evidence generation by developers (issues affecting supply of diagnostics)

Effectiveness

Funding is perceived as a major barrier to evidence collection. Assessing the value of diagnostics technologies can be costly, for example planning and organizing a study, entering and analysing data, and obtaining expert clinical and statistical advice.⁶⁹ A concern raised by stakeholders is that there is an unrealistic expectation that diagnostic companies will provide funding to health care organizations to support clinical trials, as pharmaceutical companies have done in the past. This is not always financially viable; diagnostic providers report a lower rate of return on their investment compared to the pharmaceutical industry and exist in a different risk environment, often vulnerable to the threat posed by rapid advances in technology. Indeed it has been stressed that, with such rapid technological progress, both time- and cost-related constraints lead to an incentive for diagnostics developers to produce only the minimum level of evidence required for regulatory approval.⁷⁰ In some cases developers have failed to donate their product to otherwise fully publicly funded trials to generate evidence.

A number of diagnostic companies have indicated that the principal challenge they face in evidence generation lies at the clinical setting stage. While in the initial development phase and to gain a CE marking in Europe, access to accredited samples (for example from the National Collection of Type Cultures in the United Kingdom, or American Type Culture Collection in the United States) is key, the number of positive samples is relatively small (150 positive samples, with regulatory flexibility for fewer in low prevalence indications). More pertinent to diagnostic companies' ability to sell their products to hospitals and other end users is the ability to demonstrate performance in a live clinical setting. To this end, in the United Kingdom it is common for diagnostic companies to work directly with pathology facilities within hospitals in order to generate evidence from a real-world setting. The arrangements surrounding diagnostics companies accessing hospital lab facilities may vary, with possible agreements including the manufacturer paying for lab space and marginal costs such as additional personnel, the sharing of costs between the hospital and manufacturer, and third-party funding arrangements, for example through government bodies such as Innovate UK (formerly known as the Technology Strategy Board).⁷¹ How the funding arrangements are agreed upon may depend on a number of factors, such as public health priorities (particularly where government funding is involved) and hospital pathology labs' perceptions of potential value of the diagnostic. This

latter point raises an interesting prospect in that whether or not hospitals choose to fund access to labs may be driven more by the potential for cost savings in the lab setting than by the scope for improvements across the whole patient care pathway, which may be significantly harder to quantify.

CER and patient-centered outcomes research (PCOR) have received significant federal funding in recent years. CER compares the benefit and harms of alternative methods of disease prevention, treatment and monitoring, or alternative methods for improving the delivery of care. PCOR focuses on identifying patient-centred, personalized approaches to health care that result in improved patient outcomes. Both CER and PCOR typify the shifting paradigm for health research, where evidence of effectiveness in real-world settings and evidence of impact on patient outcomes are required for demonstrating clinical utility.

Usually diagnostic tests studies focus on test performance (sensitivity or specificity) or accuracy (being able to distinguish between presence or absence of a disease or condition), but there is very rarely information available about how the test will impact patient outcomes. Outcome-related evidence is becoming increasingly important and developers are required to show that physicians can act on the information from a test to change the patient's care pathway in a way that results in improved outcomes in comparison to the standard procedure. For developers to generate this kind of information often requires access to expensive proprietary hospital data on inputs, changes to patient pathways and impact on patient outcomes. It is very difficult to link the test to patient outcomes such as improved quality or length of life.

Alternative research models may need to be considered by diagnostic developers in order to generate the effectiveness evidence that is being demanded for assessing clinical utility. For example, head-to-head clinical trials, pragmatic trials, multistate modelling studies, as well as retrospective studies using completed trial data may become increasingly common. Developers will need to improve communication with payers and the medical community in order to ensure that the evidence being generated will be appropriate for demonstrating clinical utility.

Cost-effectiveness

Beyond clinical effectiveness, developers must also make a compelling case of the overall cost-effectiveness or "business case" for their product to procurers. If there is already a competitor on the market then developers must make a strong case for why theirs is better, *more* cost-effective, and more efficient to warrant making the switch. In order to make such a case, developers must present robust evidence. However, the collection of cost-related data to make the business case is challenging, expensive and often seen to be too context specific

to be generalizable across clinical settings where clinical organization, procedures and related costs differ.

In addition, interviews with developers highlighted the difficulties that small diagnostic firms face when trying to access data on hospital utilization and volume, as well as cost information from insurers. These data are sometimes sold to developers, but at a very high price. Coding complexities also make it very difficult for payers to access information regarding what the hospitals are testing for, and how. Difficulties in accessing accurate data present a significant stumbling block in conducting economic evaluations.

Industry commentators have suggested that the lack of consensus on what constitutes an appropriate evidence base to prove the value of a diagnostic is acting as a disincentive to developers to collect cost–effectiveness data. They stress the reluctance on the part of clinicians and procurers to accept the data put forth by developers. Put simply, why should developers invest in studies if there is a significant risk that procurers or the clinical community won't accept the evidence? One solution that was advocated at a meeting of stakeholders at the University of Oxford in October 2011 was the need for the industry to work together with academics to develop an “evidence toolkit” to help clarify the most appropriate and efficient approaches to study design and provide a clearer path for manufacturers on the evidence needed to support uptake of their products.⁷²

Finally, a consistent issue raised by manufacturers is the lack of link between the value a diagnostic may add in terms of cost–effectiveness, and the pricing level hospitals or other end users are willing to pay for diagnostics. The result instead is that in many cases diagnostics are priced on a cost-plus basis. Manufacturers will set a mark-up relative to development and manufacturing costs that offers a minimum acceptable profit margin. This is a similar issue raised by pharmaceutical manufacturers who, in many cases, have led the push for value-based pricing, although the slow progress in designing and implementing value-based pricing for pharmaceuticals in the United Kingdom suggests that any possibility of extending this approach to diagnostics remains distant at best.

9.5.2 Gathering and making sense of the evidence surrounding new diagnostics being considered for the clinical setting (issues affecting demand for diagnostics)

In order for clinicians and procurers to see beyond the immediate higher cost of POC technologies – especially when they are used in addition to culture – requires seeing a clear business case. This often requires showing clear evidence of cost–effectiveness, that is, how patient care will improve and how the use of the device will bring savings. However, procurement managers and division

managers are forced to perform back-of-the-envelope calculations to determine the value of introducing new diagnostics due to the lack of good, peer-reviewed cost–effectiveness studies.⁷³ The difficulty in understanding how the use of a diagnostic affects clinical outcome is also compounded by the lack of operational research exploring the application of these technologies and their ability to alter the treatment pathway.

Little evidence is available to help procurers understand the cost realities and practice change realities of integrating these technologies within clinical management and drug selection decisions. The lack of evidence may be particularly acute for molecular diagnostics.⁷⁴ Vendors often provide hospital administrators with cost analysis templates to help prove the case for their products; however, administrators interviewed for this project found these templates to be of little use to those making the decisions. Lack of health economic in-house expertise was cited as a common challenge in using provided costing templates and more generally in assessing the value of diagnostics. One respondent suggested that, while his hospital finance managers would look into the cost per test, they lacked the capacity to measure whether the use of the test would allow patients to move out of the emergency department or ICU faster, or consider the cost per hour of that care, or patient flow, etc.

While economies of scale and scope are obvious for lab-led diagnosis with high patient throughput, POC testing does not reap such advantages (though one could argue that some can be gained through multiplex panels). The cost advantages (e.g. from shorter visits, attendance of lower-level staff, etc.) are only captured if a more comprehensive picture is captured through economic evaluation. However, discussions with clinicians and hospital staff suggested that such evaluations are rare both prior to purchase and after implementation of a new device. The level of perceived utility of diagnostic is determined largely on the grounds of a very rudimentary business case (or cost–effectiveness) to a given clinical division, unit, or practice. This will include the time savings to staff and sometimes patients. In few cases are wider considerations made, such as savings to be reaped at the level of the hospital as a whole or over the longer term – for example savings with regards to resistance. (See section 9.7 for further discussion of technical limitations of the existing evidence base.)

Where staff capacity at pathology units is limited due to budget or resourcing issues, their ability to spend time evaluating new products – indeed their existing diagnostic usage – may be hampered by more pressing day-to-day challenges. Relative staffing (and funding) levels of microbiology units in the United Kingdom versus the Netherlands were highlighted as an example by one industry expert, where facilities in the Netherlands are substantially more fully staffed, with concomitant ability to spend more time considering strategic

issues, such as the uptake of new technology and decommissioning of less effective platforms. In the United Kingdom, the difficulty in evaluating the relative merits of new diagnostics is perhaps further compounded by the weakened links between health services and university departments following the recent decline in academic pathology. The Royal College of Pathologists mentions that many medical schools today have no identifiable academic department of pathology. They also stress that increased financial controls in the NHS and universities make the informal transfer of time and expertise more difficult.⁷⁵

9.6 Need for greater role of public sector in setting format priorities

9.6.1 Format priorities

The lack of evidence generation surrounding the value of diagnostics on the part of the health and research community affects the perceived level of overall “buy-in” by the clinical community. This perceived level of buy-in – particularly regarding format priorities – in turn influences how industry allocates R&D resources. For example, a 2005 request from the NIH asked that:

Researchers in infectious disease diagnostics should consider formulating a strategy to determine whether multiplex diagnostics will lead to better therapeutic decisions, improve a patient’s outcome, and reduce health care costs, e.g. by reducing hospital stays or shortening courses of antibiotics. Demonstrating that improved infectious disease diagnoses have a positive impact on public health may stimulate industry interest in developing and marketing new technologies and their associated diagnostic tests.⁷⁶

9.6.2 Being cutting edge vs. simply falling off the edge

The lack of evidence on how new technologies affect the underlying cost structure associated with some diagnostics can affect the type of devices that are produced. Large fixed costs are associated with lab-based diagnosis and near-POC devices that include large machines. There is also a significant upfront cost in training staff to use a new device (in addition to some ongoing maintenance costs to train incoming staff, keep skills tuned and general quality control exercises). This means that procurers are, for the most part, unable to make decisions lightly over what technologies they bring in-house. They want to be fairly sure of the quality of the product they are considering, understand how it will improve patient care and/or reduce costs, and how it will link in with existing technologies and care pathway. The resulting inability to try out cutting edge devices – or apprehension

around these issues – translates into a certain degree of “wait and see” attitude on the part of developers. They want to be at the forefront of technology but only if there are already signs that their innovative prototypes are part of what will become the new standard. James Nichols of the University of Vanderbilt suggests that this hesitation on the part of developers to eagerly jump on a new technology in case it doesn’t become the standard technology is at least in part responsible for the fact that diagnostic developers have somewhat “missed the boat” regarding the integration of wireless and automated technologies into POC devices and are overall about 10 years behind the curve.⁷⁷

9.7 Cost–effectiveness evidence in reimbursement decisions

While strong evidence of the ability of diagnostics to cut costs and improve health outcomes can help market these technologies to clinicians and procurers, the value of this evidence in coverage decisions by third-party payment is not straightforward.

9.7.1 United States

In the United States, approximately 10% of coverage decisions are determined by the CMS; although technology assessments are undertaken to support this decision-making, this remains limited to assessing clinical utility rather than cost–effectiveness. The remainder of decisions are made locally by individual providers but often follow decisions made by CMS.

Diagnostics developers cannot make use of cost–effectiveness arguments for motivating coverage by Medicare, since CMS is legally prohibited from considering costs when making coverage decisions. Respondents pointed out that while cost remains the unspoken concern, cost-related issues are being included in decision-making through other means. For example, topics selected for NCDs and comparative effectiveness studies are generally those with the potential to have a significant impact either on costs or benefits for the Medicare population.

Some developers, including Genomic Health and Xdevelopers, have conducted formal economic evaluations of the impact of their diagnostic technologies in an attempt to increase favourable coverage. These studies identify savings from changed care pathways and accurate patient stratification.^{78,79} A study by Health Advances⁸⁰ (a health consulting firm specializing in market access and pricing for innovative diagnostics) finds that these kinds of economic evaluations, conducted by developers, have ambiguous effects on payer coverage decisions, some finding the evaluations helpful while others see them as having no place in decisions

about coverage, only perhaps in guiding uptake. Garber et al. (2004)⁸¹ find that in a survey of 228 managed care plans, 90% consider cost and 40% actually do consider formal cost–effectiveness analysis. In private payer contexts respondents suggested that economic evaluations may be conducted but tiptoed around.

Some stakeholders concur that it is unlikely that cost–effectiveness evidence will be openly considered by United States-based payers in the future, given the legal context for CMS and negative cultural perceptions. However, others stress that financial constraints will ultimately prevail and that cost–effectiveness evidence will be used increasingly as a determinant in coverage decisions, whether the contribution is implicit or explicit.

9.7.2 United Kingdom

In the United Kingdom, unlike for drugs, there has thus far been very little national-level assessment and subsequent guidance surrounding the cost–effectiveness of diagnostic devices to determine coverage. The lack of national-level guidance on diagnostics within a nationally run health system has been problematic at several levels. It is, of course, inefficient: where clinical units have been left to make the case for new technologies independently in-house the process can be both difficult and time consuming. The Royal College of Pathologists stresses that the local evaluation of new diagnostics is often impractical and a poor use of resources.⁸² Lack of national review processes to assess the value of tests has also led to fear of negligence allegations if problems arise as “compliance with national decisions is perceived as providing a better legal defence than local opinion”.⁸³ Finally, the lack of authoritative advice is seen to potentially slow demand for tests as medico-legal issues arise surrounding the removal of older tests.⁸⁴

In England, these problems have led to the recognition of the need for national guidance on the comparative benefits of new diagnostics,⁸⁵ a role that is being assumed by NICE, a health technology assessment agency that was set up in 1999 to assess the cost–effectiveness of drugs to determine their reimbursement status within the NHS. Although NICE has not yet assessed a POC device for treating infectious disease, it has recently established two new programmes to support this: the general Medical Technologies Evaluation Programme and a more focused DAP.⁸⁶ These initiatives provide a framework for reviews to be undertaken and, while following a similar process to the NICE appraisals of pharmaceuticals, recognize the unique challenges that apply to diagnostics, including the greater uncertainty in the link between intervention and outcome.

Other initiatives currently being planned in the United Kingdom include the establishment of an “innovation fund”⁸⁷ to quickly test and evaluate new technologies, the establishment of Academic Health Science Networks to improve knowledge exchange between academics and industry to support the diffusion

of new technologies,⁸⁸ and the provision of seed funding to a number of NHS organizations to establish the infrastructure for “diagnostic evidence co-operatives”, that is, partnerships between clinicians, the industry, commissioners and other stakeholders to generate the required evidence.⁸⁹ Time will tell how effective these potential solutions are.

Where there is not yet sufficient information to undertake a cost–effectiveness assessment, one pragmatic approach being used to manage decision-making uncertainty is payers agreeing to fund a product while evidence on the value of the product is collected in clinical practice. Also known as “risk-sharing schemes”, “patient access schemes” and “managed entry schemes”, this approach has been tried in numerous countries, including Australia, Canada, the United Kingdom and the United States.⁹⁰ Unfortunately, these schemes are not without their problems; in designing managed entry schemes, care needs to be taken to mitigate risks, such as excessive administrative burden, loosely defined evidence requirements that do not provide the necessary information for decision making and ambiguity with regard to responsibilities in relation to collection of evidence.⁹¹

9.8 Technical matters surrounding published cost–effectiveness studies of rapid POC diagnostics

From a technical standpoint the reasons behind the limited evidence base of POC diagnostics for bacterial infection are multifaceted. A key part of the challenge is that assessing the value of diagnostic tests is more difficult than assessing the value of therapeutic interventions due to greater uncertainty regarding the relationship between diagnosis and outcomes⁹² – a problem that is compounded by a lack of modelling tools, clinical complexity linked to patient co-morbidity or multiple care pathways for a single disease and incomplete data, for example because clinical trials have been focused on data collection for regulatory purposes rather than economic evaluation.⁹³

Currently full clinical trials of diagnostics (that measure health outcomes) are not needed for regulatory approval. However, the evidence provided from such trials is essential to making a case for the adoption of these technologies. Few real trials take place and cost limits their duration. In some cases their design limits the generalizability of measured outcomes.

Of the studies that are published, many are methodologically weak. For example, in a review of 134 evaluations of diagnostic tests published from 1992 to 1997, Severns and Wilt⁹⁴ found poor adherence to best-practice guidelines on economic evaluation. In 95% of the studies reviewed, no perspective was stated, there was no cost–effectiveness ratio or sensitivity analysis in 50% and 66% of the studies respectively, and in 82% of the studies the approach to calculating costs

was not made clear. In the United Kingdom the Royal College of Pathologists stresses that the poor quality of papers on diagnostic accuracy make it difficult for staff to evaluate recently introduced technologies objectively and consistently across the NHS.⁹⁵ Given the significant resources required to obtain systematic and unbiased data to use in studies it is expected that there will continue to be limitations on the level of cost–effectiveness evidence available.⁹⁶

A brief technical summary of published studies on the cost–effectiveness of POCTs specifically to support the management of sepsis, UTIs and streptococcal pharyngitis is set out in Appendices A, B, and C. A description of the evidence along with some background to its interpretation is included below.

9.8.1 Study design

A number of methods are available to value a new technology, each with its own set of pros and cons. *Cost–utility analysis* compares a new intervention to the next best alternative, describing its value as an additional cost per unit of health gain; for example, a cost per additional QALY, which captures both improvements in the quantity and quality of life lived or alternatively a cost per disability-adjusted life year averted, which measures the numbers of years lost from premature mortality as well as reductions in the quality of life due to disability or ill-health. A key advantage of this approach is that it can be used to compare the value of different interventions both within and across diverse disease states,⁹⁷ for instance whether it is better to invest scarce health care resources in hip replacements or coronary artery bypass grafts.⁹⁸ A key challenge in constructing models to determine the cost–effectiveness of diagnostics lies in the many assumptions that have to be made with regard to treatment options and subsequent disease outcome. Linking to clinical trials obviates this problem. In the case of *cost–benefit analysis*, health gains are *monetized*; this supports cross-sector decision-making, for example whether it is better to allocate funds to health, education or transport interventions,⁹⁹ but can be controversial since it essentially involves putting a value on human life.¹⁰⁰ Of the studies analysed for this work, a few utilized cost–utility analysis and none utilized cost–benefit analysis.

Another approach is *cost–consequence analysis* which, rather than providing an overall quantitative assessment of value, takes a disaggregated approach and presents a cost per outcome, for example a cost per complication avoided.¹⁰¹ A number of studies evaluating the economic benefits of POC testing for streptococcal pharyngitis have taken this approach, which has been raised as a concern by researchers.¹⁰² Decision-makers are faced with having to weigh the relative merits of avoiding particular consequences, but where complications are exceptionally rare, such as rheumatic heart disease in the case of pharyngitis, this makes studies more difficult to interpret given that the average clinician is

unlikely to have seen a case in practice. This approach also provides little support for broader comparisons, such as determining spending across disease-states or sectors. Its usefulness is largely restricted to comparisons with studies of other interventions used for exactly the same diagnostic purpose and designed in a similar manner.

A fourth approach is *cost-minimization analysis*. Under this methodology, only the costs of different interventions are compared. This is arguably the simplest approach to economic evaluation but only appropriate when outcomes are truly equivalent. In one of the first economic evaluations of PCR pathogen detection in sepsis, Lehman et al.¹⁰³ used information from the literature on morbidity and mortality to estimate the health gain from initiating earlier appropriate antibiotic treatment as an input into a cost–utility analysis. Two years later, in an evaluation of the same device, Alvarez et al.¹⁰⁴ chose to undertake a cost-minimization analysis on the basis that their study, an observational trial in a Spanish hospital, had found that introducing PCR technology had no impact on mortality rates; there was no consideration of other benefits, such as reduced morbidity. Cost-minimization studies generally do not account for overall hospital efficiency and patient-incurred costs associated with visits.

Finally, some studies have looked simply at the cost of tests and the ability of tests to correctly identify cases, such as the study by Wong et al.¹⁰⁵ on cost–effective screening for UTIs in uro-gynaecological patients. While this study noted that changes in testing could lead to earlier diagnosis and treatment, these benefits were not integrated into the analysis; as a consequence this is arguably not a true investigation of cost–effectiveness. Such analyses can of course be highly informative for comparing diagnostic alternatives all else being equal. In the case of rapid POC diagnostics, such studies ignore any efficiency gains, other care-related costs, patient-related factors, etc.

9.8.2 Perspective

Taking a societal perspective on costs and benefits incurred is arguably the ideal approach to deciding how to allocate scarce resources,¹⁰⁶ especially when the product in question provides a public health benefit (e.g. improved prescribing leads to slower growth of resistance). However, few studies on POC diagnostics have taken this viewpoint, with most focusing only on the costs incurred by the health care provider or wider health system. The perspective chosen is important as it can influence the outcome of an evaluation, for example offering a rapid test may be more expensive for providers but deliver an overall saving for society. An example of this is a 1997 study by Kassler et al. into rapid HIV testing;¹⁰⁷ from the perspective of the testing clinic, the cost of offering the rapid test was more expensive than a blood culture undertaken by a central laboratory but when

the broader societal perspective was taken, the cost of this additional workload was more than offset by productivity gains and savings in patient transportation costs when the rapid test was offered.

9.8.3 Cost selection

The types of costs that are typically considered in studies include the cost of testing (for example staff time and consumables), changes in treatment costs (for example reductions in LOS), the number of GP visits, the quantity of antibiotics prescribed and, in some cases, the complications linked to the underlying infection or drug treatment. Where a societal perspective has been taken, studies may also include indirect costs such as patient travel and changes in productivity.

Linked to this, it is important to distinguish between fixed expenditure and variable costs linked to each additional case. Fixed costs such as infrastructure, information and finance systems, and salaries remain more or less the same, regardless of the number of patients who pass through a hospital. Accountants allocate these costs to surrogate measures of activity, for example bed-days, and in this way the fixed costs are spread between many patients over an annual budgeting cycle. Variable costs are those associated with individual cases on the basis of use, for example the number of antibiotics or bags of saline. Economic evaluations limit their relevance to budget holders by failing to distinguish between variable and fixed costs.

Where a benefit of tests is reducing antibiotic consumption, a frequent omission from studies is quantifying the economic benefit gained from reducing the risk of developing antibiotic resistance. In practice, this is extremely difficult to calculate. The relationship between consumption and resistance is governed by a range of complex and time-dependent factors such as the transmissibility of a particular pathogen.¹⁰⁸ The impact of changes in resistance is also influenced by factors such as the nature of the microbe, the infection type and the clinical situation.¹⁰⁹ Where studies have sought to calculate the economic consequences of resistance, the results have been conflicting.¹¹⁰ One reason for this may be differences in methodology, for example possible approaches to capturing costing information include measuring hospital costs, charges or resources used. Each approach has different advantages and disadvantages. For example, charges can be easily identified but may be an overestimation of actual costs incurred.¹¹¹ Similarly, considering only the increased expenditure related to treating patients with a resistant pathogen understates the economic impact as the presence of resistance can trigger increases in general treatment costs, for example through changes in recommended first-line antibiotics.¹¹²

Overall, there is a significant risk that not considering the impact of antimicrobial resistance undervalues new rapid diagnostics for infectious diseases.¹¹³ Much more research is needed on techniques to calculate the economic consequences of resistance as well as how this can be captured in studies to assess the cost–effectiveness of interventions that can reduce antimicrobial resistance. More work is needed to improve modelling techniques that incorporate resistance into cost–effectiveness models and to build greater consensus around the acceptability of those models so as to improve their perceived usefulness in comparing diagnostic alternatives.

Another common weakness of studies is only considering the incremental costs of testing or not differentiating fixed costs.¹¹⁴ Incremental costs are those linked to the volume of testing, for example reagents used and staff time to perform a test, whereas fixed costs include the costs of putting the testing infrastructure in place, for example costs linked to the facility, capital equipment costs and ongoing training and maintenance. Typically, laboratory tests incur higher fixed costs and lower incremental costs, allowing them to benefit from economies of scale as volumes increase.¹¹⁵ For the most part the opposite is true for POCTs.¹¹⁶

Many studies have focused on short-term episodes of care at the expense of a longer-term time-horizon.¹¹⁷ Episodic costs, such as laboratory testing, may be dwarfed by follow-up costs, for example the cost of hospitalization if complications arise.¹¹⁸ Also, while it is common for studies to include the cost of reagents used in testing, many studies have excluded the costs of non-laboratory staff time, assuming that additional workload can simply be absorbed into existing labour costs; this may not always be the case.¹¹⁹

9.8.4 Cost quantification

As LOS is the biggest financial opportunity cost, it is important to accurately disentangle exactly what portion of excess LOS can be attributed to inappropriate treatment management of infections. Once this is quantified, the analysis must further disentangle whether (a) improvements to turn-around time in identifying the infection or (b) more precise methods for identifying the pathogen and its antimicrobial sensitivity would most improve the clinical utility of the test. This requires measuring the changes in clinical outcomes associated with both these factors.

Attributing extended LOS to specific clinical causes presents significant methodological challenges. Recent statistical developments using multistate time-to-event analyses present the most promising results.¹²⁰ This study uses this approach to estimate the excess LOS associated with nosocomial MRSA infection in a large surgical population. Their findings suggest that excess LOS can be up to 14 days longer than for patients who are MRSA-negative.

Uncertainty about the specificity, sensitivity and turn-around time of many diagnostics makes it difficult to quantify their expected benefits, particularly when moving beyond a trial situation into everyday practice. Additionally, the uncertainty regarding prevalence of infections influences economic evaluations.

The costs associated with purchasing and implementing diagnostic platforms naturally also influences the cost–effectiveness of their use.^{121, 122} Stakeholders from private payers in the United States noted that any economic evaluation that takes place would be based on the (undisclosed) price negotiated between payers or providers and diagnostic developers.

Afshari et al. (2012)¹²³ identify some challenges associated with measuring the impact of molecular testing, including the non-replicable turn-around time declared by manufacturers. Under real-life conditions, delays from transportation, batch-wise analysis, etc. can all reduce the advantage presented by a test with a short turn-around time. For example, SeptiFast's reported turn-around time is contradicted by Lehmann et al.'s (2010) findings¹²⁴ and those reported by Dierkes et al. (2009)¹²⁵ in different settings.

Similarly, effectiveness can change when clinical judgement is incorporated into decision-making. A prospective cohort study by Fischer et al. (2004)¹²⁶ finds that physicians are remarkably precise in their prognosis of children and neonates suspected of blood infections and sepsis. This highlights the fact that diagnostic tests should *add* to empirical clinical judgement in order to increase their acceptability among physicians.

Some of these challenges result in poor uptake and negative perceptions among clinicians. Stakeholders in health care provider organizations highlighted their unfamiliarity with the methods used in cost–effectiveness analysis and the fact that commercial cost–effectiveness analysis studies used to motivate uptake are often out of touch with the reality of health care processes.

A competition run by Small Business Research Initiative (SBRI) in the United Kingdom aims to generate innovative health economic tools, products, and capabilities for modelling and assessing the impact of “near-patient” tests. Awards were granted in early 2012 to Diagnostics for the Real World (Europe) Ltd, Integrated Medicines Ltd and the Health Protection Agency (UK). The projects will focus on STIs and sepsis. The project titles are (in the same order) (1) Development of tool to assess the costs and benefits of the introduction of POC chlamydia tests; (2) Quantifying the impact on sepsis patient care pathway of POC testing; (3) Development of a tool for assessment of the impact of introduction of POCTs for STIs.¹²⁷ More initiatives like this would be beneficial in confronting the methodological challenges of diagnostic economic evaluations.

The analyses mentioned in this report vary between true economic evaluations comparing alternative courses of action, cost-minimization exercises or partial cost–effectiveness analyses. Various cost perspectives are adopted, but the majority of these use a hospital budgeting approach or physician variable costs. An increase in robust methodologies for assessing the relative value of diagnostic technologies is required, particularly including a social perspective.

Innovative diagnostic devices can help move health systems beyond curative medicine to personalized, pre-emptive medical approaches. For infectious diseases, diagnostics must be able to provide evidence that enables a clinician to change the course of a patient’s pathway. This may require that the diagnostic can (a) accurately identify the pathogen and its antimicrobial susceptibility and (b) complete findings within a short turn-around time. There is still a long way to go before the true costs and consequences are reflected in economic assessments of diagnostics for infectious pathogens.

9.8.5 Context

Where cost–effectiveness studies are available, a key challenge is applicability to a particular clinical setting; context matters. Existing studies cover a heterogeneous mix of costs and benefits, specific to the environment in which the study was undertaken rather than the test itself.¹²⁸ Changing the value of cost elements in the economic model, for example laboratory fees and staff costs, or assumptions such as the level of prescriber adherence to antibiotic de-escalation protocols influence the cost–effectiveness of a particular option.

The importance of context is borne out in the existing literature. For example, through a sensitivity analysis on the cost–effectiveness of the management of pharyngitis in a paediatric population, Van Howe and Kusnier¹²⁹ demonstrated how increasing the cost of undertaking a throat culture could tip the balance in favour of using a rapid test. Using the different reimbursement costs in the public and private sector, the study concluded that for Medicaid reimbursement, throat culture had the best utility, but when treatment was provided privately, after applying private health care prices, rapid antigen testing had the best cost utility. Similarly, in a study on whole blood glucose testing by Fleisher and Schwartz, a key benefit of testing at the point of care over undertaking the same tests in a centralized laboratory was the short turn-around time to obtain results. After a pneumatic tube system was fitted to quickly transport samples to a central laboratory, this benefit was lost.¹³⁰

Differences in the proportion of patients lost to follow-up is one explanation for Tsevat and Kotagal¹³¹ and Lieu et al.¹³² reaching different conclusions in their respective studies on the management of sore throats in children. The Tsevat

and Kotagal¹³³ study was conducted in a primary care office-based setting, with complete patient follow-up, and concluded that throat cultures were the most effective strategy. In contrast, a similar study by Lieu et al.,¹³⁴ which was undertaken in an emergency room setting and assumed a high patient loss to follow-up rate, concluded that it was better to perform a rapid test and then, only if results were negative, a culture.

The prevalence of an infection also influences the cost-effectiveness of using a POCT. In a study by Neuner et al.¹³⁵ on five different management strategies for pharyngitis, the sensitivity analysis showed that the cost-effectiveness of options differed depending on the prevalence of group A streptococcal pharyngitis in the population. Where there was prevalence below 10%, empirical treatment with antibiotics was the least effective strategy, but in an epidemic scenario, with prevalence over 71%, it became a more effective option than diagnostic testing.

Ideally, the way evidence is presented should allow for individual parameter variation such that local, more appropriate values can be used and thereby increase generalizability.

Chapter 10

Underlying and purpose-driven health system incentives affecting demand for diagnostics

10.1 Introduction

This chapter details how existing reimbursement structures often provide disincentives to the uptake of new technology as well as how financial incentives may be re-tooled to better utilize innovative diagnostic devices to minimize HAIs and slow the growth of antibiotic resistance.

New financial incentive structures intended to encourage hospitals to minimize HAIs could provide the serious momentum to bring new POC diagnostic devices to the market. Health care providers, third-party payers and device developers all realize that rapid POC diagnostic devices will be integral to staving off the spread of HAIs. Bringing these technologies into care pathways will require an integrated approach that incentivizes the appropriate uptake of innovative technology among them all.

10.2 Reimbursement

From the perspective of demand, the degree of certainty surrounding whether or not a device will be reimbursed can affect whether or not it is procured by health services (see Chapter 5 for an overview of reimbursement arrangements and discussion on how these affect developer decisions).

DRGs, or HRGs as they are known in the United Kingdom, are a widely used mechanism for reimbursement of public hospitals across Europe. As opposed to a fee-for-service reimbursement model that is based on volume of inputs (in this case, testing), under a DRG system, payment rates are determined prospectively but reimbursement made retrospectively based on outputs rather than inputs, with the creation of specific DRG reimbursement codes for specific indications. This has the effect of shifting risk from the purchaser to the provider of health care services, who then bears the effect of increased costs, for example for higher levels of testing for a particular indication.

DRGs in theory create the incentive to try to increase the volume of services provided, that is the number of patients treated for any given indication, while simultaneously lowering the cost-per-episode. Given that providers may have more control over the latter, this may be the stronger of the incentives in practice.¹ However, the desire to keep cases within hospital where they will be reimbursed, rather than in an outpatient setting, may act as a perverse incentive for hospitals if care and budgets are not integrated across sectors.

Payment levels in most cases tend to be based on average costs of a given group of providers, although they can be designed based on the costs of a group of the most efficient providers, or some other subset, such as grouped by facility size, depending on both the aims of the DRG reimbursement structure and ability to manage complexity in the design and management of the system. A number of negative incentives have been associated with the use of DRGs such as premature discharge of patients, “cream-skimming” of the more straightforward patient cases where possible, shifting of services to outpatient settings where they may be reimbursed on a fee-for-service rather than DRG basis, and the under-treatment of cases in order to save on costs. The latter two points in particular may be of relevance to the utilization of diagnostics. A study by Kwon (2003)² in the Republic of Korea found implementation of DRG reimbursement triggered some shifting of diagnostics to outpatient settings in order to shift the costs from the DRG. This incentive has been witnessed in other settings; Medicare in the United States, for example, does not reimburse diagnostics employed within three days of admissions in order to counteract this. While in some senses diagnostic manufacturers may be unaware of how and where their tests are used (as long as they are securing sales), shifting testing to different settings may have implications for budgets in terms of which part of the hospital is responsible for procuring and funding the diagnostics. This in turn may affect uptake, particularly if this separation impedes a complete evaluation by the hospital of the diagnostic’s value across the full care pathway. The final point regarding under-treatment may simply provide an incentive to under-request diagnostic tests in order to save on costs, which would negatively impact manufacturers. The reduction in test volumes under a DRG system was highlighted in a 2001 report in a United States health system context.³ The cost-reduction incentives associated with the use of DRGs as a reimbursement model may have particular implications, not just for sales of existing diagnostics but also for innovation and uptake of new technology. A United States Office of Technology Assessment Report⁴ concluded that the long-run ability of a DRG system to support the uptake of technology will require flexibility and adaptability of the system in order to regularly update changing costs, in particular adjusting DRGs to facilitate the uptake of desirable but cost-raising technology. This issue of flexibility equally applies to systems where explicit tariffs are in use for elements of pathology, rather than

DRG reimbursement, which is the case for some diagnostics in some settings in France and Belgium. Lack of flexibility in adding new tariffs or updating tariff levels to reflect higher costs of new innovative technology – particularly molecular diagnostics – has been raised as an issue by some manufacturers.

How costs are calculated in a DRG system will also have important ramifications for the uptake of technology. If, for example, the costs reimbursed are based on a subset of the most efficient facilities rather than the higher average of all, this may provide a stronger incentive for other hospitals to invest in cost-saving technology, including diagnostics, that may better optimize the care pathway. For facilities whose costs are already below average, their incentive to further invest in technology may depend on restrictions around their retention and use of any surplus. If, for example, surpluses are not retained within department but instead at a hospital level, the incentive for departments to continue to invest in technology that may further reduce costs may be dampened as compared to if they have full control of any surplus. In Germany and the Netherlands, for example, the DRG system operates within a broader global budget mechanism. In Germany hospitals receive a lower marginal rate of reimbursement once a certain volume threshold is reached, while in the Netherlands hospitals must pay back all DRG revenues which take them over the global budget.⁵

There is wide variation in both how the hospital sample for reimbursement levels is determined across Europe, and the size of the samples. In the United Kingdom, for example, where the NHS is a single payer, data from all hospitals is fed into the DRG system. In parts of Europe, where the payer does not necessarily have control of hospitals (for example private hospitals), there may be a lack of incentive for facilities to provide cost data and sample sizes may be smaller. In the Netherlands, hospitals are selected for inclusion based on a number of criteria that establish a facility's representativeness of the wider hospital system. In Italy, Germany and Spain, inclusion is based on mandatory use of specific cost-accounting systems to ensure greater consistency of data. The United Kingdom also has a small number of best-practice tariffs, where costs are based not on the average of all hospitals but on a smaller number of providers who have been deemed to be effective and efficient in a particular indication (by having standards of care that can be held up as best practice, supported by good clinical and cost-effective decision-making).

Beyond which data go into the calculation of costs within a DRG, how frequently the data is collected and the DRG updated will also impact the uptake of technology. In the United Kingdom, for example, one limitation of the tariff system is the time lag between the collection of cost data and updating of tariff levels. Cost data is collected in year 1, analysed in years 2–3, and used to form levels for prospective payments in year 4. Where costs and technology are stable

this presents no problem, but in segments of medicine where the pace of new innovative technology is relatively rapid, this may hinder the speed of uptake of new diagnostics.

It is possible to build in explicit mechanisms within a DRG system to encourage uptake of a particular drug or device that is seen as desirable on a system-wide basis. This can be done through the creation of new DRG codes that reflect the costs and utilization of new technology. For example, the Lombardy region in Italy created three new DRG codes specifically to incentivize drug-eluting stent usage. In many European countries the uptake of particularly innovative technology may be reimbursed outside of the DRG system at least in some circumstances, in acknowledgement of the barriers to uptake the DRG system may otherwise present. In Germany, for example, innovative tests, most frequently in the field of oncology or genetic diseases, are often introduced to the market as LDTs employing bespoke reagents even where CE-marked products exist.⁶ This enables reimbursement of the diagnostic on a code basis (similar to CPT codes in the United States) rather than via inclusion in a DRG. While this still may not reflect the true value of a test, it is one way of securing uptake of an expensive diagnostic that may otherwise be dis-incentivized through existing DRG structures. Overall, the evidence base of the impact of DRGs on technology uptake and diffusion is scarce,⁷ although the issue remains a challenge in many markets. In the United Kingdom for example, the average time taken to achieve widespread use of a new diagnostic within the NHS is around 10 years, with the report *Innovation in diagnostics and healthcare* identifying that the Department of Health may need to take additional measures to support uptake and diffusion of technology.⁸

Alternative reimbursement models for diagnostics

- *Value-based reimbursement.* While there are a number of reimbursement challenges in both Europe and the United States for high-value diagnostics, there are some ways of navigating the reimbursement structures to capture the product's value. For example, before 2012 a number of high-value tests secured reimbursement from Medicare/Medicaid in the United States, despite the relatively rigid CPT code system. Reimbursement may be achieved by code-stacking the various elements of the diagnostic in order to achieve higher reimbursement levels, although this is not a genuine value-based approach. As of the end of 2012, molecular diagnostic codes have been unstacked, recoded as units and new single codes for reimbursement have been created ("gap-filled"). This recent policy change is addressed in more detail

in Chapter 5. Alternatively, some manufacturers have been able to rely on the use of “not otherwise listed codes” or miscellaneous CPT codes that enable a unique level of reimbursement to be achieved that may better reflect the value of the diagnostic: a number of expensive tests, for example the Oncotype DX assay for breast cancer, have secured reimbursement into the thousands of US dollars under this latter approach.⁹ There is little evidence supporting the existence of such value-based approaches to date in the EU, and indeed market penetration of the aforementioned diagnostic in Europe remains low due to reimbursement barriers. Manufacturers, unsurprisingly, are highly supportive of a move towards a reimbursement model that more explicitly recognizes the value of their products.

- *Diagnostics subsidized by pharmaceutical companies.* Given the barriers to high-value diagnostics securing reimbursement, pharmaceutical companies may choose to financially support the use of a relevant diagnostic in order to support sales of their therapy. This has been most notable in cases of co-developed drug-diagnostic combinations, where lack of reimbursement for the companion diagnostic has potentially constrained sales. This approach has been employed by a number of large pharmaceutical companies in Europe, for example Roche has funded HER-2 or KRAS diagnostics in a number of European jurisdictions until the point when the diagnostic has secured public reimbursement. This may provide a short-term solution to the uptake of particular diagnostics but is unlikely to prove a scalable solution and may remain restricted to co-developed diagnostics,¹⁰ which represent a very small subset of available diagnostics in the field of infectious disease.
- *Coverage with evidence development.* One mechanism that is employed in a number of jurisdictions for pharmaceuticals is that of conditional coverage to allow for the generation of a more extensive evidence base. Patient Access Schemes are an example of this model in the United Kingdom, although, notably, in many cases the diagnostic does not form part of the reimbursement, even though only responders to the drug therapy are reimbursed. There may be scope for such schemes to be re-designed to secure explicit reimbursement for the relevant diagnostic. There may be an argument for using a similar mechanism to encourage uptake of particularly innovative diagnostics without a specific link to a pharmaceutical product if the diagnostic shows potential to significantly alter the care pathway, yet needs further supporting evidence to support uptake (which may prove difficult within the confines of a DRG-based reimbursement system.)

Commissioning versus procurement in the United Kingdom

Particularly given the structural shifts currently taking place in the commissioning of health services in the United Kingdom with the (re-)introduction of GP-led commissioning, an understanding of the conceptual and practical differences between commissioning and procurement may provide some insight into the challenges for providers of pathology goods and services in navigating the NHS landscape. The United Kingdom Department of Health describes the commissioning process as “the means by which we secure the best value for patients and taxpayers, meaning (i) the best possible health outcomes, (ii) the best possible healthcare, (iii) within the resources made available by the taxpayer”^{11, 12} Implicit within this is that there is a strategic element to commissioning that goes beyond procurement and contracting, indeed the “commissioning of laboratory services should be based on what it contributes to the care pathway, rather than the number of results that it can deliver for a given price, i.e. commissioning vs. procurement”.¹³ Given that many diagnostic manufacturers highlighted an overemphasis in the United Kingdom on cost savings versus health outcomes in their negotiations with health facilities (an assertion supported by a number of government reports into the use of diagnostic technologies),^{14, 15, 16} an understanding of how commissioning influences the procurement process, and potential shortcomings in the connection between the two, may be valuable in understanding and overcoming some of the challenges faced by manufacturers in securing sales for their products.

A report by Price and Jones (2008)¹⁷ highlighted that training of both commissioners and users of pathology services should be a crucial feature of the service provided by laboratory medicine in order to maximize the potential for pathology services to optimize the patient care pathway. This is particularly important where POC testing is involved, since education and training will form a crucial part of the quality assurance of POC testing. However, training may well be considered complementary to, rather than a replacement for, traditional lab services. The shift to patient-centric medicine demands an approach to pathology that understands how diagnostics can best be utilized to meet overall care objectives, rather than simple objectives set for a pathology service unit (such as volume of tests, quality, budgetary control). However, neither in the United Kingdom nor other major health care markets is the resourcing of laboratory medicine truly based on commissioning (i.e. strategic), rather than procurement (i.e. cost/volume), principles.¹⁸ For example, in the United Kingdom, resourcing of pathology services has largely been based on historical patterns rather than a forward-looking perspective. Further, a number of laboratory service reviews have noted that pathology has often been overlooked in broader health care planning, meaning that changes in clinical practice have not necessarily been supported by appropriate resource and practice changes in laboratory medicine.^{19, 20, 21} Decisions

within hospitals on introducing new technology require business planning, input from pathology on opportunities and issues surrounding implementation, as well as approval from clinical directors or trust boards. This means that manufacturers may need to engage with multiple contact points within a hospital to maximize the chances of their product being employed, again presenting a potential barrier to smaller firms that potentially lack the capacity to engage with multiple stakeholders as effectively as the larger global players. A report by the MHRA recommended that similar committees should be established specifically to evaluate POC diagnostics, to address issues such as clinical need, governance, uptake and quality assurance, with such groups required for community as well as hospital pathology procurement.²²

Another challenge is that in many contexts, including the United Kingdom, there is no specific mechanism to guide either the decommissioning of outdated technology or the introduction of new tests, resulting in both slow,²³ and sometimes inappropriate,²⁴ adoption, of technology. A clearer establishment of commissioning needs, and specifically how pathology can support these needs, would perhaps mitigate this issue. Where different commissioners are involved for different services, an integrated approach is required, given that pathology underpins a number of different health areas. However, it is acknowledged that this may in reality require a complex network of communication and interactions,²⁵ which may itself present a barrier to effective uptake of technology. Given that patient interaction with the health service will often span both primary and secondary care, to maximize effectiveness pathology services will also need to be integrated across the sectors, which again may bring with it issues of how services are procured and organized. The challenge for diagnostic manufacturers in this context is in navigating a complex commissioning and procurement environment, where their arguments as to the cost-effectiveness of the diagnostic on the overall care pathway may only be presented in a fragmented way to different units responsible for different segments of patient care. This is closely linked to the issue of siloed budgets, addressed below.

Consolidation of pathology services in the United Kingdom. Following recommendations from the Carter Report into pathology services in the United Kingdom,²⁶ there has been a major drive to consolidate pathology services across the NHS. This was driven by findings including excess capacity and wide variation in prices paid for pathology services across the country, suggesting major efficiency gains could be made. For example, the report found that labs processing 4 million samples had equipment costs double those of labs processing 30 million samples. Further, some 75% of sites examined in the report had utilization rates lower than 20%.²⁷ One recommendation was the creation of pathology tariffs based on the costs of larger facilities, with the aim of forcing smaller labs to consolidate, and

while the proposed tariff introduction has not yet been implemented, the strength of the recommendation in the report has stimulated consolidation nonetheless. This shift in the landscape may be a double-edged sword for diagnostics manufacturers: there may be benefits from engaging with a smaller number of larger customers, although the new enlarged pathology networks may exert greater power over pricing than smaller labs, meaning diagnostic manufacturers can no longer exploit inefficiencies in the pathology system to secure higher prices from some end-users. A short-term impact of the consolidation drive that may have provided a boost to manufacturers was the rush for many labs to position themselves as consolidators, rather than targets, which drove something of an “arms race” in building capacity and technological capability at some of the larger facilities.²⁸ Associated with the efficiency drive is also an increased focus on outsourcing of pathology services, either fully to private providers or in the form of PPPs, such as the arrangement between Guys & St Thomas’ Hospitals and the private firm Serco to run pathology services. While in general the rationale for outsourcing includes securing efficiency gains, which may be achieved through rationalizing technology use and more effective pricing negotiations with suppliers, there is little evidence yet as to the impact this trend may be having on diagnostic manufacturers in the United Kingdom.

Challenges in supplier payments. Fiscal pressures in the European countries most affected by economic recession, namely Greece, Portugal, Italy and Spain, are having important ramifications for the cash flow of diagnostic manufacturers. The pressure in the health financing system has generated significant delays in payments to suppliers in these countries.²⁹ While this may affect suppliers across the board, smaller manufacturers are most at risk from this issue as their capital positions may not be able to withstand the volatility in their cash flow generated by late payments.

10.3 Organization of budgets

Diagnostics manufacturers frequently raise the lack of integration of health care budgets across both hospital departments and health care sectors as a barrier to the uptake of potentially effective technology. Indeed:

much healthcare provision is managed on a ‘silo’ basis with individual units managed to their own targets, e.g. clinical, operational and financial; thus laboratory services have been managed quite independently of their clinical users and patient outcomes, with a greater emphasis on the number of tests provided, the analytical quality of those results, and the cost of provision.³⁰

The very nature of diagnostics, however, is that their impact frequently spans a number of different areas of the health (and social care) system. Where these areas all have separate budgets that are managed independently, the true value of the diagnostic across the entire patient care pathway is unlikely to be fully recognized by any one budget-holding unit. This may impact diagnostics in a number of different ways, for example:

- where pathology budgets are isolated from other clinical disciplines, there may be a specific disincentive for laboratories to support the uptake of POC testing elsewhere within the hospital, as this would potentially result in diminished testing, and therefore lower funding, for centralized pathology;
- across health care sectors, hospitals may be less keen to use outpatient diagnostics or rapid testing where it may lower admission rates, as within DRG reimbursement systems there is a general incentive to maximize admissions;
- unless primary care physicians bear the financial consequences of higher hospital admission rates, there may be little incentive for them to fund POC diagnostics within the primary care setting that may lower admission rates.

All of the above points present different challenges to manufacturers in making the business case to those responsible for diagnostic procurement. Units responsible for purchasing are unlikely to have the full picture of the value a diagnostic may add across the care pathway. This links into some of the challenges manufacturers face in the generation of evidence to support sales. Proving cost–effectiveness of their product may be key, but *from whose perspective* is critical. For example, if the introduction of a diagnostic would be cost–effective for primary care physicians, but hospitals run the purchasing decision, the lack of alignment of incentives may prevent the technology from being implemented. The generation of robust cost–effectiveness evidence is a continuing challenge for manufacturers and is addressed in more detail in Chapter 9; however, one recommendation to manufacturers is that good cost–effectiveness analysis needs to consider, among other things, costs all the way along the care pathway, rather than a narrow siloed view.³¹

10.4 Group purchasing

Hospitals belong to GPOs, designed to increase purchasing power and secure low prices for medical technologies required within the hospital setting. Additionally, GPOs function to facilitate comparisons and clinical evaluations to inform selections between products and streamline the purchasing process in a fragmented

system. Manufacturers supply the information directly to the GPO in order to enter into the contracting process. Technology evaluations form part of the process, and usually offer the supplier the opportunity to review the decisions. Contracting varies from case to case and there is no standardized process for awarding the contract. Usually it is based on competitive pricing as well as achieving a certain level of quality.

Usually there are anti-kickback laws for any federally funded programme, prohibiting wilful payments or compensations for contracts. GPOs are exempt from this law and the GPO is funded by a portion of the profit generated from the contracts awarded, creating concerns about perverse financial incentives. This means that hospital market uptake of a diagnostic technology may depend on aspects beyond its clinical utility, including the percentage of the profit agreed as “contract fees” during negotiation. Premier, one of the largest GPOs operating at a national level, sets its administrative fees at 3% or less.³² A report by the United States Government Accountability Office (2010)³³ estimates administrative fees in 2008 of between 1.22% and 2.25% of purchase. This presents a challenge if it means that competition between bidders may actually be based on the level of expected profit for the GPO rather than the clinical value of the product being sold, or its cost-saving potential for hospitals. Contracts negotiated with GPOs can either be regional or national and are usually prohibited from being longer than three years in duration.

In the past, these GPOs often used sole-supplier approaches to contracting from suppliers, where the one provider wins the contract for all hospitals served by the GPO. This obviously had implications for competition and market development for suppliers. More recently, multi-source contracting has become common, allowing multiple suppliers to be contracted to member hospitals and maintaining competition between suppliers in the market. Additionally there are special contracting procedures for innovative products that come to market outside of the usual contracting cycles. For example, Premier also has a technology breakthrough procedure, where new products that offer significant developments can be considered. Auctions and tender-style contracting processes are on the increase internationally, particularly for pharmaceuticals, and there is still much uncertainty about the longer-term implications for markets.³⁴

Litan and Singer (2010)³⁵ analysed the savings accrued by hospitals using GPOs and found that savings of 10–14% were reached, across all procurement and including aftermarket transactions (a second round of competition beyond that conducted by the GPO). Data specific to clinical laboratory services prices are not publicly available, but payer respondents suggested that most hospital procurers use the Medicare Clinical Laboratory Fee Schedule as a reference price from which to negotiate with suppliers.

10.5 Performance assessment

The issue of performance assessment must be viewed in the context of both diagnostic and clinical performance assessment. Both may present incentives or barriers to diagnostic use depending on the metrics used. Assessing pathology performance should extend beyond whether an accurate result has been delivered to include an assessment of the appropriateness of test requesting and subsequent decisions made on the basis of the diagnosis. A number of issues have been raised with respect to use of pathology services,³⁶ such as:

- results for tests which had been demanded urgently not being reviewed on a timely basis despite rapid reporting;³⁷
- POCT results not changing physician actions despite results being available at time of patient interaction (HbA1c example);³⁸
- tests being either duplicated, or missed.³⁹

Such issues are significant in that, if commissioners feel that current pathology services are not being used appropriately or in an optimal fashion, they may be reluctant to commit more resources to the area – even to support new technology – until efficiencies are made in current usage/provision. The inclusion of certain pathology indicators in clinical performance monitoring such as the Quality and Outcomes Framework (e.g. HbA1c in diabetes management) supports the tracking of appropriate diagnostic usage and may support uptake.

Where hospitals or clinicians are explicitly assessed on their performance relating to particular indications or patient groups, there may be scope for this auditing or assessment to influence clinical practice. The case of MRSA in the NHS provides a useful example of this. High rates of HAIs in the early 2000s prompted public health concerns and by 2004, following reports by the National Audit Office^{40, 41} highlighting the scale of the problem, the Department of Health acted to make the control of HAIs a top priority⁴² with plans including financial penalties, performance monitoring and support given to NHS trusts. A number of actions were taken at a national level to monitor infection rates, provide guidelines on managing infections and reducing prevalence, and create a system of mandatory surveillance and performance management.⁴³ Interventions regarding surveillance may support the use of diagnostics as their use will be necessary to identify cases. For example, in 2004 the Department of Health introduced mandatory *C. difficile* surveillance for hospital patients over the age of 65.⁴⁴ Specific mechanisms supporting the use of diagnostics in managing HAI rates have been the Technology Programme (2008), which includes the Rapid Review Panel (2004) aimed at speeding up the assessment of technologies which may help combat infection rates, and the introduction of mandatory MRSA

screening in 2009 at an estimated cost to the health service of £130 million annually from 2010/2011. While the Rapid Review Panel has conducted analysis of technologies presented to them, early indications were that this had not materially impacted uptake among trusts.⁴⁵ The screening programme caused a significant shift in MRSA testing from inpatient to outpatient settings. Where possible, patients are now screened pre-admission to prevent the transfer of MRSA infections present in patients in the community to hospital settings. This is an example of how public health priority setting can steer investment. Prior to this policy there had been a focus from manufacturers on rapid POC testing for MRSA. However, as hospital test volumes declined the incentive to invest in this area of R&D diminished.

Specific financial incentives to meet targets on infection rates may include agreements on reduction in infection rates built into primary care trusts' contractual financial arrangements with hospitals, with penalties for not meeting targets, and reduced premiums payable by trusts to the NHS Litigation Authority if inspections demonstrate compliance with clinical best practice on infection control and prevention. Regarding the latter, however, a National Audit Office survey of trusts found only 36% agreed that the potential for lower premiums had helped drive infection control.⁴⁶ Hospital trusts are required to report to the regulator, Monitor, on infection rates. This degree of transparency also provides a non-financial incentive to comply with measures to combat infection.

While the use of clinical best-practice guidelines or care pathways may support the use of diagnostics, there is little evidence that that the converse is true, that is, that they may present a potential barrier to diagnostic use, beyond where the use of a diagnostic has been excluded from guidelines where clinically it would add value to the process. Even in cases of acute indications such as sepsis, best-practice guidelines such as *Surviving Sepsis*⁴⁷ indicate antibiotic therapy should be administered within an hour of the suspected diagnosis, which in most situations should leave scope both to take cultures and, if available, utilize a POC diagnostic without compromising the care pathway.

In addition to monitoring clinical and pathology performance as it pertains to current practice, performance assessment must also be viewed in the context of analysing the impact of introducing new technology. Similar principles to a clinical quality audit can be applied to evaluating the impact of the change in diagnostic process. Metrics should seek to encompass the following areas in order to ensure a complete evaluation:⁴⁸

- prevalence of the indication (including current screening, diagnosis and monitoring activities)
- current clinical practice regarding diagnostic utilization

- existing clinical guidelines regarding testing
- clinical decision-making arising from diagnostic test results
- realized treatment interventions
- relevant health outcome measures
- resource utilization both before and after introduction of new technology
- divestment in resource usage arising from new technology (including decommissioning of old tests, reduced hospital time).⁴⁹

Critical to the above is understanding and measuring the impact of a diagnostic on the patient care pathway: before a technology is implemented, an understanding of this should be derived from current best practice (e.g. a Map of Medicine or other clinical guidelines).⁵⁰ Given the proportion of errors relating to laboratory diagnostic testing that are estimated to arise from the post-diagnostic phase,⁵¹ accurately measuring changes to clinical decisions made *following* testing will be paramount to understanding the true impact the diagnostic is having on treatment. The risk otherwise is that performance analysis will focus on the more quantifiable impacts of introducing the new technology, such as resource utilization and divestment, placing an overemphasis on costs rather than patient outcomes in valuing diagnostics. One difficulty as pertains to performance assessment of diagnostics for infectious disease, however, is that a key metric of interest is the influence that diagnostics may have on antibiotic prescribing patterns. While all hospital trusts within the NHS have antibiotic prescribing protocols, inpatient prescribing often remains a very manual process, which makes it difficult to track and assess data sets. A move to electronic prescribing should be a key mechanism to support better surveillance of antibiotic use. However many trusts have experienced delays in developing and rolling out such systems⁵² meaning the impact of introducing new diagnostics can be difficult to comprehensively assess. The impact for diagnostic developers is that generating a robust post-launch evidence base may be hampered by challenges such as the above, making it harder for them to prove the impact their product may have on the patient care pathway, or the cost-effectiveness of the new technology.

An example of the impact clinical guidelines may have on metrics such as cost and inpatient admissions is the impact of introducing a Map of Medicine in NHS Western Cheshire regarding appropriate intravenous antibiotic use in community setting for cellulitis: implementation of the best-practice patient care map demonstrated reduced monthly hospital admissions and minimum savings of £2000 per patient.⁵³

10.6 Public performance monitoring

Since around 2005, there has been state-mandated tracking and public reporting of infection rates for specific HAIs. Payer stakeholders agreed that this measure contributed towards improved infection control and that such measures are likely to increase in the future. It is difficult to identify the actual impact that such reporting measures have, but they do serve to raise public awareness and “name and shame” hospitals that are not doing very well. The evidence reported is comprised of a simple pre- and post-implementation comparison of infection rates for the targeted HAIs, with comparisons between regional, state and national aggregates. Although the link between improved diagnostics and reduced HAIs is not direct, accurate rapid diagnostics play an important role in directing care and reducing cross-infections.

10.7 Financial penalties for poor performance

Infection-related penalties can also influence demand for diagnostics. For example, as part of the Deficit Reduction Act 2005, Medicare DRG payments are quality adjusted for certain hospital acquired conditions, many of which are infection-related. Hospitals reimbursed using the IPPS are not reimbursed for costs incurred as a result of infections acquired during the hospital stay, only for the conditions that were present on admission. Table 10.1 includes all the HAIs relevant to diagnostic technologies for bacterial infections. If these ailments occur during the hospital stay, then the associated costs are not reimbursed.⁵⁴

Table 10.1 *Hospital acquired conditions that are not reimbursed*⁵⁵

Catheter-associated UTI
Vascular catheter-associated infection
SSI, mediastinitis, following coronary artery bypass graft
SSI following certain orthopaedic procedures: spine, neck, shoulder, elbow
SSI following bariatric surgery for obesity: laparoscopic gastric bypass, gastroenterostomy, laparoscopic gastric restrictive surgery
SSI following cardiac implantable electronic device

With the IPPS hospitals are incentivized to minimize cost of treatment and maximize patient throughput. The reduced payments for hospital acquired conditions or HAIs mean that hospitals face all the financial risk of costs associated with nosocomial infections, including increased variable costs and increased LOS. Increased LOS slows the volume of patients treated, leading to reduced payments. Additionally, hospitals face penalties for readmissions for some illnesses, including pneumonia, discouraging inappropriately early discharge.⁵⁶

Participants suggested that, as hospitals face increasing budgetary pressures and performance monitoring, they will need to invest in cost-reducing, time-saving technologies. Stakeholders from private health plans expressed the opinion that DRG-style payment methods will become increasingly common among private payers, increasing the financial incentives for cost-minimization and maximization of patient throughput within hospitals. From 2014 the new Health Insurance Marketplace⁵⁷ will be in place, and it is anticipated that most members will be covered with DRG-style payments for hospital care. This will increase the portion of hospital income dependent on DRG payments, strengthening the associated financial incentives. Additionally, some states, such as South Carolina, have amended state legal codes to allow private insurance companies to adopt the Medicare non-payment policy. This has the effect of strengthening financial incentives for providers, who are predominantly paid by non-CMS contractors.

10.8 Financial bonuses for positive performance

The Hospital Value-Based Purchasing Program⁵⁸ is a newly adopted approach to financial incentives for hospitals. Hospitals receive bonus payments based on their performance score – 70% of which is based on process measures – designed to assess how well the provider adheres to clinical guidelines. The measures of particular interest to infectious diseases are:

- percent of pneumonia patients who had a blood culture taken before they were given antibiotics
- percent of pneumonia patients who received the correct kind of antibiotics
- percent of patients who received prophylactic antibiotic within an hour prior to surgery
- percent of surgical patients who received the correct kind of prophylactic antibiotic
- percent of patients who had their prophylactic antibiotics stopped within 24 hours of surgery.

These measures will be influenced by the turn-around time of diagnostic technologies as well as their ability to correctly identify antibiotic susceptibility and the appropriate antibiotics.

The other 30% of the performance score relies on patient satisfaction measures. Kaiser reports that hospitals were able to increase earnings by 1% extra per Medicare patient in 2012, based on this performance system.⁵⁹ Medicare plans to increase the focus on true outcomes measures over the next few years, reducing

the weight of the process measures; this will mean that hospitals need to consider how a diagnostic technology contributes to patient outcomes improving in order to justify its place in a care pathway.

Positive financial incentive programmes for encouraging compliance with HAI prevention have also been put in place. Pennsylvania awards a quality improvement payment for providers who reach a benchmark percentage reduction in HAI. Tennessee requires hospitals to participate in their HAI prevention programme as a prerequisite for attracting state employee health insurance contracts. Several states have created funding specifically for HAI control, or use the funds gained through financial penalties to fund HAI control. For example, New Hampshire established a hospital fee structure to fund HAI programmes, with effect from 2011. Other states have a variety of funding mechanisms in place, including grants for surveillance, infection control, continuing education and training.⁶⁰

Chapter 11

Co-development of antibiotics and diagnostics for bacterial infection

11.1 Introduction

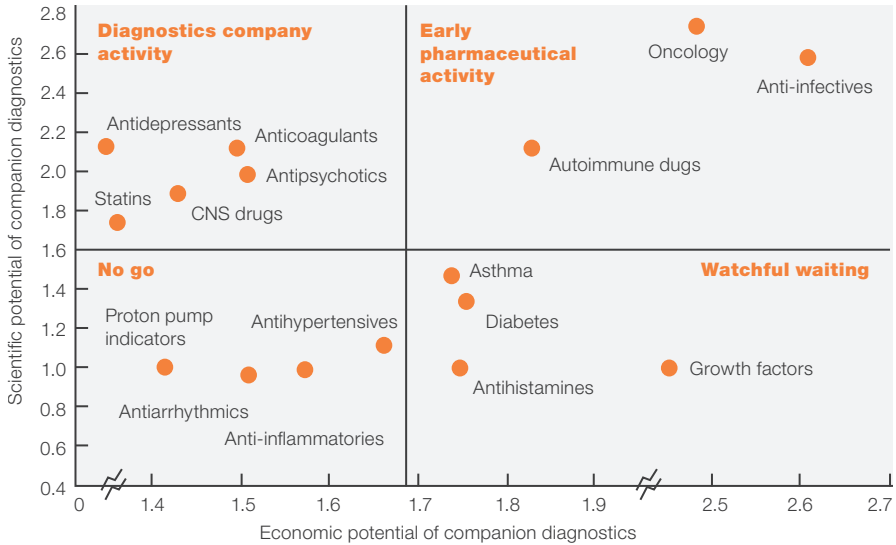
The need for new antimicrobials has become increasingly urgent with the rise of antibiotic resistant infections. However, the financial returns for pharmaceutical firms to invest in new antibiotic therapies are, in many cases, low. The development of accurate POC diagnostics has the potential to revolutionize the development of antibiotics by allowing firms to better target patients for trials and thereby lower development costs, and to better delineate target patient populations.

The co-development of antibiotics and diagnostics in particular could provide a path forward for innovating new therapies to combat bacterial infections. Promising examples of drug–diagnostic co-development in the oncology sector have provided potential models for similar endeavours in co-development of antibiotics with their companion diagnostic. However, there are significant challenges in aligning the interests of drug and diagnostic device manufacturers. For example, device manufacturers may welcome the financial support of large pharmaceutical firms, but may not want to limit their device’s scope by tying it to a specific therapy. This chapter highlights the challenges to co-development while emphasizing the important role POC diagnostics can play in shaping the future of antibiotic development.

11.2 Potential of co-development

This section lays out some of key issues surrounding co-development in general and in the area of bacterial infection in particular. A recent McKinsey & Co. study¹ based on both industry stakeholder interviews and quantitative price data highlights “companion” diagnostics for drugs in infectious disease as an area with both high scientific and high economic potential (see Fig. 11.1).

Fig. 11.1 *The scientific and commercial potential of companion diagnostics²*



11.3 Background: the nature and underlying differences in the market for antibiotics and diagnostics

In order to understand the possible synergies and challenges of co-developing diagnostics and drugs in this area, it is necessary to have a basic understanding of these two very different markets.

11.3.1 The new drug development architecture

Developers of antibiotics have come up against numerous challenges in recent years, leading to many firms de-prioritizing antibiotic development (for example, AstraZeneca in 2013) or pulling out of antibiotic development altogether (for example, Pfizer in 2012). This has left only a handful of companies still active in this area of R&D. The players that are left are making significant changes to the way they work. For example, recent years have witnessed a shift at major pharmaceutical companies from intensive R&D models to a structure characterized by smaller R&D teams complemented by broad horizon-scanning capabilities. With many new therapies, innovation often originates in small biotech firms that enter into partnerships with or are acquired by larger pharmaceutical companies once molecules/compounds show promise. David Payne, head of antibiotics drug discovery at GSK, said the business had changed the way it carries out research “to try to improve the economics of doing antibacterial discovery. In the past, we would have enormous numbers of people working

in this area. To be frank, I don't think we were very successful with those large teams," he said. But the company has since broken up its scientists into smaller groups and its approach "is based on creating partnerships and alliances with innovative biotech companies".³

Large pharmaceutical companies scaling back internal antibiotic R&D may have the unintended effect of reducing the level of in-house expertise required for successful horizon scanning in the space. This in turn may hamper the prospects (and therefore expected return on investment) of biotech firms conducting research in the antimicrobial sector. Furthermore, a shift of R&D out of large pharmaceutical firms with existing portfolios of antimicrobial products to SMEs that may have little or no existing product suite may reduce levels of incremental innovations as the SMEs do not have access to such broad portfolios to draw upon. Information sharing across various partners may be key to optimizing antibiotic research across the industry spectrum, although outside impetus may be required to stimulate such arrangements. The IMI's NewDrugs4BadBugs initiative, supported by EC funding, is an example that aims to have an underpinning of "an unprecedented level of knowledge and data sharing",⁴ and to reduce some of the inefficiencies of future antibiotic research by minimizing duplication.

An analysis of the companies behind these antibiotic candidates demonstrates the dominant role SMEs now play in the sector: 86% of the candidates come from 57 separate SMEs.⁵ This figure supports the aforementioned shift in R&D in the field from major global players. However, it is worth noting that large players may take an interest in candidates from SMEs as they progress through the development pipeline.

The relationship IVD manufacturers have with laboratories may play an important role in their ability to fully develop both the technology and, potentially, an evidence base for the diagnostic platform. It has been suggested that a triangular relationship between pharmaceutical, diagnostic and reference (or academic) labs could create a combination of partners better placed to push early LDT platforms through the FDA process as fully marketable IVD devices.⁶

11.3.2 Current challenges in the antibiotics market

Challenges in antibiotics market are outlined in full in previous work published by the Observatory,^{7,8} with a few key points summarized below.

Scientific/technical barriers

The first issue on the scientific front is one which faces many mature areas of research, namely that the low-hanging fruit and easy discoveries have already

been made, meaning incremental gains are more time and capital intensive as the industry has moved along the discovery spectrum. This is then closely linked to the financial barriers to R&D and reimbursement issues, namely that as each new potential candidate is more time consuming and expensive to research, pricing and sales volumes necessarily need to be higher to support the additional investment required to bring the product to market. Other scientific barriers specific to infectious disease relate to the nature of pathogens and their ability to evolve, which creates challenges. In the development stage, there are technical challenges in sampling in some indications: challenges include sample deterioration before specimens reach a lab for processing, and inability to gain sufficient concentration of the pathogen within a sample. The dynamic, evolutionary nature of bacterial organisms also presents specific issues to antibiotic developers. First, as the time taken to develop new antibiotics is in the region of 10 years, firms face the risk that over this period the target pathogen may evolve such that the antibacterial compound's effectiveness may be diminished before the drug even reaches approval stage. Second, pathogens may evolve to develop resistance to the compound once it is on the market, reducing the shelf-life of the product and therefore expected total sales.

Financial returns on investment

A recent report commissioned by the Office of Health Economics in the United Kingdom found the net present value of an antibiotic at discovery point is negative US\$ 50 million to the developer, as compared to positive US\$ 1 billion for a musculoskeletal drug.⁹ That the return on investment in the field of antibiotic development is so much lower than other categories of drugs makes it difficult to generate compelling internal arguments for firms to divert resources to this area relative to others, and explains why so few of the global pharmaceutical firms remain active in the space. While the cost of bringing a new antibiotic to market may not be higher than for new drugs overall, the low price payers are willing to reimburse antibiotics at, the short duration of antibiotic therapy (particularly as compared to that for chronic conditions, treatment of which may last the duration of a patient's life), and the fact that novel antibiotics are in general held back as a treatment of last resort – limiting the number of patients using the therapy – all contribute to the overall poor expected profitability.

Regulatory barriers

A regulatory change in the required delta values relative to approved comparator therapies is often cited as part of the reason antibiotic R&D has been in

decline. This change was made in response to concerns that inferior drugs were winning approval and then being used as comparators for newer therapies, thus lowering the bar for new approvals. While the motives behind the regulatory change were very positive, the result was a significant increase in the size of clinical trials required to meet approval, thus considerably adding to the costs of the approval process (Phase III trials are by far the most expensive stage in drug development). More recently, the most pressing regulatory challenge faced by antibiotic developers for some of the most acute indications is the difficulty in enrolling trial patients due to stringent rules in trial design, not least those which stipulate a patient cannot be administered therapy pre-enrolment. This presents a significant barrier to trials for serious infections where it would be clinically and ethically inappropriate to delay treatment to patients in order to facilitate trial enrolment. Many developers have suggested it is all but impossible to run trials for certain indications such as sepsis and ventilator-associated pneumonia. The extent to which United States regulation in particular has stifled antibiotic development has been the subject of much discussion, and prompted Janet Woodcock at the FDA to announce a “reboot” of the approach to clinical trials for antibiotics.¹⁰ Topics such as pathogen-rather than indication-specific trials, use of Bayesian methods in trial design, change in trial requirements in certain situations (such as LPAD – approval for an intended limited population) have all been up for discussion at recent discussions and round-tables.

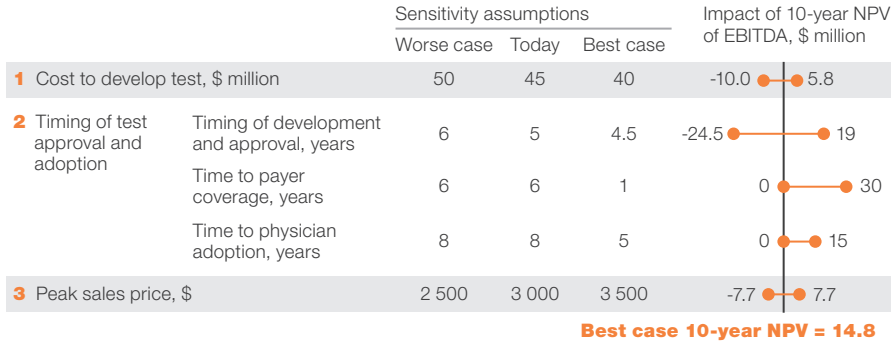
11.3.3 Cost of rapid POC diagnostic development

Industry estimates of the cost of developing a rapid POC diagnostic are broad, ranging from US\$ 10 million to US\$ 50 million depending on the platform and technology employed. This range covers both the costs of developing and of bringing a product to market. Depending upon the regulatory setting, trial costs alone are not insignificant: to achieve a CE mark in Europe, the trial element of the self-validation process can be expected to cost anything from £10 000 to £100 000. However, getting through the additional trial-related requirements of an FDA 510k process can cost manufacturers in the hundreds of thousands of dollars. While at these levels trial costs may not form the most significant part of the overall development costs, it is the stage at which these costs are incurred that may present a barrier. The trial stage, by definition, comes at a point when the diagnostic manufacturer has not yet proven the product and established a clear route to market, and therefore access to capital at this stage may be more limited than, for example, sourcing capital to support the manufacturing of a product with a proven clinical trial record.

Opinion is more mixed regarding the technical costs of development. One major diagnostics manufacturer suggested that the technical costs of R&D have not changed significantly over the past 10–15 years, as technical advances and operational efficiencies have offset more general inflationary effects. Rather, this manufacturer believes that the overall increase in cost of developing is driven by more onerous regulatory requirements. There is some evidence supporting a steep drop in the cost of some technical processes, such as genome sequencing. For example, it cost US\$ 300 million to sequence the human genome in 1990. This had fallen to US\$ 60 000 by 2008, with costs approximately halving every two years.¹¹ Others suggest that the move towards increasingly complex molecular diagnostics has been a driver of increased costs of development in recent years (Fig. 11.2). Historically it has been suggested that the cost of diagnostic development may have been in the “hundreds of thousands” of US dollars, but today these costs can creep well into the millions. A complex immunoassay may cost around US\$ 10 million to develop. In general it is acknowledged that molecular and PCR technology is more expensive to develop, and a shift towards such platforms may partially explain an increase in development costs. Further, payers are increasingly demanding greater functionality from diagnostics, including an increased demand for panel diagnostics and the ability to add drug resistance tests, both of which may add to complexity and hence development costs. Once a diagnostic platform is developed (which, for a rapid POC diagnostic, may be up to a five-year process), the incremental cost for developing and gaining approval for a new assay for the platform in Europe is frequently below €1 million, with the process taking less than a year. Both costs and time frame for approval are higher in the United States, with comparable costs expected to be in the region of €3–5 million and the process taking around 24 months.

The cost of diagnostic development pales in comparison to drug development. Improvements in technology development over the years have brought about a reduction in costs of diagnostic development. The aforementioned decline in the cost of human genome sequencing provides a good example of this. However, as compared to the overall prescription drugs market, the return on investment for diagnostics is also generally lower. The profit margin for diagnostics is typically lower due to a prevailing sentiment that diagnostics should cost less than drugs. Coupled with the short life-cycle of most diagnostic products (typically 5–7 years), this low profit margin presents challenges to developers seeking to ensure return on investment. Additionally, the speed of technological change in diagnostics is faster: a 2011 presentation to the FDA by Roche Diagnostics¹² highlighted the “unprecedented pace” at which both the science, and technology, in the field of molecular biology is moving forward.

Fig. 11.2 Estimates of cost and time to approval for molecular diagnostics developers¹³



NPV – net present value

11.4 Considerations for co-development strategies

11.4.1 Time to market and approval/success rate

Industry estimates from study participants indicate that the time taken to develop and bring to market a platform for a rapid diagnostic for infectious disease can be up to five years. Developing and gaining approval for incremental assays for the platform is generally a much more rapid process, often taking less than one year in Europe, although the time frame can be closer to 18 months to two years in the United States due to the additional regulatory hurdles there. This relative speed as compared to drug development (with antibiotic development potentially taking up to 15 years)¹⁴ highlights a significant mismatch in the development time frame of diagnostics as compared to pharmaceuticals, which consequently has ramifications for the potential for co-development of diagnostics alongside antibiotic therapies. A second important factor to consider is that diagnostics generally have a very high approval success rate given that the evidence requirements are much less stringent than the equivalent for drug approval. When this is compared to the high failure rate of therapeutic developments, this again presents another potential barrier to the co-development of diagnostics and antibiotics. The differing returns on investment, time scales and success rates of the two industries leads to differing risk appetites of diagnostic versus pharmaceutical firms. In particular, it means diagnostic firms tend to be more risk averse and, given the high failure rate of many drug therapies, a diagnostic manufacturer may rightly perceive that a co-developed product stands a much lower chance of regulatory approval if its use is explicitly linked to a drug that is still in development phase and may yet fail.

11.4.2 Technical skills

For non-culture based diagnostics, development can broadly be split into two parts: the development of the diagnostic platform and the development of assays for use on the platform (Fig. 11.3). The platform itself can vary widely from small POC cartridge-type devices which may have only a narrow range of diagnostic capabilities, to larger lab-based processing platforms which may be able to detect a combination of viral, bacterial or fungal organisms from a range of sample types (e.g. blood, urine, tissue), and may be configured for use with a number of different assays depending on the diagnostic requirements. As indicated previously, the bulk of the development costs and time lie in the development of the platform itself, which may take up to five years, with assay development being a more rapid process at less than one year (in the European regulatory environment). With an increasing shift towards more complex diagnostics that are molecular based, such as gene sequencing, the degree of technical expertise required to produce a successful platform is increasing. Beyond the challenges in successful design of a platform, the critical process of manufacturing is often overlooked in discussions of the R&D of diagnostics. However, industry stakeholders have identified this stage as one that contains both major challenges in ensuring quality control and consistency, and also potential scope for greater efficiencies. These are particularly notable at larger diagnostic developers that may have global manufacturing capabilities with scope for more effective capacity management.

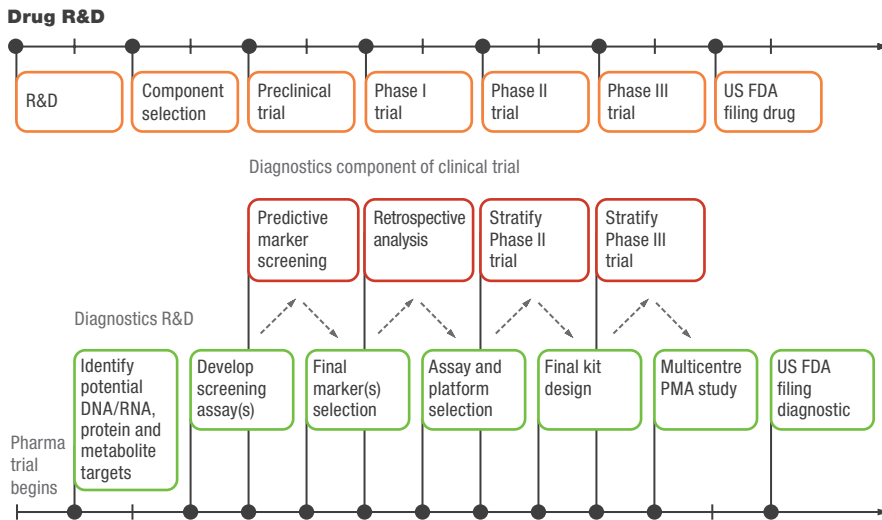
Fig. 11.3 Typical components required to develop a companion diagnostic (separate from drug development)¹⁵



11.4.3 Potential scientific and technical synergies of co-development

Particularly in the field of infectious disease therapy R&D, the identification (i.e. diagnosis) of the target pathogen or biomarker is a critical first step in attempting to find a therapy that is effective against said infection. The need for effective diagnostics is therefore deeply embedded in the drug discovery process. Further, technological improvements in diagnostics in particular have increased the opportunity for the effective development of companion diagnostics.¹⁶ The question of the need for co-development of diagnostics alongside the drug therapy is then one of determining at what stage of development, and exactly how, a new diagnostic can add value to the development process. In the case of personalized medicine, where the aim is to identify particular gene sequencing or biomarkers that may help stratify patients' response to a therapy, engaging early in the research phase with diagnostics manufacturers to identify potential biomarkers will be critical. Fig. 11.4 shows just how early in the drug development cycle engagement with diagnostics firms to identify potential target markers and screening assays needs to take place.

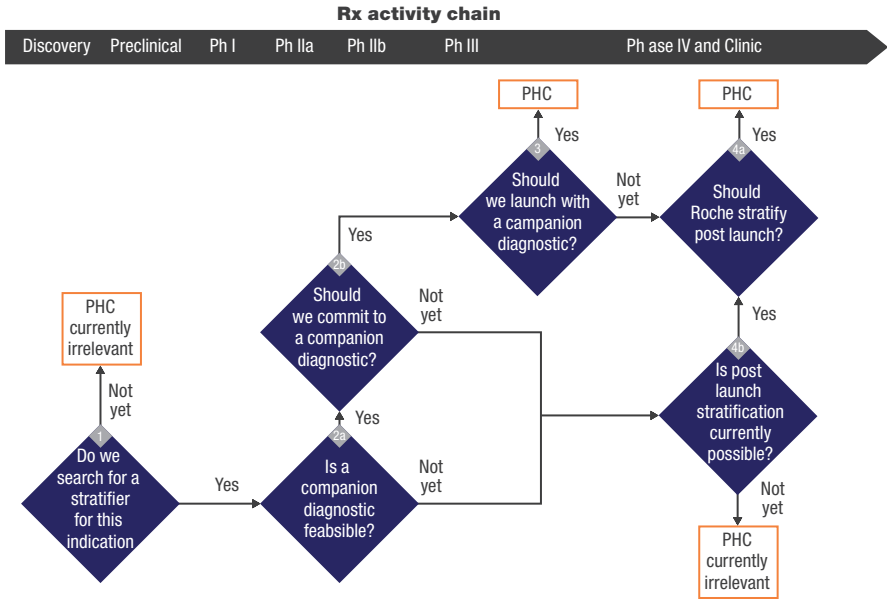
Fig. 11.4 Potential time-line for co-development of drug and companion diagnostic¹⁷



However as Fig. 11.5 suggests, while it makes sense for pharmaceutical firms to *consider* very early in the drug development stage whether or not to search for stratifying biomarkers, the full question of whether or not a companion diagnostic may be feasible is not necessarily addressed until later in the development cycle, for example at early Phase II. Indeed Fig. 11.4 (potential time-line

for co-development) also shows that, while early engagement with diagnostics firms is required, assay and platform selection may not necessarily take place until Phase II of the drug development.

Fig. 11.5 Life-cycle for co-development of a predictive diagnostic¹⁸



Where the aim of the antibiotic manufacturer is not to stratify patient populations, but rather to simply find a more effective diagnostic that may support patient enrolment in clinical trials, then engagement with a diagnostics partner may come slightly later in the drug development cycle.

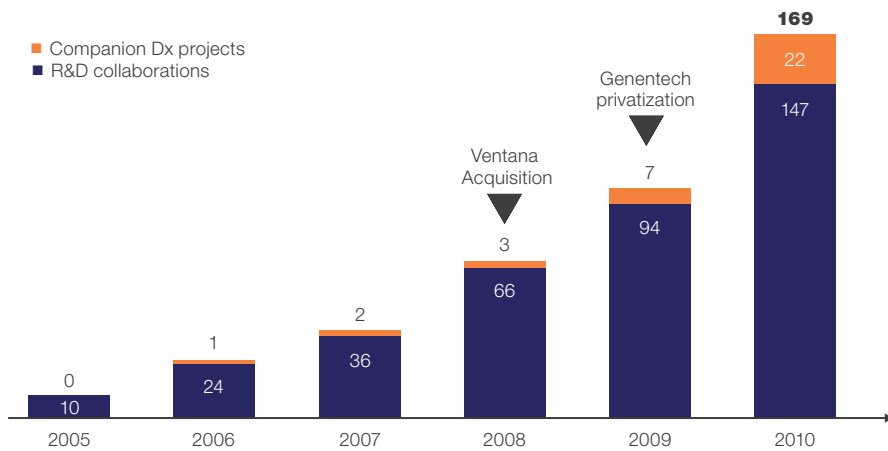
Whatever the objectives of the drug–diagnostic partnership, managing the concurrent development time-lines is critical. This is particularly important given the widely different development time-lines for the two products, with drug therapy development often taking up to 15 years, as compared to five years for a rapid diagnostic for infectious disease.¹⁹ This presents significant challenges to partnering when the diagnostic company needs to be involved at the earliest stage to determine the relevant pathogen/biomarker to be identified. Diagnostic manufacturers in general may be reluctant to engage in such an extended process when a stand-alone diagnostics product may reach the market significantly more quickly. This issue, alongside other barriers to co-development, is addressed in section 11.3.6.

11.4.4 Potential models for co-development

In-house development

Several of the large global pharmaceutical companies also have sizeable diagnostics businesses, although the extent to which the two are integrated may vary depending on corporate structure. Where in-house diagnostics businesses are long-established, that is, where they have been in operation long before the potential for companion diagnostics and personalized medicine has been a theme, the technical and strategic focus of the diagnostics arms may be quite different to that required for co-development and there may not necessarily be immediate synergies to exploit. However, some businesses are reconfiguring to meet the evolving scientific and medical landscape. For example, Roche has significantly increased the number of both R&D collaborations and specific companion diagnostic programmes between their pharmaceutical and diagnostics businesses over the past few years, driven by a calculated strategic focus on personalized health care (PHC) (Fig. 11.6).

Fig. 11.6 Increase in Dx/developers' collaborations within Roche²⁰



The issue of how companies that contain both diagnostic and pharmaceutical businesses are organized could potentially have a significant impact on barriers to collaboration and partnering, overlap of expertise and focus in the different business units, and incentives to co-develop. For example, where the diagnostics business sits completely separately, there may be direct competition for resources between units, little overlap in R&D pipeline, and weak managerial incentives or employee compensation structures in place to support improved communication and collaboration between units. An alternative model, where

firms have a diagnostics operation embedded into the pharmaceutical business, may offer greater potential for alignment of incentives, strategic goals and areas of R&D focus, in addition to potentially facilitating improved communication and exchanging of technical expertise between the therapeutic and diagnostics groups. The risk of this model, however, is that attention in the diagnostics business is purely aligned to the priorities of the pharmaceutical pipeline, which may mean profitable stand-alone diagnostics investment opportunities are overlooked, depending on the strategic goals and balance of power between the different units.

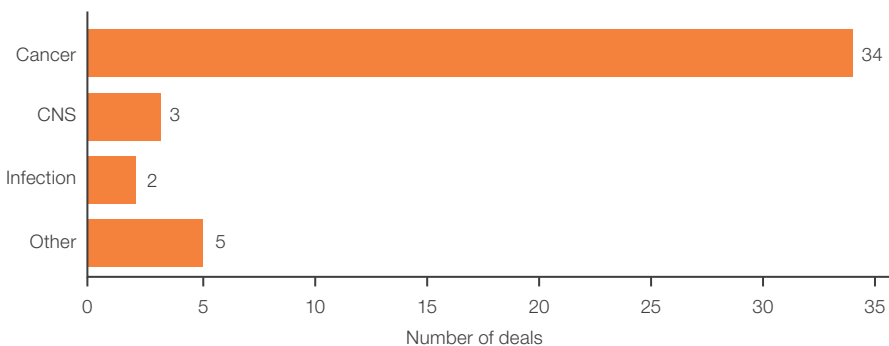
As discussed in Chapter 3, pharmaceutical firms have not been particularly active in acquiring diagnostics businesses, and have rather gone down the route of partnering with diagnostic firms for specific development needs. This raises the question of the relative attractiveness of in-house development versus partnering, and whether or not the evolving marketplace for personalized medicine and companion diagnostics are likely to alter the economics of internal versus external development in the future. That pharmaceutical firms without significant diagnostic businesses have focused on partnering suggests that currently the financial returns are such that it is more efficient to engage in specific, narrow relationships that bring particular diagnostic expertise to a drug development programme, rather than building in-house diagnostic capabilities from scratch. While intuitively internal development may offer economies of either scale or scope, this would be dependent on the portfolio of therapeutics the pharmaceutical firm owns and is developing, and what proportion of these may be suitable candidates for a companion diagnostic. To date, the bulk of companion diagnostics have been in the area of oncology, due to advances in tumour biomarkers and other gene sequencing in the field. This may explain why Roche, whose portfolio is heavily skewed towards oncology (particularly post the acquisition of Genentech in 2009) has placed such strong emphasis on aligning in-house diagnostic capabilities with their drug development pipeline. Their portfolio is such that they may stand to benefit from scale efficiencies of internal investment in diagnostics. Depending on configuration of the firm, internal diagnostic development may also bring various cost efficiencies and there may be opportunities to capitalize on manufacturing capabilities if facilities are flexible to accommodate adding products. As technical and scientific gains are made across a number of disease areas, the possibility of companion diagnostics for a greater range of therapies will increase, and this shift may lead to the case of in-house diagnostic development becoming more compelling versus external partnering for a larger number of pharmaceutical firms given the potential to exploit greater scale efficiencies. In short, the relative attractiveness of bringing diagnostic manufacturing in-house will be dependent on a number of factors as mentioned above, and in many current cases it may make more sense for firms to seek external partnerships, as discussed in the next section.

External development

Where firms' portfolios encompass fewer potential candidates for companion diagnostics, it will often make more sense to bring in external expertise to work on specific projects rather than aiming to build in-house capabilities from scratch. This approach offers potential efficiencies from only engaging with specifically relevant elements of the diagnostics industry. Further, it renders the pharmaceutical company free to seek an appropriate, best in class, diagnostics developer with whom to partner, rather than being reliant on in-house capabilities that may not be well aligned with the drug development requirements. This targeted approach may bring cost-savings versus building an internal platform, and enables the drug developer to capitalize on the most innovative technology available in the marketplace, which may bring further advantages to the drug development process.

While currently companion diagnostics partnerships are concentrated in the field of oncology (Fig. 11.7), the trend is beginning to extend to other disease areas. As shifts in technology make more companion diagnostics feasible, the economic arguments for pharmaceutical firms may tip in favour of building their own in-house capabilities rather than managing a diverse range of partnerships with a number of different diagnostic firms. This may be supportive for the diagnostic industry in the medium term should pharmaceutical firms become active in the diagnostics mergers and acquisitions space. However, likely targets may remain smaller niche players that add specific capabilities rather than large diversified diagnostic firms.

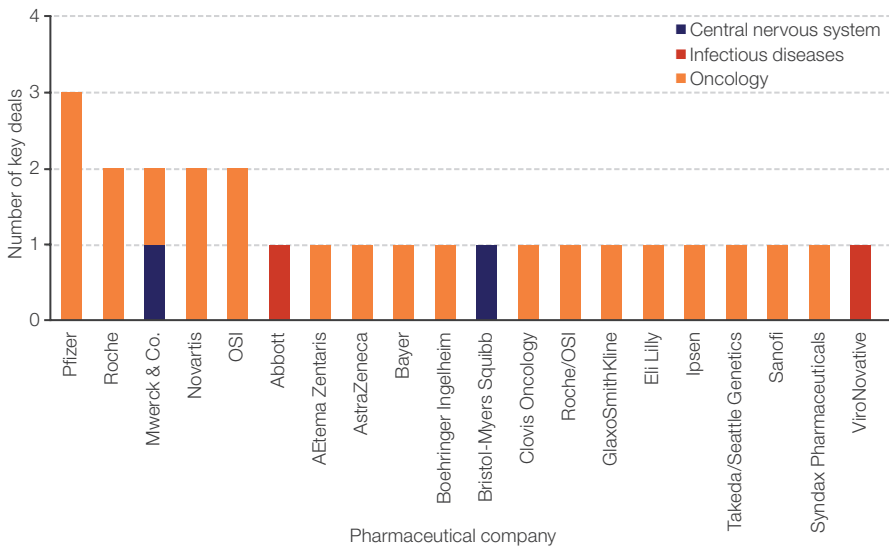
Fig. 11.7 *Number of companion diagnostic partnerships by disease area, 2009–2010²¹*



Source: PwC analysis, using data from Windhover, IVD Technology, and company press releases
CNS – central nervous system

Currently, many drug–diagnostic partnerships are dominated on the therapeutic side by larger pharmaceutical companies, as shown in Fig. 11.8. This may, however, be an artefact of the complexity and cost of structuring external partnerships, where smaller companies may have less capacity and expertise, rather than a reflection of partnering being of higher value to larger drug developers. Indeed, the reverse may be true in that smaller firms are less likely to be able to build any in-house capacity and would benefit from external relationships. However, particularly for small, early-stage enterprises, committing time and resources to external partnering may detract sufficiently from research priorities as to make it unfeasible to pursue.

Fig. 11.8 Key pharmaceutical–diagnostic deals by company and therapy area²²



Source: Datamonitor; MedTRACK Deals and Alliance Database, copyright Datamonitor, May 2012

Possible external partnership arrangements

There are a number of different forms that external partnering between drug and diagnostic firms may take depending on the nature of both the firms involved, and of the development project. Furthermore, as shown in Fig. 11.9, the relationship may evolve over the course of the development, with initial partnerships being based on research agreements and more detailed arrangements regarding commercialization and product development being formed once the concept has shown promise on both sides by clinical Phase II.

and a single diagnostic platform, with the partnership most likely entered into at the early stages of clinical development.

- *Framework agreements*, in the context of companion diagnostics, are not strictly a form of true co-development, and instead the diagnostic company may be brought in having already developed valid assays. In this instance, the benefit to the diagnostic firm is that the pharmaceutical partner may help to commercialize the companion diagnostic. Framework agreements may cover single or multiple drugs/biomarkers, on several platforms.

Partnering arrangements to develop companion diagnostics may use a range of financing mechanisms to support development; such hybrid deals may see exchanges in equity stakes, transfers of R&D funding and formal arrangements on profit-share on future sales. The possibility of the diagnostic manufacturer benefiting from royalty agreements based on the volume of future sales of the therapeutic has been mooted as one potential incentive to assist diagnostic companies in overcoming the barrier of uncertainty of uptake that companion development entails.

While the majority of companion diagnostic arrangements are between commercial partners, as areas of public health need have been identified that may benefit from research initiatives, PPPs have been used as a mechanism to support collaboration between drug and diagnostic companies. One such example is the EC-backed RAPP-ID programme²⁶ through the IMI to address the lack of rapid POC diagnostics for a number of infectious disease areas, including blood infections, lower respiratory tract infections and TB. Consortia members include major pharmaceutical companies (GSK, J&J, Merck, Novartis, Sanofi); diagnostic companies (LIONEX, microfluidic ChipShop, Mobidag, Q-Linea) plus academic research institutions. The programme is aimed at acting both as a funding mechanism to support research, but also to facilitate greater collaboration and knowledge sharing between the various partners in an attempt to find solutions to key public health challenges.

11.4.5 Rationale in support of pharmaceutical company engagement in co-development partnerships

For the most part, drug–diagnostic partnerships are initiated by pharmaceutical firms²⁷ rather than diagnostic developers. This suggests that the benefits accruing from such agreements may be stronger for the former. There are a number of potential incentives for drug developers to embrace companion diagnostics, ranging from potential benefits at clinical trial stages through to regulatory approval, to the opportunity to speed up drug development, lower costs and potentially

achieve premium pricing if higher efficacy can be proven in stratified populations. While at present medical practices mean empirical therapy is necessary, there are indications that more targeted therapy supported by diagnostic use will become more prevalent given cost pressures on health systems.²⁸ The above factors create a range of incentives for antibiotic manufacturers to engage in effective diagnostic use at various stages of the drug development and marketing process, which are explored in more detail below.

Increased therapeutic efficacy

Where an appropriate biomarker can be identified, efficaciousness of the therapy may be improved through being able to identify the stratified population who will respond most positively to treatment.

Improved risk/benefit profile

Again, by identifying the relevant population subset who stand to benefit most from treatment, the risk–benefit profile of the drug will be higher for this subset than the broader patient population. This may be particularly valuable in cases where a therapy has potentially serious side-effects that may hamper broader regulatory approval. By identifying a smaller strata of better responders to treatment, the risks of the side-effects may be outweighed by the improved efficacy in the limited population, increasing the likelihood of approval even if it is only for a more limited patient population.

Lowering clinical trial costs

Currently, antibiotic clinical trials rely on standard methods (biochemical identification of the bacteria and susceptibility values by either disk diffusion or MIC [minimum inhibitory concentration] micro-titer plates). Enrolment is currently based on clinical syndrome and other relevant findings. By improving the speed of diagnosis, rapid POC diagnostics could substantially facilitate RCTs.²⁹ Usually one site is planned for approximately every 10 patients (1000 patients would require setting up 100 sites). A fully powered trial in most indications (abdominal infection, UTI) is around 1000 patients.³⁰ POC diagnostics may help increase the possible venues for data collection and may allow for increasing the number of hours in the day in which patients can be enrolled (e.g. may extend beyond the work hours of the trial leaders or lab personnel). Crucially, better diagnostics may help minimize the use of prior effective antibiotics (a key factor in disqualification of patients).³¹

It has been stressed that the diagnostic device needed to facilitate trials need not be a fully marketable device. Indeed, it could be developed sufficiently for trial purposes only. However, the test would have to be validated if it was not approved already, and the validation of the test would be reviewed along with the other safety and efficacy data for the drug.

John Rex of AstraZeneca stresses that a diagnostic does not need to be perfect to be useful in trials: “Speed is as valuable as a specific diagnosis.”³² He explains that predictive diagnostics (the use of predictive markers) would have much value. Even just through providing some more microbiological info to trials predictive tests could help enhance trial findings. The lack of microbiological data due to insufficiencies in culturing doesn’t prevent patient data from being useful in trials. For example, since we do know that the patient took the drug, even without microbiological results the patient data still helps us understand the drug’s safety analysis and helps us understand more about the efficacy of the drug in general use (assuming that normal use doesn’t require firm microbiological findings). Rex explains that for bacterial infection you do have to make decisions without full information due to the deficiencies in culture. Knowing more about the organism – even if not a definitive identity – could offer greater diagnostic certainty, permit by-organism outcome analyses, and allow for susceptibility testing and subsequent correlation of susceptibility with clinical response.³³

Rex estimates that significant savings can be made from the use of such diagnostics in trials. Rex gives the example of community acquired pneumonia, which sees an average of only 30% positive cultures (leaving 70% non-evaluable). If a diagnostic could increase the proportion of evaluable tests from 30% to 50%, he estimates this would result in a 40% reduction in study size – and roughly 70% savings (cost reduction) in the case of being able to run just one Phase III trial.^a Rex suggests that the savings would be of a similar proportion in Phase II and Phase III – which have tended to cost approximately US\$ 20–25 million and US\$ 50–100 million respectively in trials for treatments of intra-abdominal infection and UTI. If this same estimate is applied to hospital-associated pneumonia and the proportion of evaluable patients is raised from a typical 50% up to 75%, this would result in the study size shrinking by a third.³⁴

Rex adds that the same diagnostic that supported the trial could also have value in routine care.³⁵

a This is based on the argument that one Phase III should suffice when preclinical evidence of efficacy is strong.

Enrichment of trial data

Co-developing a diagnostic alongside antibiotic may enrich clinical trial data if no appropriate diagnostics were already available to support the same functions. Furthermore, the co-use of rapid diagnostics, particularly in the case of molecular diagnostics, which may be able to offer a rapid tailored diagnosis, supports the ability to study more seriously ill patients in later stage clinical trials.³⁶

Increased probability of regulatory success

Targeted use of an appropriate diagnostic in the clinical trial and regulatory approval stages may increase the chances of regulatory success driven by the benefits outlined in the above points. In particular, regulators may be supportive of pharmaceutical developers identifying best responders, for example through the use of biomarkers, due to the ability of an effective diagnostic to support the process of proving clinical validity for a drug's intended use. Indeed "companion diagnostics [are] being driven by the FDA", according to Debra Leonard, MD, PhD, Chairperson College of American Pathologists Personalized Health Care Committee.³⁷ The regulatory benefits of co-development in antibiotics may increase over time as regulators adapt to the increasing trend for companion diagnostics in other disease areas, and the regulatory framework becomes more supportive of the approach. This could be in the way of regulation around the need to use appropriate biomarkers or diagnostics in clinical trial design, or by making the regulatory pathway of co-development easier for firms to navigate, as currently the process is not well mapped out in any major regulatory regime. Both drug and diagnostic firms may benefit from going through the regulatory approval process simultaneously as they are able to cross-reference their applications with supporting evidence, although this requires good lines of communication between the relevant departments for drug and diagnostics on the regulatory side.

Lowering risk profile of the development pipeline

For pharmaceutical firms, the ability to employ an appropriate diagnostic early in the drug discovery process may offer "early proof of concept *in the appropriate patient population*".³⁸ This lowers the risk of subsequent development, therefore reducing overall R&D costs as it enables the developer to focus resources on development projects that carry a higher likelihood of success. Furthermore, early use of a companion diagnostic may speed up time to market. For example, Roche's Zelboraf took only five years from Phase 1 to approval.³⁹

Faster drug development

Dr Kathryn Becker, Global Marketing Director for oncology at Abbott Molecular, comments that drug–diagnostics partnerships are starting increasingly early, with pharmaceutical companies no longer waiting until Phase II or III, noting that “earlier involvement may help studies and trials move faster”.⁴⁰ The need for early engagement is particularly relevant where the pharmaceutical company is not just seeking a new assay, but may require a whole new diagnostic platform and associated software to achieve the required results. The availability of a rapid diagnostic may support more efficient trials by improving the ability to select appropriate patients to enrol in trials (subject to regulatory restrictions) and by improving the speed of patient data collection and analysis. From a regulatory perspective, should the diagnostic provide higher quality patient data and more favourable risk–benefit profiles of the drug due to patient stratification, the review process is likely to be expedited.⁴¹

Opportunity for premium pricing

In addition to offering the potential for improved clinical outcomes, companion diagnostics may also drive more favourable commercial outcomes. The process of stratifying patients to target therapy more effectively lays the foundations to develop more nuanced arguments of cost–effectiveness of treatment. The co-marketing of drug and diagnostics may also encourage uptake and reimbursement of both products should the evidence be supportive of the ability to stratify appropriate patient populations quickly, driving improved clinical outcomes. This may support both premium pricing and uptake of the therapy concerned.⁴² There has also been some evidence suggesting that the pairing of a drug with a companion diagnostic may offer some protection from generic competition at the later stages of the drug’s life-cycle,⁴³ although this form of partnership post-therapy market launch does not require full co-development at an early stage. With regard to antibiotics specifically, where the R&D efforts are focused on a broad-spectrum antibiotic, there is little incentive to work to develop a companion diagnostic that may narrow the diagnosis. Instead, this paves the way for a more targeted treatment, but in the reverse case, where the compound under consideration has a very narrow target (for example *Pseudomonas* antibodies targeting a single pathogen), then drug–diagnostic partnerships are particularly compelling.⁴⁴ However, the partnership may have to be heavily supported by the pharmaceutical partner if the narrow focus is likely to limit the use of the diagnostic.

11.4.6 Barriers to co-development partnerships

While there are clearly a number of incentives to engage in the co-development of diagnostics alongside antibiotics, there may be significant barriers that prevent the conceptual benefits of external partnering from coming to fruition, which may be broadly categorized under strategic, logistical, financial and regulatory.⁴⁵

Strategic barriers

Given the different firm sizes, organizational structures, risk profiles and market landscape facing diagnostic versus pharmaceutical firms, it is unsurprising that strategic goals between the two industries are not necessarily well aligned. In particular, partnerships are often not seen as compelling for diagnostics companies for a number of reasons. First, their priorities are maximizing end-market sales, and therefore limiting a product to potentially being tied to a single therapy is seen as a negative. Furthermore, given the high failure rates of new therapeutics (especially when compared to that of diagnostics) the risk profile of a cooperative agreement may not suit the diagnostics firm. On a more fundamental level, infectious disease diagnostics developers are focused on identifying pathogens and antibiotic resistance, rather than patient response to any given therapeutic. Given the growing demand from both payers and clinicians for more flexible panel diagnostics which are able to detect a broad range of pathogens, and diagnostics to detect antibiotic resistance, this is likely to shift the strategic goals of infectious disease diagnostic manufacturers further away from wanting to be linked to a single therapy. More generally, partnering between any firms involves issues such as trust, the ability to effectively engage with diverse partners, and to structure complex contractual agreements. These may all act as barriers to firms forging external partnerships.

Logistical barriers

Even once external agreements have been secured, the challenges in managing fragmented partnerships may present a barrier to success. Cultural differences between the firms and difficulties in effective communication are cited as some of the potential issues, which may be particularly acute when getting distinctly different sets of product researchers working together effectively.⁴⁶ Where pharmaceutical firms outsource part of the early drug development work to contract research organizations, this adds an additional layer of organizational challenges to navigate within the partnerships and may make effective communication and alignment of goals more challenging.⁴⁷ A major logistical

challenge (that may also be somewhat strategic) is managing the time scale of drug-diagnostic development partnerships. As outlined earlier in this chapter, the time-line for the development of a diagnostic is generally much shorter than that of an antibiotic therapy, yet for effective co-development the diagnostic manufacturer may need to be involved at a very early stage of the drug development process, effectively extending time to market for the diagnostics manufacturer. This may lead to the diagnostics manufacturer being reluctant to commit significant resources at the early stages of the project when market success remains a distant prospect.

Financial barriers

The relative risk profile of drug versus diagnostic development raises a number of challenges for cooperation between the two industries. With generally significantly higher regulatory approval rates, diagnostics firms may be reluctant to partner with pharmaceutical firms when drug approval rates are so much lower. Given the different risk profiles, convincing a diagnostic company to engage in a co-development, particularly at an early stage when chances of therapeutic success may be hard to gauge, may be difficult. Even if this conceptual challenge can be overcome, particularly relevant for smaller, niche diagnostics players may be their lack of financial resilience to undertake such risky projects compared to a more “bread and butter” diagnostic for indications with well-established therapeutic pathways. Critical to addressing this challenge is negotiating appropriate economics of the deal such that cooperation from diagnostics manufacturers is incentivized. The often low share of value that diagnostics firms are able to negotiate in such partnerships has been identified as a recurring issue across the industry.⁴⁸ Furthermore, co-development projects may be particularly capital intensive for diagnostics firms, which may require financial support from the pharmaceutical partner to overcome this. In the case of a partnership between Pfizer and Monogram Biosciences, this was addressed by way of a US\$ 25 million secured loan offered by Pfizer to the diagnostic partner.⁴⁹ Where co-development is fostered internally, allocation of sufficient resources to the diagnostic arm at the correct stage will be critical. Feedback from a number of diagnostic manufacturers over the course of this study suggests that, given the risks of co-development, uncertainty over regulatory approval, potential labelling limitations, and approval of the diagnostic only for a narrower range of uses than a stand-alone development may enable, diagnostics manufacturers would expect the pharmaceutical firms to fund the lion’s share of the required R&D.

Regulatory barriers

The critical barrier facing early-stage co-development of rapid diagnostics alongside antibiotics is the regulatory challenge presented by using unvalidated diagnostics in clinical trials. In particular, using an unvalidated diagnostic to enrol patients in a trial would carry labelling implications, and the risk is that, if for some reason the diagnostic does not receive approval at the time of drug launch, then reimbursement for the therapy would become impossible. Even if there are no issues with approval of the diagnostic, having explicitly linked labelling limitations regarding diagnostic use is seen as undesirable for antibiotic developers, who do not want to risk sales being hampered by reimbursement and uptake challenges on the diagnostic side. Further, labelling implications may restrict use of the antibiotic to narrower populations which, where possible, would be avoided by the pharmaceutical developer. If it is not possible to use the rapid diagnostic to support trial enrolment, then much of the benefit of the diagnostic to the clinical trial may be lost as the use of rapid diagnostics to reduce trial population size is one of the largest cost-efficiencies the diagnostic may bring to the development process. However, the diagnostic may still provide information that enriches population data and enhances the development process. These restrictions on using diagnostics to enrol trial populations make co-development a less compelling option in cases where there is already a validated diagnostic option available. In antibiotics, given the “gold standard” of culture required by the FDA, the argument for adding an unproven rapid diagnostic which may have negative regulatory and reimbursement implications may be seen as too risky. This may explain why co-development has been more prevalent in fields such as oncology, where there is no equivalent to culture in terms of a universally accepted gold-standard diagnostic and the use of novel biomarkers is increasingly common. For co-development to become more accepted both in infectious disease and more broadly, it is argued that much greater clarification is needed on both the regulatory pathways for companion diagnostics, and clinical trial design for both the therapeutic and diagnostic in cases of co-development.⁵⁰ Given these issues, antibiotic developers engaged in this study indicated that, while there may be clear conceptual benefits accruing from using rapid POCTs in clinical trial settings, the *co-development* of these may be impractical and therefore not a high priority. Developers have a strong preference to use an already validated diagnostic wherever possible.

11.4.7 Industry dynamics of partnering and consolidation

Some of the barriers to co-development discussed above can be more broadly applied to the practical challenge of any business or industrial partnerships. These barriers may be overcome through more effective contracting, communication

and management of the partnerships. Of greater relevance are the barriers that are specific to drug–diagnostic partnerships, and in particular those in the field of infectious disease. Understanding these factors, and how the landscape may evolve, can bring some insight into the future of co-development, particularly regarding regulatory and scientific challenges.

On the scientific side, for a companion diagnostic to add the greatest value, it either needs to bring significantly improved speed of diagnosis with no loss of sensitivity or specificity, or it needs to be able to offer improvements on previous diagnostics through the use of novel biomarkers or assays. Not only does an appropriate biomarker need to be identified, its relationship to factors such as disease progression and therapeutic efficacy needs to also be understood.⁵¹ This may be easier in some medical fields than others, either on an absolute level due to the nature of the disease mechanism, or on a technical level given current scientific capabilities and understanding of certain diseases. To date, there has been greater incentive for pharmaceutical manufacturers to seek biomarkers in areas such as oncology, due to both the absence of effective diagnostic alternatives and the blockbuster potential of oncology drugs. This is linked to relative reimbursement issues for antibiotics compared to other sectors, for example oncology, where premium pricing is more achievable. However, as issues such as antibiotic resistance come to the fore, the need for manufacturers to be able to stratify responders will become more acute in order to prove the value of their product, thus potentially expanding the companion diagnostic trend into the field of infectious disease.

As pertains to regulatory challenges, should the landscape become either more supportive of companion diagnostics through the establishment of clear regulatory pathways, or more demanding of co-development through regulatory requirements around the use of biomarkers and other stratifying diagnostics, then there will be greater incentive for pharmaceutical firms to engage in co-development opportunities. While “currently pharmaceutical companies understand companion diagnostics as a way of salvaging an existing drug, rather than true co-development of a new drug entity”, says Dr David Dolinger, Head of Business Development for Seegene, a South Korea-based diagnostics company,⁵² greater regulatory onus for diagnostics in proving clinical validity of the therapeutic may force pharmaceutical companies to engage with diagnostics firms earlier in the drug development cycle, as is indeed beginning to happen in some cases. Further, should the regulatory environment become more demanding and/or supportive of companion diagnostics, then large pharmaceutical companies may be more likely to take diagnostic development in-house, rather than handle multiple external partnerships. This trend may take considerable time to manifest itself,⁵³ however, until companion diagnostics are a more firmly established part of the drug development landscape.

11.4.8 Examples of existing co-development arrangements

To date there has been no marketable co-development of an antibiotic and diagnostic alongside each other, with the majority of the high-profile co-development examples being from other areas such as oncology.

- Herceptin is often held up as the “poster child” of co-development. An analysis of the relative time frames of the drug discovery and diagnostic development process in this case are informative as to some of the potential challenges in partnering, and the appropriate stage for this to take place. The identification of the HER-2 gene as a biomarker for a particularly aggressive type of breast cancer dates back to 1987 when Genentech was developing Herceptin’s parent drug 4D5 alongside work by UCLA and the Texas Health Science Centre identifying the role of HER-2 over-expressing in tumor growth. The teams worked together to demonstrate proof of concept that 4D5 was able to suppress tumor growth of HER-2 over-expressing cells. Genentech initiated Phase I trials for the HER-2 antibody in 1992 and, while Phase III trials commenced in 1995, it was not until 1996 that Genentech partnered with diagnostic developer DAKO to develop a commercial test to identify patients who over-expressed the HER-2 gene, which acted as a marker for Herceptin best responders. Phase III trials were completed in 1998, at which point Genentech and DAKO simultaneously submitted applications to the FDA (biologic licence application, and PMA applications respectively). In September 1998, Herceptin, and DAKO’s HercepTest were approved simultaneously by the FDA, with Herceptin approval in the EU following in 2000.⁵⁴ That nearly a decade passed between Genentech working with academic partners on the diagnostic side, to signing a commercial agreement for the development of a marketable companion diagnostic, demonstrates clearly the time-frame issues involved in drug–diagnostic partnerships, namely the length of time often taken for drug development relative to commercialized diagnostic development. It is this mismatch that may often act as a barrier to the earlier involvement of commercial IVD manufacturers in the drug development process, although it is acknowledged by some IVD manufacturers that as diagnostics become more complex and time taken to develop them is increasing, the mismatch is becoming less of an issue than it may have been in the past. Once approved however, Herceptin and the companion diagnostic faced reimbursement challenges. In England for example, prior to NICE assessment of Herceptin, the manufacturer Roche paid for the HER-2 diagnostics.⁵⁵ The companion diagnostics to Herceptin, HER-2 and KRAS are rare examples of companion diagnostics that have been

assessed by NICE, but even following this appraisal, reimbursement of the diagnostics has been largely on a cost rather than value basis,⁵⁶ with the test generating estimated savings per test of US\$ 28 000 but only costing US\$ 100.⁵⁷ Elsewhere, for example in Spain, the manufacturers of Herceptin have resorted to subsidization of the diagnostic tests in order to maximize market penetration.⁵⁸

- *Pfizer/Abbot: Xalkori/Vysis ALK Break Apart FISH Probe Kit.* This drug–diagnostic combination is aimed at identifying the presence of the ALK fusion gene, which indicates likely patient responsiveness to Xalkori (crizotinib) treatment for late-stage non-small cell lung cancers. The drug and diagnostic were both approved at the same time by the FDA in 2011, with the drug, Xalkori, being reviewed under the FDA’s priority review programme.⁵⁹ However, pricing may be a barrier to uptake relative to other companion diagnostics in this instance. For example, while companion tests for Herceptin are in the region of US\$ 100 with a “hit rate” (i.e. proportion of potential responders in the patient group) of c.25%, Abbott Molecular’s companion diagnostic for Xalkori costs in the region of US\$ 1500, with only c.7% of non-small cell lung cancer patients being potential responders to treatment.⁶⁰
- *Oncotype DX.* Not strictly a companion diagnostic but one that supports stratified medicine. While uptake has become widespread in the United States, variations in the structure and timings of reimbursement between private payers have been highlighted as a challenge, with differing evidence hurdles required by different payers featuring among the challenges faced by the manufacturer in securing uptake.⁶¹
- *Curetis/Cempra.* Again, while not strictly co-development, this represents an interesting example of partnership, where Cempra seek to use Curetis’ platform in clinical trials for their antibiotic targeting community acquired pneumonia, despite Curetis’ platform not yet securing FDA approval.
- *IMI RAPP-ID programme.* A consortium of antibiotic and diagnostic manufacturers, alongside academic bodies, addressing rapid POCT for infectious disease.

Finally, it should be noted that much of what is understood about the potential for co-development partnerships between diagnostics and drug developers comes from the experience in cancer. This is, however, an imperfect model for co-development partnerships for drugs and diagnostics in bacterial infection due to overall greater reliability, predictive nature and time insensitivity of cancer diagnostics.⁶²

Chapter 12

Policy response

12.1 Rationale for intervention in the diagnostics market

While much progress is being made in the area of diagnostic development, there is little sign that these advances will be made in the areas of most interest to public health, including towards improved prescription of antibiotics or slowing the speed of growth of pathogen resistance. Indeed, this is an area with vested interests as companies stand to lose high-volume sales of broad-spectrum antibiotics. While perhaps not a lucrative market compared to others such as drugs for chronic infection (e.g. cancer, musculo-skeletal, etc.), global sales of broad-spectrum antibiotics have nonetheless provided a steady revenue stream – in some cases well beyond patent expiration. So overall, compared to other diagnostic categories that can in fact boost sales of expensive therapeutics substantially (see discussion of certain cancer-related companion diagnostics for example) this may not be an obvious area for investment.

While the amount of robust evidence supporting the use of rapid POC diagnostics to guide antibiotic treatment is limited, there are reasons to assume that much could be gained from encouraging the development of well-designed, fast and well-adapted diagnostic technologies at patient bedside. However, the fragmentation of demand and challenges in interpreting it leave a critical void that can for the most part only be filled by public intervention. Recent failure of uptake of new devices due to small but critical problems emphasizes the need to help steer any resources that are spent towards the most needed innovation.

As with all infectious diseases, bacterial infection has ramifications beyond the individual. This translates to there being a certain aspect of public good in improving diagnosis and treatment of bacterial infections. Other market failures include asymmetries of information, imperfect agency relationships, and an opaque price signal due to third-party payment. Together, these underlying complexities of the market suggest that there are allocative inefficiencies preventing resources from being expended in a way that maximizes overall societal benefit. On a purely economic basis this could suggest that some intervention is justified.

There is also an economic rationale for public support for diagnostic development and uptake. Cost-effectiveness associated with better targeting antibiotic treatment is changing. While most antibiotic therapies are currently available cheaply in generic form – creating few financial incentives to reduce clinically determined or presumptive treatment – this is likely to change. Higher-priced third line antibiotics and, perhaps to a greater extent, any new antibiotics (that we hope will come from the pipeline in the coming years) will make a much stronger cost argument for the need to improve and speed up the identification of bacteria and rule out differential diagnoses. From a public health perspective the need to protect these drugs – our small and shrinking arsenal – also places much emphasis on the need to better target prescription.

12.2 Initiatives to support diagnostics development

12.2.1 Background: the main types of incentives

Financial incentives generally come in the form of “push” or “pull” forms, the respective merits of which are outlined in Table 12.1.

Table 12.1 *Merits of incentive types¹*

PUSH MECHANISMS (subsidies to targeted research or development activities)	
Advantages	Disadvantages
Require smaller financial outlays	Pose the risk of funding unsuccessful research
Remove barriers to entry	Principal-Agent problems
Attract smaller companies (SMEs)	Risk is borne almost entirely by funder
Useful for encouraging discrete steps in R&D	Risk of dampening entrepreneurial momentum
PULL MECHANISMS (outcome-based rewards)	
Advantages	Disadvantages
Reward only successful research	Risk is borne entirely by developer
Minimize developer inefficiencies	Attract only developers with significant funding
More likely than push mechanisms to encourage final product development	Promise of large reward may lack credibility due to political and budgeting changes over the duration of product development
Can be designed to dampen developer incentive to over-market the product	Difficulty in predicting appropriate award size

Financial incentives to promote innovation in diagnostics have generally come in the form of push incentives, although with a few exceptions. Due to the relatively

small size of the reward compared to other sectors (e.g. drug development, space exploration), it is also an area that has seen considerable innovation in the shape of the financial incentive itself. Indeed, diagnostics are one of the first areas of research that have seen innovative incentive design.

Pull strategies to promote innovation in diagnostics are potentially suitable in that the financial outlay required to undertake development is not high compared to drug development – namely due to the current lack of expensive Phase III clinical trial requirements. However, for small companies the cost is still substantial and without earlier funding few could afford such an endeavour. Given the major presence of small companies and research groups at the forefront of diagnostic innovation all incentives should either contain early push funding or early milestone payments. Beyond these basic concepts, an exploration of previously implemented incentives can help shed light on further design ideas.

12.2.2 Funding (push incentives)

National Institute of Allergy and Infectious Diseases, United States

The NIH, an agency of the United States DHHS, is responsible for approximately a third of biomedical research funding in the United States.² Comprised of 27 different institutes and centres, funding for research into POC diagnostics is available from the National Institute of Allergy and Infectious Diseases (NIAID); its remit is to conduct and support “basic and applied research to better understand, treat, and ultimately prevent infectious, immunologic, and allergic diseases”.³

The NIAID offers both general and targeted funding awards relevant to diagnostic development.

The most popular research grant, known as the R01,⁴ is open to organizations of all types including small and large businesses, academic institutions and foreign organizations. There are no restrictions on the topic to be investigated – as long as it is in keeping with the goals of at least one NIH institute. There is also technically no financial limit on the amount of funding that can be requested. However, requests above US\$ 500 000 direct costs per annum are passed through a robust pre-approval process and even if a proposal is accepted, there is no guarantee, due to budgetary priorities, that the project will be funded. Most new investigators request US\$ 250 000 per annum or less, with awards lasting for a maximum term of five years.⁵ One key success story from the programme has been the development of the Xpert MTB/RIF test. Funding from both the NIAID and the Foundation for Innovative New Diagnostics was used to supplement the R&D investment made by the device manufacturer, Cepheid⁶ (see section 3.4.1 for more information on the Xpert MTB/RIF test).

Another popular grant is the R21, which is designed to support high-risk research. Investigators can apply for a maximum of US\$ 275 000 in direct costs over two years with a maximum of US\$ 200 000 for any single year; the maximum term of the award is two years.⁷ This grant is also suitable for projects that are smaller than would be appropriate for R01 funding and can be used by investigators to establish preliminary data that would support a future R01 grant.

Opportunities specific to small businesses are the Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) awards. Approximately 2.5% of the NIH extramural budget is set aside for funding for small businesses and is paid out through these schemes.⁸ Applications for grants are investigator-led, with funding priority given to projects where particular need has been defined by the NIAID; the development of POC diagnostics to identify a range of infectious diseases has been listed as a NIAID priority research area.⁹

The NIAID's targeted diagnostics initiatives have sought to encourage the development of diagnostics in a number of clinical areas including the identification of resistant bacteria. Key projects include:

- The 2006 “Partnerships to Improve Diagnosis and Treatment of Selected Drug-Resistant Healthcare-Associated Infections (U01)” (RFA-AI-06-036) research initiative which disbursed approximately US\$ 3 million to four projects supporting the development of therapeutics or rapid diagnostics for specific bacterial strains and drug-resistant phenotypes for the following health care associated pathogens: *C. difficile*, *Pseudomonas*, *Acinetobacter*, *Enterobacter*, *Klebsiella*, *Serratia*, *Proteus* and *Stenotrophomonas maltophilia*.¹⁰
- The 2008 “Partnerships for Point of Care (POC) Diagnostic Technologies for Nontraditional Health Care Settings” (RFA-AI-08-003) research initiative budgeted approximately US\$ 4 million to support projects advancing the development of POC diagnostics for pathogens causing STIs, UTIs, and respiratory infections, many of which demonstrate a high degree of resistance.¹¹ Research under the five awarded grants is ongoing.
- The 2010 “Partnerships for the Development of Therapeutics and Diagnostics for Drug-Resistant Bacteria and Eukaryotic Parasites” research initiative (RFA-AI-09-029), focused on advancing the development of diagnostics and therapeutics for drug-resistant pathogens. The maximum applicants could apply for was US\$ 1 million total costs per year up to a maximum of three years.¹²

- The “Partnerships for Biodefense” programme began in 2001 with periodic allocation of project funding. The scope includes the development of POC diagnostics for pathogens that pose a threat to national security, including the identification of drug-resistant microbes.¹³

The NIAID also provides non-financial support in the development of diagnostics. The Tuberculosis Clinical Diagnostics Research Consortium was established by the NIAID in 2009 through the award of a contract to Johns Hopkins University. Comprised of scientists, clinicians and support personnel, the consortium undertakes feasibility and evaluation studies of new diagnostics in order to provide feedback to the technology holder. Developers can apply to have their technology reviewed. At present, four early-stage diagnostic tests are being evaluated for clinical feasibility and the consortium is contributing to cost-effectiveness modelling studies for the Xpert MTB/RIF TB test.

To ensure the NIAID is targeting funding appropriately, there is an extensive planning process that begins three years in advance of funding being offered. The view of Dr Alec Ritchie was that stakeholder engagement was essential to identify the correct priorities to target through funding. Other important considerations he suggested included: finding the correct balance between being inclusive towards a variety of development approaches, being specific in what is required so that output is focused and measurable, and also ensuring that the duration and amount of funding is appropriate for the type of science required in the development process.

Although Dr Ritchie believes that the NIAID grants play a part in influencing R&D investment decisions by diagnostics manufacturers, he was clear that they are never sufficient to fully fund development. Investigators also need to find funding from elsewhere. Typically, it tends to be smaller organizations that apply for grants.

Information on topics discussed by the NIAID’s Advisory Council provide an indication of likely future funding opportunities¹⁴ and there is the option to sign up to an electronic newsletter to receive electronic alerts.

Biomedical Advanced Research and Development Authority, United States

While the NIAID supports early-stage development of new diagnostic tools, the Biomedical Advanced Research and Development Authority (BARDA), an organization within the Office of the Assistant Secretary for Preparedness and Response (ASPR) in the United States DHHS, supports the advanced R&D of products considered a priority for national health security.¹⁵ Its portfolio includes projects to develop antibiotics, vaccines and diagnostics.

In 2010, BARDA awarded contracts to two consortiums to support the development of platform technologies to rapidly diagnose influenza. A key success was BARDA's support helping to achieve FDA 510(k) clearance for the Focus Diagnostics Simplexa Flu A/B & RSV Direct Test on the 3M™ Integrated Cycler; the moderate complexity test can be undertaken by a broader range of health professionals compared to previous tests.¹⁶

As part of President Obama's National Action Plan for Combatting Antibiotic Resistant Bacteria, BARDA and the ASPR have agreed to fund at least three novel diagnostic development projects that take advantage of next-generation sequencing technologies, multiplexing assays and other innovative technologies. The ultimate goal is to fund technologies that will shorten the time required for accurate diagnoses and assessments of drug resistance.¹⁷ The NIH, ASPR and BARDA hope that their combined funding schemes will develop at least one new diagnostic product that can be submitted for FDA approval or clearance within a year.

Defense Advanced Research Projects Agency, United States

The Defense Advanced Research Projects Agency (DARPA), an agency of the United States Department of Defense, commissions translational research to bridge the gap between new scientific discoveries and military use.¹⁸ DARPA use a range of possible funding instruments, matching their approach to the needs of a specific challenge.

In the area of diagnostics, with the aim of providing service personnel with on-demand information about their health, DARPA has recently commissioned a five-year programme known as ADEPT (Autonomous Diagnostics to Enable Prevention and Therapeutics).¹⁹ The programme has a number of branches. In 2011, DARPA solicited for proposals for a credit-card sized point-of-need diagnostic that would support decentralized self-collection of a sample that could then be transported under ambient conditions for analysis at a centralized laboratory with minimal degradation of biomarker integrity.²⁰ Benefits of this approach include overcoming the current challenge of specialist staff such as phlebotomists being required to support sample collection, while ensuring that clinical staff, and not just the individual who has taken the test, have access to the test results to support clinical care.

In another arm of the project, investigators are working to develop novel platform molecular diagnostics with integrated technology that can generate clinically actionable data from a specimen deposited in the device. This technology could be used either at the point-of-need or within a clinical/laboratory setting.²¹

Any organization type, ranging from universities to large corporations can respond to a request for proposals and each funding agreement is bespoke. The funding level agreed for a particular project is tailored to the degree of technical risk and the nature of the capability to be achieved. IP rights are also individually negotiated, but typically DARPA does not seek IP rights that would be a barrier to commercialization of a technology.²²

In DARPA, programme managers play a pivotal role in conceiving and driving forward projects. Therefore, they require significant expertise in their area of interest. Lt Col. Daniel J. Wattendorf, MD, USAF, project manager of the ADEPT initiative viewed his role as not simply facilitating funding for research but also supporting the close management of research projects that have been commissioned, including monitoring progress, adapting the agreed work plan or terminating projects that are not producing the required outcomes. Success factors cited by Lt Col. Wattendorf included having a strong relationship between the programme manager and contracting officer, ensuring that all people relevant to a discussion are represented and openly discussing the possible issues of concern such as IP to ensure that the expectations of all parties are clear.²³

A disadvantage of having a tailor-made approach to commissioning research is that it can be burdensome to design individual funding contracts, but a silver lining identified by Lt Col. Wattendorf is that this can ensure that all parties have a clear understanding of the agreement.²⁴

In the 1980s, faced with problems engaging civilian companies as a consequence of the administrative burden inherent in traditional contracting methods, DARPA was given federal approval to optionally use a method of contracting known as “other transaction authority”,²⁵ a more flexible approach than contracts, cooperative agreements and grants.²⁶ Although not yet used by DARPA in the area of POC diagnostics, this approach has been used in projects linked to vaccine development.

Bill & Melinda Gates Foundation, United States

The Gates Foundation partners with organizations internationally to tackle critical problems in a number of programme areas including global health.²⁷ Focused on the challenges of the developing world, much of the funding available is allocated to United States tax-exempt organizations which have been proactively identified by Gates Foundation staff.²⁸ Organizations are able to submit funding requests that are relevant to the Foundation’s published funding priorities. Recent grants that have been awarded to support the development of POC diagnostics in the identification of infectious disease include a US\$ 960 749 award made in June 2012 to the Research Institute of the McGill University Health Centre,

Montreal, Canada for a two-year project to develop TPPs for POC TB testing to aid validation work for TB POC devices and a US\$ 1 435 615 award made in November 2011 to the Foundation for Innovative New Diagnostics for a three-year project to identify and validate biomarkers that could be used to support the POC detection of TB.²⁹

Framework Programme for Research and Technological Development, Europe

The 7th Framework Programme for Research and Technological Development (FP7) is the EU's main funding instrument for R&D and aims to boost Europe's growth and competitiveness. The budget for the scheme between 2007 and 2013 is €50 billion, with €6 billion allocated to health-related projects.^{30, 31}

Grants are provided to co-finance research, development and demonstration projects, and funding is allocated on the basis of calls for proposals and a highly competitive peer review process. Almost any type of organization, including academia, SMEs, civil society and corporations can apply for funding. Cooperation with organizations in non-EU countries is strongly encouraged, but there are some restrictions on access to funding by researchers in non-EU countries.³² Any funding provided is not repayable and, within a consortium, partners are responsible for making their own provision to protect the IP rights to their work.

FP7 is comprised of four main funding programmes:

- the *Cooperation* programme, which represents two-thirds of the overall budget, fosters collaborative research in 10 thematic areas (including health);
- the *Ideas* programme supports basic research in area of science and technology with no requirement for transnational cooperation;
- the *People* programme supports researcher training, mobility and career development; and
- the *Capacities* programme aims to strengthen Europe's research capacity, for example through funding the development of research infrastructures.

The scheme aims to offer "European added value" to complement national research programmes; for example a requirement of certain types of funding is that research is undertaken by an international consortia, or a funding call may be made where there is a benefit in raising the level of competition for funding from national to European level.³³

Examples of current or recently completed projects include:

- An €8 million contribution over four years towards the TheraEDGE project, which aims to improve diagnosis of lower respiratory tract infections in primary care through developing a rapid POC diagnostic that simultaneously detects pathogens and their antibiotic resistance.³⁴ The project is coordinated by the diagnostics manufacturer BioKit, which worked with 15 different clinical, academic and commercial partners. Recently, the FP7 co-financing for the project has finished. Project Co-ordinator Francesc Guasch reported that the funding had helped in the development of a prototype device. Work is currently under way to commercialize the product. Lessons learned included the importance of selecting the right partners, ensuring that collectively they have the relevant skills to support the project and also commitment to the work that needs to be undertaken. In both respects, Francesc Guasch believed the project has been successful. The project involved developing a number of separate components for the device and one problem that did affect the project was unforeseeable delays occurring in the development of individual components, which slowed progress overall.
- A €3 million contribution towards the Tempotest-QC project, which aims to develop a toolkit to support the clinical evaluation of POCTs that detect microbes and antibiotic susceptibility. The scope includes surveying Europe-wide demand for POCTs and developing an archive of freely available samples to support quality control/assurance.³⁵ The project is being coordinated by the Erasmus University Rotterdam with five partners.
- A €2 million contribution towards the SLIC project which aimed to develop a cost-effective platform for the identification of bacteria based on the SLIC-Nanobiosystem.

The 8th Framework Programme for Research and Technological Development, known as Horizon 2020, will run from 2014 to 2020 with an €80 billion budget.³⁶

Grand Challenges Canada, Canada

Funded by the Government of Canada, Grand Challenges Canada is an independent, non-profit-making organization that works in a consortium with Canada's International Development Research Centre and the Canadian Institutes of Health Research to fund innovation in low- and middle-income

countries and Canada.³⁷ As the name suggests, it adopts a “grand challenges” approach to funding: first, critical barriers are identified that if removed would help solve a high-priority global health problem; the scientific community is encouraged to find solutions to the problem through competitive selection as well as project funding; and, finally, support is provided to implement solutions that emerge.³⁸

Creating a new simple, cheap, multiplexed POC diagnostic for the developing world has recently been identified by the organization as a “Grand Challenge” and, in partnership with the Bill & Melinda Gates Foundation, almost US\$ 32 million is in the process of being disbursed to 22 different grant recipients over three years to work on five different research areas:³⁹ sample collection, concentration and preparation; amplification and detection technologies; readout and signal transduction; enabling technologies and implementation research.⁴⁰ In 2014, after the first three years of the project, an anticipated second wave of development will integrate the best-in-class diagnostic components that have emerged into one or more interoperable POC platforms that support running a menu of tests from different developers.

Dr Ken Simiyu, Program Officer at Grand Challenges Canada, explained that the motivation behind developing an interoperable platform approach included lowering barriers to entry to the market so that developers could focus on a specific plug-in test rather than the complete device. This approach also offers simplicity for users and makes it easier to achieve regulatory approval.

To maximize the chances of an innovation achieving global impact, Grand Challenges use a strategy known as “integrated innovationTM”; scientific and technological innovations are developed in parallel with research into how the technology can be implemented in a specific context,⁴¹ for example identifying how a product can be delivered at an affordable price and how to establish enablers such as regulatory approval and having sufficient human resources. When applying for grants, investigators were asked to submit a proposal outlining how they would engage clinicians in development and how the technology would be deployed in a real-life setting. Grand Challenges also supports grant recipients by connecting them with relevant experts in low- and middle-income countries to help inform developers. For Dr Simiyu, this integrated approach to developing technology is critical to the success of projects. Ultimately, if barriers to implementation are not addressed, projects will fail.

Grand Challenges also contributes to related initiatives that are working to overcome barriers to implementation. This includes the “Affordable Access Project”, a collaboration between the London School of Hygiene & Tropical Medicine, the Bill & Melinda Gates Foundation, and others to identify approaches to harmonize regulatory approval processes for POC diagnostics.⁴²

The 22 grant recipients meet twice a year through community meetings, offering an opportunity for networking and scientific peer review of projects. Dr Simiyu viewed this as an important way of encouraging collaboration between investigators that has translated into benefits such as exchange of specimens and technology.

The IP of any technology developed remains with the developers; however, in accepting funding from Grand Challenges, developers need to sign a “Global Access” agreement, which requires that products are accessible to those in need in the developing world, both in terms of availability and price.⁴³

In addition to the dedicated POC diagnostics programme, developers can apply for funding through a more general “Stars in Global Health” programme. Investigators define their own challenge and can request funding of CAD\$ 100 000 for proof-of-concept studies and up to CAD\$ 1 million for transition to scale.

Innovate UK

Innovate UK (formerly the Technology Strategy Board) is an executive non-departmental public body which was established by the British government in 2007 with a remit to boost United Kingdom growth and productivity through encouraging technology-enabled innovation.⁴⁴

Innovate UK’s work on diagnostics was born out of a United Kingdom government foresight report on the detection and identification of infectious diseases. The report identified both the potential benefits of rapidly diagnosing infections at the point of care, as well as the presence of funding gaps to develop such technologies.⁴⁵ With the support of the NHS NIHR, Innovate UK has budgeted £55 million over a five-year period (2010–2015) for projects that support the detection and identification of infectious agents. Defined priority areas for investment include TB, sepsis, chlamydia, gonorrhoea and antimicrobial resistance (including certain hospital and community acquired infections, and diagnostic tools that could reduce unnecessary antibiotic prescribing in primary care).⁴⁶ Any business, research organization, charity or public sector organization can participate in competitions for funding.⁴⁷

To date, there have been three major funding competitions as part of the initiative. The first took place in 2010 with £11 million made available to fund feasibility studies, fast-track projects and larger R&D projects that support the development of rapid/POC diagnostic tests. Funding awards and time scales varied depending of the nature of individual projects, with limits on the proportion of costs that would be covered through public funding. Applied R&D projects were eligible

for a maximum of 50% public funding, whereas experimental development projects could receive a maximum of 25% funding.⁴⁸

In 2012, in an £8 million funding award, 12 projects were allocated funding to improve the diagnosis, detection and management of sepsis.⁴⁹ At the same time, Innovate UK awarded over £1 million to three projects to develop tools for commissioners to assess the costs and benefits of POC diagnostic devices.⁵⁰

A third funding competition is currently under way. £5 million has been allocated to support the development of rapid diagnostics for the detection of human and bovine TB. Projects are expected to last no longer than three years, with a maximum award proposed of £2.5 million. In addition to diagnostic companies, Innovate UK is encouraging applications from non-health care industries that may have relevant technical expertise in areas such as biosensors and microfluidics.⁵¹

To design the project brief for potential bidders, Innovate UK organized workshops to gauge stakeholders' views on areas of unmet clinical need and to assess what developments may be technically feasible. Dr Penny Wilson, Lead Technologist in the Detection and Identification of Infectious Agents at Innovate UK indicated that a lesson learned from this experience had been the need to encourage a “challenge-” rather than “technology-”led approach. A tendency in workshops was for participants to suggest incremental improvements to current technology rather than thinking more radically. They also found that there was disparity in views on clinical need, for example the acceptable turn-around time for test results. The projects commissioned reflected these different perspectives, with one project aiming to detect the presence of bacteria in blood in less than three minutes and another designed to detect the pathogen and host response within 15 minutes.

In designing the funding scheme, Innovate UK contracted a health economist to look at the impact and benefits to be gained from investment in a particular POC diagnostic and the likelihood of uptake; Dr Wilson felt this was invaluable. Dr Wilson also supported encouraging the collection of cost–effectiveness evidence to support the uptake of new devices. However, in practice it was challenging to obtain consensus from commissioners on what evidence they need.

National Institute for Health Research, United Kingdom

The NIHR, funded by the Department of Health in England, provides support for translational R&D into innovative medical technology through its Invention for Innovation (i4i) programme.⁵² Since 2008, over £6.5 million has been committed to the development of diagnostics.

Project teams composed of at least two partners from industry, the health service, and academia can apply for funding for projects lasting 1–3 years that aim to develop prototype devices. The funding award is linked to the scale and nature of the proposed project, with no cap on the amount of funding that can be requested.

Applicants need to submit a full proposal; applications are assessed on the basis of the relevance of the research topic to the needs of the NHS, the degree of technological innovation, the case for further development, the economic case, the strength of the overall business plan, and the evidence that a novel technology or intervention that delivers a clear benefit to patients will be the ultimate output of the R&D.

As well as providing funding, the NIHR monitors the attainment of funding-dependent milestones and the continuing feasibility of projects, offering relevant support where needed. Support is tailored to the needs of the individual project and may include independent advice from an NIHR-convened project advisory group and access to expertise in IP and translation strategy.

Not all projects by the NIHR are successful; the projects which have attained the greatest level of success, in terms of bringing a new technology to market, have been those which are led by a balanced team, comprising appropriate clinical, academic and commercial experts. This is the reason the programme encourages this level of collaboration within its guidance.

An example of a project that has been funded under the scheme includes the provision of a £100 000 award in 2010 to the University of Liverpool to support the development of a POCT for sepsis based on calcium-induced turbidity in blood. This was then extended by £300 000 over three years to support the ongoing development of the device.⁵³

For products that do reach market, the NIHR seeks a return on its investment in research funding. This could include a commercial return such as a share in revenue from a product that has been commercialized, access to discounts on the price when the product is sold to the NHS or, alternatively, broader returns such as patient benefit, cost savings for the health service, or public good. The detail of the return depends upon the level of funding provided as well as the nature of the project, and is agreed between the NIHR and the grant recipient either at the time a technology is ready for commercialization or earlier in some cases, if this is requested by the grant recipient.

Wellcome Trust, United Kingdom

To help bridge the gap between research and commercialization of products, the Wellcome Trust, a United Kingdom-based charitable foundation, offers

“Technology Transfer” grants that are open to non-profit-making research institutions as well as commercial companies.⁵⁴

Dr Meher Antia, Business Analyst at the Wellcome Trust’s Technology Transfer Division explained that compared to venture capital funding, which is typically offered on the basis of financial returns, the Wellcome Trust selects projects where there is potential to improve health outcomes and address unmet need. Similarly, once a product has been developed there may be scenarios where developers could profit from selling the IP rights rather than making it available to patients and, while this might be acceptable to a venture capital firm, this would not be permitted under the Wellcome Trust’s grant conditions.

Where products are commercialized, under the terms of the funding agreement entered into with grant recipients, the Wellcome Trust is entitled to either a share of revenue or an option to take equity in the company. All proceeds are then channelled back into the pursuit of the Trust’s charitable mission.⁵⁵ To ensure that a project has the best possible chance to succeed, there are extensive support mechanisms that the Trust provides its award holders, such as funding for expert advisers on steering committees. In addition, there are governance and oversight arrangements in place linked to grant funding, including the Trust requiring involvement in the conduct of projects and specific safeguards to protect IP, such as delaying publication of research results until patent protection of innovations is in place. This adds a layer of complexity to projects. However, Dr Antia reported that in a recent review of some of the Trust’s funding schemes, feedback suggested that award holders generally were appreciative of the support provided and the terms and conditions of funding were not a deterrent to developers seeking funding.

An example of an innovation which has benefitted from Wellcome Trust funding is the “OdoReader”, a device which can analyse a stool sample to diagnose *C. difficile* infection in as little as 15 minutes.⁵⁶ Led by Professor Chris Probert (University of Liverpool) in collaboration with Professor Norman Ratcliffe (the University of the West of England, Bristol), the project was initially awarded a £35 000 “University Transfer Award” to develop a proof of concept before, in 2010, being awarded a £1.3 million Translation Award over three years to build a prototype device. Now in the final stages of the project, work is focused on collating evidence of the effectiveness of the device and getting it “investor ready” so that it can progress to commercialization.

The view of Professor Probert was that the Wellcome Trust’s support has been critical to the development of the product. In the early stages, obtaining traditional venture capital funding would have been unlikely given the risks inherent in the project but now that the product is at a later stage in development and has been extensively peer reviewed through the Wellcome Trust process, it has

reduced the risk for investors. The Wellcome Trust's approach to funding is very different to traditional academic grants because it links funding to continually hitting milestones. This acted to focus efforts on delivering a device as the project output. However, while this contributed to the success of the Odometer project, Professor Probert was aware of other grant recipients with an academic background who weren't able to cope with this culture change. Professor Probert believed that employing a project manager, particularly someone with expertise in working with industry and an understanding of regulatory frameworks helped in this regard.

Other funding schemes offered by the Wellcome Trust that support device development include the Health Innovation Challenge Fund, which offers support for research into repurposing approved medical devices for use in new therapeutic indications or disease states.⁵⁷

12.2.3 Publicly backed venture capital funding (push incentives)

Finance Wales

Finance Wales is a fund management company that provides growth capital for SMEs throughout Wales. Funded from a mix of public and private sources, the organization manages a £40 million investment fund, backed by the Welsh government and Barclays as well as a £150 million fund which uses funding from the European Investment Bank and EU under the JEREMIE (Joint European Resources for Micro to Medium Enterprises) initiative.⁵⁸

Working across a range of technology sectors, Finance Wales has provided support to a number of projects linked to diagnostic development with funding determined on a purely commercial basis after reviewing a company's business plan. Initially developers can request between £50 000 and £1 million in funding, this is then extended by up to £5 million during follow-up rounds and is structured around an individually negotiated debt and equity package.⁵⁹ Funding is available for projects at any stage in the development process.

Dr Melanie Goward, Senior Investment Executive at Finance Wales, stated that a key benefit of Finance Wales public backing was improving developers' access to capital. Within the United Kingdom, Dr Goward cited a recent trend towards venture capital firms withdrawing from the market and targeting fewer but larger investments. This has been compounded by traditional investors being reluctant to support early-stage development because of barriers to achieving regulatory approval increasing the risk of investments.

12.2.4 Prize funds (pull incentives)

An alternative approach to stimulating R&D is the creation of prize funds. Researchers are incentivized to undertake development with the promise of monetary reward if they are successful. Unlike grants, which can reward failure, prizes are only awarded on delivery of specified outcomes; the product developer assumes the risk of development.

There are two key approaches, prizes for end products or, alternatively, for achieved defined milestones. Advantages of prizes that have been suggested include that they enable funders to specify characteristics of the development that are mandatory to win the prize and they may encourage new researchers to enter a research field. In the case of end-product prizes, in addition to augmenting the incentive of a commercial monopoly for the device through the patent system, prizes have also been suggested as an alternative approach to patents to encouraging innovation.⁶⁰ Prizes could encourage innovation in areas where products are not commercially marketable and, by attaching conditions to a prize, it may be possible to guarantee subsequent access to a product, for example by de-linking the incentive to innovate from the price of the finished product.^{61, 62, 63}

A number of prize funds for POC diagnostics have been suggested in recent years. The non-profit-making organization Bioventures for Global Health proposed a “Global Health Innovation Quotient Prize (IQ Prize)” to reward SMEs for developing a POC diagnostic to determine the cause of fever in children under 5.⁶⁴ Rather than a lump sum being paid only once a final product had been developed, a milestone-based approach was proposed, with funds disbursed as developers achieved specific milestones along the development pathway. The award at each stage was intended to reflect both the cost and risk incurred by developers with risk premiums applying where achievement of a milestone involved significant technical risk.⁶⁵ An advantage of offering intermediate awards over an end-prize is that it can attract a broader range of participants, increasing the probability of success. However, in designing such a scheme consideration needs to be given to how to encourage open collaboration to prevent duplication of effort and to help facilitate development.⁶⁶

The United Kingdom and United States governments have taken strides to design prize incentives to catalyse R&D in the POC sector. The Longitude Prize is the United Kingdom’s most notable recent prize fund designed to incentivize POC diagnostic development. After the prize’s announcement by Prime Minister David Cameron in 2013, a public vote dedicated the £10 million prize fund to developing a POC device that will “identify when antibiotics are needed and, if they are, which ones to use.”⁶⁷ The prize is being operated by Nesta and Innovate UK.⁶⁸ In the United States, President Obama issued an

executive order on 18 September 2014 that directed federal agencies to take action to combat the rise of antibiotic resistant bacteria. One component of this executive order directed US\$ 20 million to a prize fund aimed at facilitating the development of POC diagnostic devices. This prize is co-sponsored by the NIH and BARDA.⁶⁹

Other initiatives include a US\$ 100 million “TB Diagnostic Grand Prize” proposed by the governments of Bangladesh, Barbados, Bolivia and Suriname in 2008–2009⁷⁰ and a TB diagnostic X-prize which is currently being developed by the X-prize Foundation, a non-profit-making organization with a history of fostering innovation through incentivized competition.⁷¹ Katy Athersuch, Medical Innovation and Access Policy Adviser, Médecins Sans Frontières – Access Campaign indicated that, while a number of end-product prizes had been proposed linked to POC diagnostics, the barrier to launching these schemes had so far been a lack of funding to implement the proposals.

An example of a milestone prize that has successfully been awarded is the US\$ 1 million Amyotrophic lateral sclerosis prize which was awarded by Prize4Life in 2011 to Dr Seward Rutkove, a neurologist at Beth Israel Deaconess Medical Centre in Boston, for identifying a biomarker that could track progression of Amyotrophic lateral sclerosis. A total of 2969 “solvers” competed for the prize and 108 solutions were proposed.⁷² Talking to the *New York Times* after winning, Dr Rutkove commented that, although he had previously been working in this area, supported by public finance, the prize focused his attention and resulted in quicker development than would have been achieved otherwise.⁷³

Prizes have also been used successfully to back up “crowd-sourcing” approaches to identify solutions to complex problems in the development process. In 2008, Roche Diagnostics challenged two separate networks of scientists to find a better means of measuring the quality and amount of a clinical specimen as it passed through a device manufactured by Roche. One network was Roche Diagnostics’ in-house R&D community and the other was a global network of scientists connected to InnoCentive, an organization that has specialized in crowd-sourcing innovation problems.⁷⁴ InnoCentive’s network was open access and anyone could participate. As one profile of the project put it, you could have been a 20-year-old “PhD chemist, a graduate student, or a scientifically trained housewife”. Problem solvers competed for a US\$ 20 000 prize and within 2 months, 113 proposals had been received through the InnoCentive network with suggestions that were more detailed than those of Roche’s in-house network. Although suggestions mirrored the history of Roche’s R&D programme, the responses from the open network helped Roche solve a problem that it had been working on for 15 years and at a cost that could not have been achieved using traditional approaches. For example, this approach minimized the organizational

and travel costs involved in arranging face-to-face meetings to brainstorm ideas. The view of Tod Bedilion from Roche Diagnostics' Technology office was that the prize incentivized people to get involved, but he felt that participants also seemed to "get intrinsic value out of sharing their expertise through this community".⁷⁵ Challenges that Roche identified included: the importance of carefully designing the question put to solvers (for example, how much detail to provide on the problem), the need for marketing expertise to ensure that potential solvers are aware of the opportunity, and the need to involve new as well as long-standing staff members in reviewing proposals. For example, one experienced employee argued against the eventual winning solution simply because it wasn't "his" solution.

Not all prize funds have been successful; for example, in 1994, the Rockefeller Foundation advertised a US\$ 1 million prize for the development of a POCT for gonorrhoea and chlamydia. The prize went unclaimed, arguably because the criteria set for the winning test were too challenging, requiring a low-cost device with 99% accuracy, non-invasive sampling and immediate results that could be easily interpreted by staff without specialist training.⁷⁶ Other critiques of the prize have been that the prize fund was too low and was offered for too short a period.⁷⁷

In a paper published by the Brookings Institution, Kalil identified a number of examples of opportunities for learning from prizes for technological innovation in other industries. Design factors with potential to influence the success of a prize fund include the size of the reward, the eligibility criteria, the criteria to win, the stage of the innovation process, the potential to capitalize on distributed innovation, controls on IP rights, the level of confidence in the promised prize being honoured, and the level of public interest in the prize.⁷⁸

In a 2009 submission to the WHO's Expert Working Group on Research and Development Financing, Médecins Sans Frontières argued that in designing a prize fund, there is also a need to look beyond the research and consider how to ensure sustainable access to products that are being developed. For example, they emphasized considering how the licensing arrangements and manufacturing capacity can enable the product to be supplied in sufficient quantities, at an acceptable level of quality and at an affordable price.⁷⁹

Dr Martina Casenghi, Scientific Advisor, Médecins Sans Frontières – Access Campaign, highlighted that an area that requires further research is how different types of medical device developers would respond to end-stage prizes as an incentive. For example, would organizations that may be used to obtaining upfront funding through grants be prepared to accept the additional risk inherent in a prize-based scheme?

12.2.5 Practical support (push incentives or effective push incentives)

Biobanks

Biobanks are in essence organized collections of biological specimens that are stored alongside a comprehensive description of the sample donors and details of how the sample has been collected and maintained.⁸⁰ The design of a bank is closely linked to its goals. Population banks, such as UK Biobank, collect samples from a large number of healthy donors for purposes such as research into biomarkers for disease susceptibility, whereas disease-oriented banks, such as WHO's TB specimen bank, collect samples with particular attributes which can be used to support the validation of new diagnostic tools.⁸¹

The Infectious Diseases BioBank at King's College London is an example of a recently established bank that archives samples containing HIV, hepatitis B/C viruses and a variety of bacteria, and distributes these to researchers approved by the bank's governance committee.⁸² Opened in 2007, it is one of only a handful of banks in Europe that have chosen to focus on the collection of infectious disease samples. The centre is affiliated with Guy's and St Thomas' Hospitals, which serve as tissue collection centres. The centre collects blood, urine and faeces specifically as research samples, as well as residual materials that have been collected primarily for diagnostic purposes such as excess tissues or biopsies. The bank also maintains a database of clinical information on donors. For example, for HIV donors this includes basic demographic information, the history of CD4+ cell numbers and viral loads, date of diagnosis, details of treatments and any complicating infections. Sample processing information that is maintained includes the time the sample was taken, processed and frozen, and details of when aliquots have been taken by researchers.⁸³

Cited by *Time Magazine* in 2009 as an idea with the potential to change the world,⁸⁴ improving access to specimen repositories is perceived to reduce the time it takes to develop a new diagnostic.⁸⁵ Establishing shared banks also has the potential to minimize the resources required. In a 2012 statement before the House Committee on Energy and Commerce's Subcommittee on Health, the IDSA argued that a centralized biobank would strengthen diagnostics R&D by assuring that quality specimens were obtained and would remove duplication in the collection of specimens.⁸⁶ This is a view echoed by Dr Oliver Schacht, Chief Executive of a German-based SME, Curetis. He believed that, even on normal commercial terms, improving access to well-characterized specimens could help overcome existing bottlenecks in device development. However, specimens would need to be of sufficient quality to meet strict clinical trial requirements.

Dr Kozlakidis, Manager of the King's College BioBank believed that most developers will source samples from banks at some point in the development cycle. In

the case of large firms, although many have their own specimen banks, because of the costs involved, typically their collections will be carefully targeted and are only sufficient for a small pilot, for example to confirm the potential effectiveness of a new assay. The King's College BioBank has had less contact with SMEs. Dr Kozlakidis attributed this to some SMEs not being aware of the support that they could receive from shared banks or still believing that establishing independent collections is more cost-effective. While in the past some developers have sought to associate themselves with a particular medical facility and prospectively recruit patients, there is increasing recognition that this practice can introduce bias if specimens are not representative of the diverse ethnic mix of target patients for a new technology.⁸⁷ For this reason, most developers now source specimens from multiple banks to ensure appropriate diversity.

Despite the clear potential benefit of banks, the evidence to confirm their value remains anecdotal. Dr Kozlakidis expressed that, through personal experience, he has witnessed projects getting access to research funding more quickly where the researchers have been able to prove they can access appropriate samples and, by providing access to samples, he has seen projects succeed which might otherwise have failed. Similarly, the impact of the WHO's TB Specimen bank has not been evaluated but there are examples of where the bank has played a role in diagnostic development, including supporting the early evaluation of the Cepheid Xpert MTB/RIF platform (see section 3.4.1).⁸⁸ A key challenge for banks going forward is finding a way to measure and quantify this impact.

While a simple concept in theory, setting up a BioBank is complex and expensive in practice.⁸⁹ In the United Kingdom, under the Human Tissue Act 2006, BioBanks must obtain a licence from the Human Tissue Authority and comply with standards that have been defined in a range of areas including consent; governance and quality systems; premises, facilities and equipment; and disposal of samples.⁹⁰ Banks are also subject to periodic inspections by the regulator.⁹¹ Dr Kozlakidis reported that it took two years of preparation and then three years of operation until the BioBank at King's College gathered a critical mass of samples. For moral reasons, the bank is operated on a non-profit basis.

In the United States, NIAID is supportive of the idea of specimen banks as a resource for developers. Through the *Aspergillus* Technology Consortium, diagnostic developers can currently access a repository of prospectively collected clinical specimens, including from patients either at high risk for and who develop invasive aspergillosis.⁹² Dr Jane Knisely, Program Officer at the NIAID's Bacteriology and Mycology Branch, indicated that, going forward, NIAID was hoping to introduce a broader specimen service within two years as part of the re-competition of NIAID's Vaccine and Treatment Evaluation Units.

As it is expensive to collect and store samples without having a candidate diagnostic in mind, a key dilemma of any bank is when to collect samples. The experience from the King's College BioBank has been that collecting samples both prospectively and retrospectively to a study being defined has provided flexibility. Dr Kozlakidis believed that a key strength of the King's College bank was its strategy to target exceptional cases, for example patients with very slow HIV progression. It would otherwise have taken researchers a significant period of time to collect these types of samples on-demand in trials.

One approach that ensures developers can access a statistically significant and ethnically diverse mix of specimens in the shortest possible time is transferring specimens between banks,⁹³ however this is hampered by a myriad of regulations on the transportation of specimens and a lack of harmonization between banks' operating procedures. For samples to be comparable, they need to be collected in a standardized way using similar coding practices.⁹⁴ There is a particular challenge where the subject of a collection is a neglected disease and samples need to be sourced from remote impoverished areas, as is the case with WHO's Human African Trypanosomiasis Specimen Bank.⁹⁵ A recent initiative in Europe intended as a step towards more integrated working between existing banks is the European Biobanking and Biomolecular Resources Infrastructure (BBMRI).⁹⁶ Supported by the EC, the aim is to create a federated network of centres across European Member States, connected through shared information technology.⁹⁷

Diagnostic evidence cooperatives, England

While shared banks can offer support at the clinical trial stage for collecting evidence on the benefits of a test in practice, developers need access to real patient cohorts, for example through joint working with hospitals. The establishment of diagnostic evidence cooperatives is a new initiative in England. Through a competitive selection process, NHS organizations are being given the opportunity to bid for funding from the NIHR to facilitate collaborative working between health professionals, the diagnostics industry, providers of NHS pathology services, academia and patient representatives. The selection process to appoint organizations began in late 2012 and cooperatives are expected to be in place for four years starting on 1 September 2013. Diagnostic evidence cooperatives will prioritize areas where improved evidence of the validity, utility and cost-effectiveness of diagnostics has the potential to improve care. A number of organizations have proposed to focus on POC diagnostics.

The concept has been born out of a broader initiative known as health technology cooperatives. Initiated in 2008 with two pilot health technology cooperatives,

eight NHS organizations appointed in 2012 will act as centres of expertise in defined clinical areas such as chronic gastrointestinal disease and trauma management. Their role is to facilitate collaborative working and to act as a catalyst for technology “pull” into the NHS. In the evaluation of an early pilot of the initiative, undertaken by the RAND Corporation on behalf of the Department of Health, researchers found that cooperatives faced a number of challenges. These included ensuring effective engagement with industry to move beyond simply being centres of excellence, and finding the right balance between protecting IP and sharing learning while avoiding overly rigid project governance.⁹⁸ Although the pilots had different approaches to managing the clinician–industry–patient relationship, influenced by the disease field and the culture of the host organization, the evaluation concluded that these were equally legitimate. Finally, cooperatives needed to find significant financial support to be sustainable. The report found that it was appropriate that government funding was being used to fund relationship management because as this could be considered a “public good” and is unlikely to attract private sector funding.

Support with needs assessment and device evaluation

In 2007 the National Institute of Biomedical Imaging and Bioengineering, an Institute within the NIH, established POCTRN.⁹⁹ This initiative is aimed at accelerating the development of clinically relevant POC diagnostics. The first wave of the project took place between 2007 and 2012. Through a competitive tender process four institutions, predominantly universities, were provided with a total of US\$ 32 million funding over five years to act as POCTRN centres and undertake functions including the assessment of clinical need to inform device design, the evaluation of prototypes and the development of partnerships with industry to facilitate bringing products to market. Each centre was given the ability to initiate new technology development and prototype testing projects while managing progress through go/no-go decisions. Each centre independently identified a particular clinical area to focus on; these included disaster readiness, global health, neurotechnologies and STIs.

Given the time it takes to bring a diagnostic to market, it is still too early to say how successful the initiative has been. The outputs from one of the centres, the Center for POC Diagnostics for Global Health, which was hosted by the international non-profit-making organization PATH, include evaluating and/or supporting the development of 19 prototype technologies. This included field evaluation of six devices and partnering with a commercial partner on three devices to support product commercialization. Four of the prototype development projects were funded by PATH. However, with only limited funding available

to disburse, the view of the Director of the Center, Dr Bernhard Weigl, was that the more effective approach was providing support such as lab and field evaluations and advice to partners on user need, especially where technologies had potential applicability to low resource settings, but the developer had little experience of these settings themselves.

Dr Brenda Korte, Program Director for the POCTRN programme, cited a number of lessons learned that could benefit organizations planning similar initiatives. First, identifying clinical and user need and then translating this into a design specification can be challenging. Centres need to have access to relevant expertise in methodologies that support both needs assessment and translational research. It is also important to have experience in building partnerships that include relevant stakeholders. Progress can be limited by not thinking outside of established circles. Finally, a key success metric for funding recipients needs to be the development and commercialization of technology. In academic centres, a challenge can be ensuring that the delivery of new technology is prioritized over traditional academic goals such as publishing research.

A second wave of the programme will run from 2012 to 2017, with three centres focusing in whole or in part on the development of POC technologies for primary care settings. Johns Hopkins University is hosting a Center for POCTs for Sexually Transmitted Diseases, Boston University is hosting a Center for Future Technologies in Cancer Care, and the Center for Integration of Medicine and Innovative Technology has been appointed a POC Technology Research Center in Primary Care.

12.2.6 Encouraging public–private partnerships (push incentives with future market sales acting as natural pull incentive)

The IMI facilitates collaborative working between networks of industrial and academic experts in Europe with the aim of boosting innovation in health care. Funded jointly by the EU's FP7 programme and the European Federation of Pharmaceutical Industries and Associations and with a €2 billion budget for 2008–2013, the IMI seeks to act as a neutral third party in creating innovative partnerships.¹⁰⁰

An example of a project by IMI is the RAPP-ID initiative, a PPP combining 10 research organizations, 4 SMEs and 5 pharmaceutical companies. Project manager for the initiative, Dr Pieter Moons explained that the SMEs and academic and research partners came together to jointly bid for funding from the IMI. After being ranked first among the competing consortia, five pharmaceutical companies – all members of the European Federation of Pharmaceutical Industries and Associations – were added to the consortium, and they worked

jointly to finalize the project description. The project began in 2011 and will run for five years.

The aim of the €14.5 million initiative is to develop rapid POC diagnostics that can simultaneously detect a variety of pathogens and determine their resistance to antimicrobial drugs. Apart from its potential in clinical practice, for pharmaceutical companies such a diagnostic offers potential reductions in clinical trial costs through quicker identification of patients eligible for those trials. The project will itself not result in a commercial product. The expectation is that a company will acquire the patents from the project for further development.

A key benefit of this collaborative approach is leveraging the different types of expertise among the partners. Given the novel techniques and technologies being used, no one organization has all of the necessary capabilities. The academic partners offer clinical expertise, samples, laboratory capabilities and knowledge of innovative technologies. SMEs offer knowledge of innovative approaches and bring a flexible attitude, while larger companies offer expertise in clinical development, regulatory affairs, communication, samples and laboratory capabilities.¹⁰¹ The collaborative approach also delivered indirect benefits, with Dr Moons citing improved collaboration between industry and academia on topics, even outside the scope of the project.

A key challenge that was identified was integrating the work and interests of so many partners. To help manage this, the project has been split into subprojects, each involving a small number of partners and with each partner having defined set of responsibilities. Regular all-consortium meetings, especially during the start-up phase of the project, have aided decision-making and communication, as did regular teleconferences between the leads and informal links between the PhD students who are doing much of the day-to-day project work.

Among potential risks cited by Dr Moons were conflicts of interest. These could include the potential for individual partners to gain from the device being used in a particular setting which could influence decision-making on the device characteristics, for example the minimum sensitivity requirements differ for a device used to support clinical trials versus a device used in clinical practice. In RAPP-ID, the decision was made to develop a device that supports clinical practice, which, although more difficult, will also offer utility in clinical trials. Another possible scenario is disputes over the degree to which each partner contributed to the project, particularly where this links to IP rights. Fortunately this is a problem that has not affected the project to date, with risks managed through appropriate governance arrangements and internal agreement between the partners on the use of information gained during the project.

12.3 Final recommendations

Funding should be made available to support key areas of diagnostic development:

1. Greater *public–private partnership* for diagnostic R&D. PPP arrangements may be a particularly suitable approach to promoting R&D in diagnostics given the comparative advantages of the potential partners. For example, university hospital labs can offer access to real (often complex) samples, while private companies have greater capabilities with regard to automation and sample prep technologies. Additionally, if the development of more narrow-spectrum antibiotics to slow the growth of resistance is to be prioritized, then collaboration between developers of the antibiotic, developers of the associated diagnostic, and hospital labs would be optimal.
2. Funding should be made available to improve *modelling techniques that incorporate resistance into cost–effectiveness models* and to build greater consensus around the acceptability of those models and/or their parameters so as to improve their perceived usefulness in comparing diagnostic alternatives. It should also help support more *operational research to understand better how to affect prescribing patterns* and the role that diagnostics can and cannot play in improving them.
3. Nationally driven antibiotic stewardship policies should *encourage basic intra-hospital streamlining of incentives to better support wider societal concerns and efforts surrounding antibiotic resistance*. This should include hospital-by-hospital incentives analysis to help align underlying structures, with particular attention to broadening performance assessment of laboratories to encourage a broader perspective when considering the adoption of technologies (to widen their assessment of costs and benefits, including the growth of antibiotic resistance, and to take into consideration the perspective of a broader patient-base or population).
4. Far more effort should be made to move from a fee-for-service model of financing to one that focuses on outcome, looking at the particular technologies in the context of the care pathway rather than a testing silo. In particular, funding should be made available to *explore viable alternatives to the current American reimbursement system* of gap-filling and cross-walking that better reflect both absolute and relative product value and consider dynamics affecting political palatability. This should include documentation and analysis of how recently implemented reimbursement reforms affect the market for molecular diagnostics and their position in the market relative to non-molecular devices.

5. Funding should be made available to explore *methods to mitigate the discrepancies in regulation between small diagnostic developers and large clinical laboratories* (Labcorp, Quest, etc.) in the United States. Much consideration should be given to the power of key diagnostics-related interest groups (e.g. clinical laboratories in the United States).
6. The opportunity and novelty of the reformulated global harmonization (IMDRF) forum should be seized, to bring new life to global *harmonization efforts relating to “non-core” regulatory requirements*, that is, device registration, labelling, documentation, tracking, post-market surveillance, quality assurance, etc.
7. *FDA resourcing should increase in line with the greater demands placed on the agency through more stringent regulatory requirements*. Resource allocation must take account of the relative rapid pace of technological change in the diagnostics space. The regulatory lag relative to the speed of technological progress must not become an institutional norm. In this regard, the appropriate funding of the relevant agencies should be seen as direct support for technological innovation and they should be considered for earmarked funds for this purpose.
8. More formal dialogue on the use of (and the regulations surrounding) *predictive diagnostics* in antibiotic clinical trials as well as in clinical practice should be supported.

Technical areas to support:

1. *Sample preparation*. A key challenge in the development of diagnostics (and indeed cited by several interviewees) surrounds methods for sample preparation. One respondent suggested that, while we know how to find biomarkers that will help in finding the pathogens causing infection in blood and so on, we are forced to go through sample prep. The great majority of molecular methods used are enzymatic and they are susceptible to and inhibited by many environmental factors. Sample preparation entails ridding the native sample of all the things that inhibit the detection of the molecular marker. For example, a 2–3 ml sample of blood contains proteins and cells that can inhibit the detection of the marker and lead to a negative result even if there is an abundance of the target gene.¹⁰²
2. *Automation*. Automation can offer incredible gains with regard to speed and across all major costs associated with diagnosis (e.g. staff levels). While careful attention should be paid to not “crowd out” private sector initiatives, public money could do much to support the movement of the market towards standardized components such

that efforts are not lost or duplicated. However, careful consideration must be taken as automation is not always suitable and may be disruptive in some cases (e.g. if it requires transport to central laboratories).

3. *Speeding up sensitivity testing.* To help guide treatment in the face of variable levels in drug resistance and to be able to know when treatment with older therapies is sufficient (and therefore that third-line, last resort, or new antibiotics are not necessary) we must know the susceptibility profile of the pathogen. Generally speaking this can be very difficult due to the fact that complex resistance patterns often cannot be reflected in a simple genotypic test.¹⁰³ As noted earlier, developers are currently actively trying to create devices that identify organisms and provide sensitivity results (with some using optimized proteomic methods.) These proteomic methods use markers and the presence of the drug rather than culture to determine susceptibility – thereby avoiding the need to grow the organism in the presence of the respective drugs. The intent of this technology is to cut time requirements from one day (minimum) to 1–2 hours. The inclusion of some organisms in such techniques is straightforward while for others it is significantly more complicated by the need for marker to be triggered (e.g. by the presence of the drug, for inducible marker) or when resistance is not tied to a gene (but is rather the result of other modifications or point mutations). Support for efforts to bring such markers into the fold of innovative approaches to sensitivity testing could help to bring us closer to creating the much needed “game changer” in diagnostics for bacterial infection.

General areas to support:

1. Discussions undertaken for this work have highlighted some variation in views surrounding the most pressing priorities in developing diagnostics to improve antibiotic prescribing and ultimately help slow the growth of resistance. There is much agreement that a real “game changer” or ideal technology is one that is accurate, can isolate and quantify organisms, and conduct sensitivity testing to available therapies in a matter of 30 minutes to 2 hours. However, beyond this ideal device, there is little consensus regarding target pathogens and technical specifications. *Support for consensus-building* in these areas could do much to optimally target funding.
2. *Efforts must be made to generate the political will* to enact necessary reforms. All of the reforms proposed above require leadership and collaboration between the public sector, academia and industry. The

long-term cost of inaction on issues of diagnosis and prescribing is the widespread emergence of antibiotic resistant infections. Unfortunately, this immense cost is often masked by the high up-front costs and small profits associated with the short life-cycle of most diagnostic devices. Overcoming these barriers will require cooperation, political will and visionary leadership.

Appendix A

Summary of studies on the cost-effectiveness of POCTs to diagnose sepsis

Sepsis cost-effectiveness studies^a

Citation	Summary	Perspective of the study (hospital, society, patient, etc.)	Types of costs included in the study	Who funded the study?
Alvarez J et al., Cost analysis of real-time PCR microbiological diagnosis in patients with septic shock. <i>Anaesthesia Intensive Care</i> , 2012; 40(6):958–963.	A cost-minimization analysis of blood culture techniques and PCR pathogen detection using data from a retrospective, observational study of patients with severe sepsis or septic shock in a university hospital in Spain in 2006.	Health care provider	Antibiotic costs, costs of the test (including reagent costs, staff costs and contribution towards capital costs) and costs of changes in LOS (broken down into ICU and ward costs).	No external funding ¹
Lehmann LE et al., Cost and mortality prediction using PCR pathogen detection in sepsis: evidence from three observational trials. <i>Critical Care</i> , 2010; 14(5):R186.	A cost-utility analysis of blood culture techniques and PCR pathogen detection using synthesized data from three separate clinical trials. Outcomes were expressed as a cost per QALY and a cost per incremental survivor.	Health care provider	Cost of the test, reduced LOS (daily treatment costs).	Diagnostics manufacturer
Walke T et al., Cost-effectiveness of a rapid and accurate test for diagnosing infection in severe sepsis and septic shock patients. <i>Critical Care</i> , 2010; 14(Suppl. 1):P48.	A cost-utility analysis of blood culture techniques and a theoretical new rapid diagnostic test with assumed attributes. Outcomes were expressed as a cost per QALY.	Health care provider ²	Reduced LOS (daily treatment costs). ³	Diagnostics manufacturer ⁴

^a In these studies, testing was assumed to be undertaken in the laboratory rather than at the POC.

Appendix B

Summary of studies on the cost-effectiveness of POCTs to diagnose UTI

Citation	Summary	Perspective of the study (hospital, society, patient, etc.)	Types of costs included in the study	Who funded the study?
Awonuga DO et al., Asymptomatic bacteriuria in pregnancy: evaluation of reagent strips in comparison to microbiological culture. <i>African Journal of Medicine and Medical Sciences</i> , 2011 Dec.; 40(4):377–383.	A comparison of the relative cost-effectiveness of a dipstick test versus laboratory culture to screen for asymptomatic bacteriuria in pregnancy, the major risk factor for symptomatic UTI during pregnancy. The analysis was based on a study of 205 patients presenting at a university college hospital in Nigeria in mid-2006. The study considered the ability of tests to identify significant bacteriuria rather than the clinical benefits.	Health care provider	Cost of diagnostic tests.	No external funding ¹
Bachman JW et al., A study of various tests to detect asymptomatic urinary tract infections in an obstetric population. <i>JAMA: The Journal of the American Medical Association</i> , 1993; 270(16):1971–1974.	A comparison of rapid screening techniques for detecting asymptomatic UTIs in pregnant women. The study was undertaken at the Mayo Clinic in Rochester and the outcomes were expressed as an incremental cost per additional positive culture.	Health care provider	Cost of diagnostic tests.	Boehringer Mannheim Corp.
Barry HC, Ebell MH, Hickner J, Evaluation of suspected urinary tract infection in ambulatory women: a cost-utility analysis of office-based strategies. <i>Journal of Family Practice</i> , 1997; 44(1):49–59.	A cost-utility analysis of approaches for managing suspected UTIs in otherwise healthy adult women presenting to their primary care physician with dysuria and no symptoms of pyelonephritis. Strategies included dipstick analysis, complete urinalysis and laboratory cultures with data drawn from published studies and costing information from a Michigan hospital. Results were presented as a cost per quality-adjusted life month.	Payer	Cost of diagnostic tests, physician office visits and treatment costs, including medicine and the inpatient care costs for treating pyelonephritis.	No external funding disclosed

Citation	Summary	Perspective of the study (hospital, society, patient, etc.)	Types of costs included in the study	Who funded the study?
Downs SM, Technical report: urinary tract infections in febrile infants and young children. The Urinary Tract Subcommittee of the American Academy of Pediatrics Committee on Quality Improvement. <i>Pediatrics</i> , 1999 Apr.; 103(4):e54.	A comparison of alternative management approaches for suspected UTI in children between 2 months and 2 years of age who are examined because of fever without an obvious cause. A decision-tree model was developed with data extracted from the literature. Outcomes were expressed as an incremental cost per major clinical outcome averted.	Payer	Costs of the tests and treatment costs including complications.	No external funding disclosed. The study was used by the Urinary Tract Subcommittee of the American Academy of Pediatrics Committee on Quality Improvement to develop recommendations on the management of UTI.
Etherington IJ, James DK. Reagent strip testing of antenatal urine specimens for infection. <i>British Journal of Obstetrics and Gynaecology</i> , 1993;100:806–808.	A comparison of dipstick analysis with microscopy and laboratory cultures to identify significant bacteriuria using data from a study of 898 women having their urine screened during pregnancy in an English maternity hospital. The study considered the ability of tests to identify significant bacteriuria rather than the clinical benefits. The outcome of the study was reported as a cost saving per 100 specimens.	Health care provider	Cost of diagnostic tests.	Undefined support was received from Bayer Diagnostics
Fenwick EA, Briggs AH, Hawke CI. Management of urinary tract infection in general practice: a cost-effectiveness analysis. <i>British Journal of General Practice</i> , 2000; 50(457):635–639.	A comparison of the cost-effectiveness of empirical antibiotic treatment, a dipstick test and urine culture using a decision analytic model which was developed using available published information and expert opinion. The outcome was expressed as a cost per symptom day averted per episode of UTI.	Health care provider	Antibiotic costs, costs of the tests, changes in the number of GP appointments.	No external funding disclosed
Fowles GA, Waters J, Williams G. The cost-effectiveness of combined rapid test Multistix in screening for urinary tract infections. <i>Journal of the Royal Society of Medicine</i> , 1994; 87(11):681–682.	A comparison of a dipstick test and the traditional laboratory methods of microscopy and culture to screen for a UTI. The analysis was based on a study of 400 patients attending the urology outpatient department or renal transplant unit of a London hospital. The study considered the ability of tests to identify significant bacteriuria rather than the clinical benefits.	Health care provider	Cost of diagnostic tests.	No external funding disclosed

Citation	Summary	Perspective of the study (hospital, society, patient, etc.)	Types of costs included in the study	Who funded the study?
Little P <i>et al.</i> , Dipsticks and diagnostic algorithms in urinary tract infection: development and validation, randomised trial, economic analysis, observational cohort and qualitative study. <i>Health Technology Assessment</i> , 2009; 13(19):iii–iv, ix–xi, 1–73.	A comparison of alternative management approaches for suspected UTI, including empirical antibiotic treatment, delayed antibiotic treatment, antibiotic prescribing based on symptom score, a dipstick test and urine culture. Data was taken from an RCT involving women aged 17–70 in the United Kingdom with suspected UTI.	Health care provider	Antibiotic costs, costs of the test and the cost of any follow-up care, for example additional GP visits and repeated tests.	NIHR Health Technology Assessment Programme, United Kingdom
Rouse DJ <i>et al.</i> , Screening and treatment of asymptomatic bacteriuria of pregnancy to prevent pyelonephritis: a cost-effectiveness and cost-benefit analysis. <i>Obstetrics and Gynecology</i> , 1995; 86:119–123.	A comparison of the relative cost-effectiveness of approaches to prevent pyelonephritis in pregnancy, including comparing a dipstick test, urine culture and a strategy that involved no screening or treatment. A decision analytic model was created using probability estimates collected from the literature as well as costing information from a survey of pharmacies and laboratories in Birmingham, Alabama. Results were presented as a cost per case of pyelonephritis prevented.	Payer	Direct medical costs, including the cost of testing, a course of antibiotics and average inpatient costs for treating pyelonephritis.	AHRQ
Shaw KN <i>et al.</i> , Screening for urinary tract infection in infants in the emergency department: which test is best? <i>Pediatrics</i> , 1998 June; 101(6):E1.	A comparison of alternative management approaches for suspected UTI in infants, including urine dipstick, a combination of dipstick and microscopy, enhanced urinalysis and gram stain alone. Cost-benefit data was taken from a cross-sectional study undertaken in an urban tertiary care children's hospital emergency department and clinical laboratories in Philadelphia with data covering 3873 infants under the age of 2 who had a urine culture obtained in the emergency department by urethral catheterization.	Health care provider	Costs of testing, including staff time.	Maternal and Child Health Bureau (Title V, Social Security Act), Health Resource and Services Administration, DHHS (United States)

Citation	Summary	Perspective of the study (hospital, society, patient, etc.)	Types of costs included in the study	Who funded the study?
Tissot E et al., Cost-effectiveness of urinary dipsticks to screen asymptomatic catheter-associated urinary infections in an intensive care unit. <i>Intensive Care Medicine</i> , 2001; 27(12):1842-1847.	A prospective comparison of the cost-effectiveness of a dipstick test compared with urine culture in the medical ICU of a French hospital. Outcomes were expressed as an incremental cost-effectiveness ratio.	Health care provider	Costs of testing including staff time, consumables and recognition of the capitals costs incurred in purchasing equipment.	No external funding disclosed
Whiting P et al., Clinical effectiveness and cost-effectiveness of tests for the diagnosis and investigation of urinary tract infection in children: a systematic review and economic model. <i>Health Technology Assessment</i> , 2006; 10(36):iii-iv, xi-xiii, 1-154.	A cost-effectiveness model was developed using the best available evidence to compare alternative management approaches for UTI in children, including a dipstick test, urine culture and imaging strategies such as renal ultrasonography.	Health system	Short-term diagnostic and treatment costs and the cost of long-term complications.	NHS R&D Health Technology Assessment Programme, United Kingdom.
Wong HF, Lee LC, Han HC, Cost-effective screening for urinary tract infections in urogynaecological patients. <i>International Urogynecology Journal and Pelvic Floor Dysfunction</i> , 2008; 19(5):671-676.	A comparison of a dipstick test and urine culture to screen for UTIs using data from a retrospective review of 708 female patients who underwent cystometry at a Singapore hospital during a one-year period in 2004/2005. While this study noted clinical benefits, these were not integrated into the analysis.	Health care provider	Cost of diagnostic tests.	No external funding disclosed

Appendix C

Streptococcal pharyngitis cost-effectiveness studies

Citation	Summary	Perspective of the study (hospital, society, patient, etc.)	Types of costs included in the study	Who funded the study?
Barenfanger J et al., Clinical and financial benefits of rapid detection of respiratory viruses: an outcomes study. <i>Journal of Clinical Microbiology</i> , 2000; 38(8):2824–2828.	A comparison of standard clinical virology techniques such as enzyme immunoassays, shell vial assays and culture tube assays with rapid immunofluorescent testing using data from a historical cohort analysis at a teaching hospital in Illinois for two consecutive winters, 1996 and 1997. Testing was undertaken in a laboratory rather than at POC.	Health care provider	Costs linked to LOS as well as the cost of testing, including staff time.	The Memorial Medical Center Foundation. Reagents were funded by a diagnostics manufacturer.
Ehrlich JE et al., Cost-effectiveness of treatment options for prevention of rheumatic heart disease from group A streptococcal pharyngitis in a pediatric population. <i>Preventive Medicine</i> , 2002 Sept.; 35(3):250–257.	An assessment of the cost-effectiveness of five management options for patients with pharyngitis, including a rapid test versus a culture. The model was developed using evidence from the literature with cost-effectiveness expressed in cases of rheumatic heart disease prevented annually in the United States paediatric population.	Society	Testing and treatment costs, including antibiotics and subsequent allergic reactions, as well as the cost of pharyngitis complications. Indirect costs of lost productivity and reduced disease transmission were not included.	No external funding disclosed
Humair JP et al., Management of acute pharyngitis in adults: reliability of rapid streptococcal tests and clinical findings. <i>Archives of Internal Medicine</i> , 2006; 166(6):640–644.	A comparison of alternative management approaches for acute pharyngitis, including undertaking systematic rapid streptococcal antigen testing, selective rapid streptococcal antigen testing or systematic culture. The analysis was based on an observational study conducted in a cohort of adult outpatients in Switzerland in 1999–2001.	Health care provider	Testing and antibiotic costs.	No external funding disclosed

Citation	Summary	Perspective of the study (hospital, society, patient, etc.)	Types of costs included in the study	Who funded the study?
Giraldez-Garcia C et al., Diagnosis and management of acute pharyngitis in a paediatric population: a cost-effectiveness analysis. <i>European Journal of Pediatrics</i> , 2011; 170(8):1059–1067.	A comparison of six management strategies, including throat culture versus a rapid antigen test. The study was based on a hypothetical cohort of 4 million children presenting at a primary care physician with acute pharyngitis symptoms based on estimates of consultations for sore throat that occur annually in Spanish primary care centres.	Payer	Direct medical costs associated with testing, therapy and care of complications.	No external funding disclosed
Lieu TA, Fleisher GR, Schwartz JS, Cost-effectiveness of rapid latex agglutination testing and throat culture for streptococcal pharyngitis. <i>Pediatrics</i> , 1990; 85(3):246–256.	A comparison of the cost-effectiveness of four strategies to manage pharyngitis in children, including use of a rapid antigen test and culture. A decision tree was constructed using data from previous studies and results were presented as a cost per complication prevented.	Society	Despite the societal perspective, only the health care provider's costs were considered, including the costs associated with testing, treatment and follow-up.	Charles A. Dana and John A. Hartford Foundations
Majeed HA et al., Office diagnosis and management of group A streptococcal pharyngitis employing the rapid antigen detecting test. A 1-year prospective study of reliability and cost in primary care centres. <i>Annals of Tropical Paediatrics</i> , 1993; 13(1):65–72.	A comparison of the cost-effectiveness of four strategies to manage group A streptococcal pharyngitis, including use of a rapid antigen test and clinical diagnosis. The results were drawn from a one-year prospective randomized study involving children aged 5 to 14 presenting at primary care clinics in Kuwait. Cost-effectiveness was presented as a cost per episode of pharyngitis.	Health care provider	Testing and antibiotic costs.	Ministry of Public Health, Kuwait and the WHO
Neuner JM et al., Diagnosis and management of adults with pharyngitis: a cost-effectiveness analysis. <i>Annals of Internal Medicine</i> , 2003; 139:113–122.	A comparison of six management strategies, including throat culture versus a rapid antigen test. The study was based on data from the published literature with the outcome expressed as a cost per quality-adjusted life-days.	Society	Direct costs associated with testing, therapy and care of complications.	No external funding disclosed

Citation	Summary	Perspective of the study (hospital, society, patient, etc.)	Types of costs included in the study	Who funded the study?
Syrmis MW et al., A sensitive, specific, and cost-effective multiplex reverse transcriptase-PCR assay for the detection of seven common respiratory viruses in respiratory samples. <i>Journal of Molecular Diagnostics</i> , 2004; 6(2):125–31.*	A comparison of cell culture and a direct fluorescent antibody technique with a multiplex reverse transcriptase polymerase chain reaction (m-RTPCR) assay. The analysis was based on a study aiming to detect seven common respiratory viruses from nasopharyngeal aspirate samples from 598 paediatric patients who presented to an Australian children's hospital with suspected acute respiratory infection. The testing was undertaken in a laboratory rather than at POC.	Health care provider	Costs of testing including staff time.	Grants from the Royal Children's Hospital Foundation which were sponsored by the Woolworth's "Care for Kids" campaign
Tsevat J, Kotagal UR. Management of sore throats in children: a cost-effectiveness analysis. <i>Archives of Pediatric and Adolescent Medicine</i> , 1999; 153:681–688.	A comparison of six strategies for managing pharyngitis in children and adolescents including use of throat cultures and rapid tests. Outcomes were expressed as a cost per additional life saved.	Society	Testing and treatment costs, including antibiotics and subsequent allergic reactions as well as the cost of pharyngitis complications. Consideration was also given to parental time lost from work and patient co-payments for office visits and prescriptions.	ChoiceCare, a managed care organization
Van Howe RS, Kusnier LP 2nd, Diagnosis and management of pharyngitis in a pediatric population based on cost-effectiveness and projected health outcomes. <i>Pediatrics</i> , 2006 Mar.; 117(3):609–619.	A comparison of six strategies for managing pharyngitis in children and adolescents, including throat cultures versus rapid tests based on data from the literature. Cost-effectiveness was expressed as a cost per QALY.	Society	Testing and treatment costs, including the cost of treating complications and parental time lost from work.	No external funding disclosed

Citation	Summary	Perspective of the study (hospital, society, patient, etc.)	Types of costs included in the study	Who funded the study?
Woo PC et al., Cost-effectiveness of rapid diagnosis of viral respiratory tract infections in pediatric patients. <i>Journal of Clinical Microbiology</i> , 1997; 35:1579–1581.*	A comparison of viral culture and a rapid diagnostic to treat paediatric patients with suspected respiratory tract infections. The study was based on a retrospective review of the records of paediatric patients admitted to the Queen Mary Hospital in Hong Kong between September 1994 and September 1996 and for whom a virological diagnosis of respiratory tract infection was available. Testing was undertaken in a laboratory rather than at POC.	Health care provider	Costs of testing, including staff time and costs linked to LOS.	Committee on Research and Conference Grants of the University of Hong Kong

* Device used in the study to detect viral rather than bacterial infections of the respiratory tract. By ruling out bacterial infections, the devices supported reducing antibiotic consumption.

Appendix D

United Kingdom HGC recommendations 2010

Recommendation 1: Given the reported growth in patenting by academic researchers, the UK research councils and other major biomedical research funders, such as the Wellcome Trust, Cancer Research UK and the British Heart Foundation, should review their guidelines on licensing.

Recommendation 2: To establish a biomarker IP monitoring function within the Department of Health or in an appropriate cross-departmental office. Duties should include: a) evidence gathering and analysis and reporting on the impact of current policies on the incentives for public sector and private sector biomarker-based innovation in diagnostics, b) encouraging private sector IP biomarker holders to contribute genetic data arising from diagnostic tests to public databases which aim to develop libraries of the relevant DNA sequences which are as comprehensive as possible, yet ensure confidentiality of individuals' data, and reporting on any problems encountered in this area, and c) developing guidelines for out-licensing and in-licensing of IP by public sector funded staff.

Recommendation 3: At present it is unclear who within the NHS might be responsible for dealing with the practical implementation of policy in this area. Support should be given to senior management at a national level to help develop the capacity to manage biomarker IP issues.

Recommendation 4: More independent evidence needs to be generated on the impact of biomarker IP on diagnostic innovation. A starting point would be research to address the questions that were raised and evidence gaps identified by this seminar. An appropriate forum and process will be required that provides time for detailed deliberation and an assessment of the divergent needs and preferences of a range of stakeholders.

Appendix E

Recommendations of the SACGHS to the United States DHHS in 2010 report

Recommendation 1: Support the Creation of Exemptions from Infringement Liability

The Secretary of Health and Human Services (HHS) should support and work with the Secretary of Commerce to promote the following statutory changes:

- A. The creation of an exemption from liability for infringement of patent claims on genes for anyone making, using, ordering, offering for sale, or selling a test developed under the patent for patient-care purposes.
- B. The creation of an exemption from patent infringement liability for those who use patent-protected genes in the pursuit of research.

Recommendation 2: Promote Adherence to Norms Designed to Ensure Access

Using relevant authorities and necessary resources, the Secretary should explore, identify, and implement mechanisms that will increase adherence to current guidelines that promote nonexclusive licensing of diagnostic genetic/genomic technologies.

The Secretary should convene stakeholders – for example, representatives from industry and academic institutions, researchers, and patients – to develop a code of conduct that will further broad access to such technologies.

Recommendation 3: Enhance Transparency in Licensing

Using relevant authorities and necessary resources, the Secretary should explore, identify, and implement mechanisms that will make information about the type of license and the field of use for which rights were granted readily available to the public.

Recommendation 4: Establish an Advisory Body on the Health Impact of Gene Patenting and Licensing Practices

The Secretary should establish an advisory body to provide ongoing advice about the health impact of gene patenting and licensing practices. The advisory body

also could provide input on the implementation of any future policy changes, including the other recommendations in this report.

Recommendation 5: Provide Needed Expertise to U.S. Patent and Trademark Office (USPTO)

The Secretary should work with the Secretary of Commerce to ensure that USPTO is kept apprised of scientific and technological developments related to genetic testing and technology.

Recommendation 6: Ensure Equal Access to Clinically Useful Genetic Tests

Given that genetic tests will be increasingly incorporated into medical care, the Secretary should ensure that those tests shown to have clinical utility are equitably available and accessible to patients.

References

2. Overview

- 1 IMS Institute for Healthcare Informatics. *Advancing the responsible use of medicines. Applying levers for change*. Report prepared for the Ministers Summit organized by the Dutch Ministry of Health, Welfare and Sport, 3 October 2012, with the theme “The benefits of responsible use of medicines: setting policies for better and cost-effective healthcare”. Parsippany, NJ: IMS Institute for Healthcare Informatics, 2012.
- 2 ECDC. *Summary of the latest data on antibiotic consumption in the European Union*. Stockholm: European Centre for Disease Prevention and Control, 2012 (<http://www.ecdc.europa.eu/en/eaad/Documents/ESAC-Net-summary-antibiotic-consumption.pdf>, accessed September 2015).
- 3 Versporten A et al. Antibiotic use in eastern Europe: a cross-national database study in coordination with the WHO Regional Office for Europe. *Lancet Infectious Diseases*, 2014; 14(5):381–387.
- 4 Ibid.
- 5 ECDC. *Summary of the latest data on antibiotic consumption in the European Union*. Stockholm: European Centre for Disease Prevention and Control, 2012. (<http://www.ecdc.europa.eu/en/eaad/Documents/ESAC-Net-summary-antibiotic-consumption.pdf>, accessed September 2015).
- 6 Versporten A et al. Antibiotic use in eastern Europe: a cross-national database study in coordination with the WHO Regional Office for Europe. *Lancet Infectious Diseases*, 2014; 14(5):381–387.
- 7 ECDC. *Summary of the latest data on antibiotic consumption in the European Union*. Stockholm: European Centre for Disease Prevention and Control, 2012. (<http://www.ecdc.europa.eu/en/eaad/Documents/ESAC-Net-summary-antibiotic-consumption.pdf>, accessed September 2015).
- 8 ECDC. *Summary of the latest data on antibiotic consumption in the European Union*. Stockholm: European Centre for Disease Prevention and Control, 2012 (<http://www.ecdc.europa.eu/en/eaad/Documents/ESAC-Net-summary-antibiotic-consumption.pdf>, accessed September 2015).
- 9 CDDEP. Antibiotic use and resistance at a glance: 1999–2010. Washington, DC: Center for Disease Dynamics, Economics & Policy (http://www.cddep.org/sites/cddep.org/files/resistance_map_infographic.jpg, accessed 6 December 2012).
- 10 IDSA et al. Combating antimicrobial resistance: policy recommendations to save lives. *Clinical Infectious Diseases*, 2011; 52 Suppl. 5:S397–428.
- 11 Huttner B, Samore M. Outpatient antibiotic use in the United States: time to “get smarter”. *Clinical Infectious Diseases*, 2011; 53(7):640–643.
- 12 Jacob JT, Gaynes RP. Emerging trends in antibiotic use in US hospitals: quality, quantification and stewardship. *Expert Review of Anti-infective Therapy*, 2010; 8(8):893–902.
- 13 Huttner B, Samore M. Outpatient antibiotic use in the United States: time to “get smarter”. *Clinical Infectious Diseases*, 2011; 53(7):640–643.
- 14 Steinman MA et al. Variation in outpatient antibiotic prescribing in the United States. *American Journal of Managed Care*, 2009; 15(12):861–868.
- 15 Versporten A et al. Antibiotic use in eastern Europe: a cross-national database study in coordination with the WHO Regional Office for Europe. *Lancet Infectious Diseases*, 2014; 14(5):381–387.
- 16 Zhang Y, Steinman MA, Kaplan CM. Geographic variation in outpatient antibiotic prescribing among older adults. *Archives of Internal Medicine*, 2012; 172(19):1465–1471.
- 17 CDDEP. Antibiotic use and resistance at a glance: 1999–2010. Washington, DC: Center for Disease Dynamics, Economics & Policy (http://www.cddep.org/sites/cddep.org/files/resistance_map_infographic.jpg, accessed 6 December 2012).
- 18 Ibid.

- 19 CDDEP ResistanceMap. Washington, DC: Center for Disease, Dynamics, Economics & Policy (<http://www.cddep.org/resistancemap/overview>, accessed October 2015).
- 20 Klepser DG, Bisanz SE, Klepser ME. Cost-effectiveness of pharmacist-provided treatment of adult pharyngitis. *American Journal of Managed Care*, 2012 Apr; 18(4):e145–154.
- 21 Holloway K et al. Surveillance of community antimicrobial use in resource-constrained settings—experience from five pilot projects. *Tropical Medicine and International Health*, 2011; 16(2):152–161.
- 22 Holloway K, van Dijk L. *The World Medicines Situation 2011: Rational use of Medicines*. Geneva: WHO, 2011.
- 23 Ferech M et al. European Surveillance of Antimicrobial Consumption (ESAC): outpatient antibiotic use in Europe. *Journal of Antimicrobial Chemotherapy*, 2006; 58(2):401–407.
- 24 Monnet DL et al. The more antibacterial trade names, the more consumption of antibacterials: a European study. *Clinical Infectious Diseases*, 2005; 41(1):114–117.
- 25 Hawker, JI et al. Trends in antibiotic prescribing in primary care for clinical syndromes subject to national recommendations to reduce antibiotic resistance, UK 1995–2011: analysis of a large database of primary care consultations. *Journal of Antimicrobial Chemotherapy*, 2014; 69(12):3423–3430.
- 26 Little P et al. Dipsticks and diagnostic algorithms in urinary tract infection: development and validation, randomised trial, economic analysis, observational cohort and qualitative study. *Health Technology Assessment* 2009; 13(19):iii–iv, ix–xi, 1–73.
- 27 Cals JW et al. Effect of POC testing for C-reactive protein and training in communication skills on antibiotic use in lower respiratory tract infections: cluster randomised trial. *British Medical Journal*, 2009; 338:b1374.
- 28 Lehmann LE et al. Potential clinical utility of polymerase chain reaction in microbiological testing for sepsis. *Critical Care Medicine*, 2009; 37(12):3085–3090.
- 29 Jayaraman R. Antibiotic resistance: an overview of mechanisms and a paradigm shift. *Current Science*, 2009; 96:1475–1484.
- 30 Fleming A. Penicillin. Nobel lecture, 11 December 1945.
- 31 Waksman S. Streptomycin: background, isolation, properties, and utilization. Nobel lecture, 12 December 1952.
- 32 Tenover F. Mechanisms of antimicrobial resistance in bacteria. *American Journal of Medicine* 2006; 119(6) Suppl. 1:S3–10; discussion S62–70.
- 33 WHO. *The evolving threat of antimicrobial resistance: options for action*. Geneva: World Health Organization, 2012.
- 34 ECDC. *Antimicrobial resistance surveillance in Europe: annual report of the European Antimicrobial Resistance Surveillance Network (EARS-Net) 2011*. Stockholm: European Centre for Disease Prevention and Control, 2012.
- 35 WHO. *Antimicrobial resistance: global report on surveillance*. Geneva: World Health Organization, 2014.
- 36 Hidron A et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006–2007. *Infection Control and Hospital Epidemiology*, 2008; 29(11):996–1011.
- 37 Jacob JT, Gaynes RP. Emerging trends in antibiotic use in US hospitals: quality, quantification and stewardship. *Expert Review of Anti-infective Therapy*, 2010; 8(8):893–902.
- 38 ECDC. *Point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals*. Stockholm: European Centre for Disease Prevention and Control (http://www.ecdc.europa.eu/en/healthtopics/Healthcare-associated_infections/point-prevalence-survey/Pages/Point-prevalence-survey.aspx, accessed 9 March 2014).
- 39 CDC. Gonococcal Isolate Surveillance Project (GISP). Atlanta, GA: Centers for Disease Control and Prevention (<http://www.cdc.gov/std/gisp/>, accessed 7 December 2012).
- 40 Eurofins. The Surveillance Network (<http://www.eurofins.in/pharma/laboratory-testing-capabilities/global-infectious-disease-services/the-surveillance-network.aspx>, accessed 7 December 2012).
- 41 Frazee BW et al. High prevalence of methicillin-resistant *Staphylococcus aureus* in emergency department skin and soft tissue infections. *Annals of Emergency Medicine*, 2005; 45(3):311–320.
- 42 Skov R et al. Update on the prevention and control of community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA). *International Journal of Antimicrobial Agents*, 2012; 39(3):193–200.
- 43 Ferry T, Etienne J. Community acquired MRSA in Europe. *British Medical Journal*, 2007; 335(7627):947–948.
- 44 Moran GJ et al. Methicillin-resistant *Staphylococcus aureus* infections among patients in the emergency department. *New England Journal of Medicine*, 2006; 355(7):666–674.

- 45 Hoffmann K et al. Antibiotic resistance in primary care in Austria: a systematic review of scientific and grey literature. *BMC Infectious Diseases*, 2011; 11:330.
- 46 Kalter HD et al. Risk factors for antibiotic-resistant *Escherichia coli* carriage in young children in Peru: community-based cross-sectional prevalence study. *American Journal of Tropical Medicine and Hygiene*, 2010; 82(5): 879–888.
- 47 WHO. *Antimicrobial resistance: global report on surveillance*. Geneva: World Health Organization, 2014.
- 48 ECDC. *Antimicrobial resistance surveillance in Europe: annual report of the European Antimicrobial Resistance Surveillance Network (EARS-Net), 2013*. Stockholm: European Centre for Disease Prevention and Control (<http://ecdc.europa.eu/en/publications/Publications/antimicrobial-resistance-surveillance-europe-2013.pdf>, accessed 26 March 2015).
- 49 Goossens H et al. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet*, 2005; 365(9459):579–587.
- 50 Knight GM et al. Shift in dominant hospital-associated methicillin-resistant *Staphylococcus aureus* (HA-MRSA) clones over time. *Journal of Antimicrobial Chemotherapy*, 2012; 67(10):2514–2522.
- 51 CDDEP. Antibiotic use and resistance at a glance: 1999–2010. Washington, DC: Center for Disease Dynamics, Economics & Policy (http://www.cddep.org/sites/cddep.org/files/resistance_map_infographic.jpg, accessed 6 December 2012).
- 52 Thornsberry C et al. Regional trends in antimicrobial resistance among clinical isolates of *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* in the United States: results from the TRUST Surveillance Program, 1999–2000. *Clinical Infectious Diseases*, 2002; 34 Suppl. 1:S4–S16.
- 53 ECDC. *Antimicrobial resistance surveillance in Europe: annual report of the European Antimicrobial Resistance Surveillance Network (EARS-Net) 2011*. Stockholm: European Centre for Disease Prevention and Control, 2012.
- 54 Zignol M et al. Surveillance of anti-tuberculosis drug resistance in the world: an updated analysis, 2007–2010. *Bulletin of the World Health Organization*, 2012; 90:111–119D.
- 55 Siegel J et al. *Management of multidrug-resistant organisms in healthcare settings*. Atlanta, GA: Centers for Disease Control and Prevention, 2006.
- 56 Pitout JD, Laupland KB. Extended-spectrum beta-lactamase-producing Enterobacteriaceae: an emerging public-health concern. *Lancet Infectious Diseases*, 2008; 8(3):159–166.
- 57 ECDC. *Antimicrobial resistance surveillance in Europe: annual report of the European Antimicrobial Resistance Surveillance Network (EARS-Net) 2011*. Stockholm: European Centre for Disease Prevention and Control, 2012.
- 58 CDDEP. Antibiotic use and resistance at a glance: 1999–2010. Washington, DC: Center for Disease Dynamics, Economics & Policy (http://www.cddep.org/sites/cddep.org/files/resistance_map_infographic.jpg, accessed 6 December 2012).
- 59 Sanchez GV et al. In vitro antimicrobial resistance of urinary *Escherichia coli* isolates among U.S. outpatients from 2000 to 2010. *Antimicrobial Agents and Chemotherapy*, 2012; 56(4):2181–2183.
- 60 ECDC. *Antimicrobial resistance surveillance in Europe: annual report of the European Antimicrobial Resistance Surveillance Network (EARS-Net) 2011*. Stockholm: European Centre for Disease Prevention and Control, 2012.
- 61 Borer A et al. Attributable mortality rate for carbapenem-resistant *Klebsiella pneumoniae* bacteremia. *Infection Control and Hospital Epidemiology*, 2009; 30(10):972–976.
- 62 Mezzatesta ML et al. Outbreak of KPC-3-producing, and colistin-resistant, *Klebsiella pneumoniae* infections in two Sicilian hospitals. *Clinical Microbiology and Infection*, 2011; 17(9):1444–1447.
- 63 Marchaim D et al. Outbreak of colistin-resistant, carbapenem-resistant *Klebsiella pneumoniae* in metropolitan Detroit, Michigan. *Antimicrobial Agents and Chemotherapy*, 2011; 55(2):593–599.
- 64 Perez F et al. Global challenge of multidrug-resistant *Acinetobacter baumannii*. *Antimicrobial Agents and Chemotherapy*, 2007; 51(10):3471–3484.
- 65 Jones A et al. Importation of multidrug-resistant *Acinetobacter spp* infections with casualties from Iraq. *Lancet Infectious Diseases*, 2006; 6(6):317–318.
- 66 Cai Y et al. Colistin resistance of *Acinetobacter baumannii*: clinical reports, mechanisms and antimicrobial strategies. *Journal of Antimicrobial Chemotherapy*, 2012; 67(7):1607–1615.
- 67 Bolan GA, Sparling PE, Wasserheit JN. The emerging threat of untreatable gonococcal infection. *New England Journal of Medicine*, 2012; 366(6):485–487.
- 68 ECDC. *Antimicrobial resistance surveillance in Europe: annual report of the European Antimicrobial Resistance Surveillance Network (EARS-Net) 2011*. Stockholm: European Centre for Disease Prevention and Control, 2012.

- 69 Jenkins SG, Brown SD, Farrell DJ. Trends in antibacterial resistance among *Streptococcus pneumoniae* isolated in the USA: update from PROTEKT US Years 1–4. *Annals of Clinical Microbiology and Antimicrobials*, 2008; 7:1.
- 70 Klein E, Smith DL, Laxminarayan R. Hospitalizations and deaths caused by methicillin-resistant *Staphylococcus aureus*, United States, 1999–2005. *Emerging Infectious Diseases*, 2007 Dec.; 13(12):1840–1846.
- 71 Burton DC et al. Methicillin-resistant *Staphylococcus aureus* central line-associated bloodstream infections in US intensive care units, 1997–2007. *Journal of the American Medical Association*, 2009; 301(7):727–736.
- 72 Kallen AJ et al. Health care-associated invasive MRSA infections, 2005–2008. *Journal of the American Medical Association*, 2010; 304(6):641–648.
- 73 Köck R et al. Methicillin-resistant *Staphylococcus aureus* (MRSA): burden of disease and control challenges in Europe. *Eurosurveillance*, 2010; 15(41):1–9.
- 74 Tacconelli E et al. Rapid screening tests for methicillin-resistant *Staphylococcus aureus* at hospital admission: systematic review and meta-analysis. *Lancet Infectious Diseases*, 2009; 9(9):546–554.

3. Overview of the diagnostics market

- 1 Credit Suisse. *Life science tools and diagnostics initiation*. North America: Credit Suisse, 2011.
- 2 Coleman K. Companion diagnostics and personalized medicine. *Datamonitor Healthcare*, 2012.
- 3 Olanow AE, Jungling MK, Bradshaw K. DiaSorin S.p.A: test results. In: *~25% Upside*. New York: Morgan Stanley Research Estimates, July 2011.
- 4 Cowen & Company. *Cowen diagnostics kit – first edition*. New York: Cowen Med Tech Research Team, October 2012.
- 5 Deutsche Bank. *European pharmaceuticals: pharmaceuticals for beginners*. London: Deutsche Bank, 2010.
- 6 *The Economist*, Medicine, the final frontier? 10 October 2011 (<http://www.economist.com/blogs/democracyinamerica/2011/10/great-stagnation-thesis>, accessed September 2015).
- 7 Antibiotic Resistance Project. Tracking the pipeline of antibiotics in development. Washington, DC, Pew Charitable Trusts (<http://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2014/03/12/tracking-the-pipeline-of-antibiotics-in-development>, accessed 9 March 2015).
- 8 Coleman K. Companion diagnostics and personalized medicine. *Datamonitor Healthcare*, 2012.
- 9 Witonsky J. IVD market moving rapidly on an upward trajectory. *Genetic Engineering and Biology News*, 2012 Dec.; 32(21).
- 10 Olanow AE, Jungling MK, Bradshaw K. DiaSorin S.p.A: test results. In: *~25% upside*. New York: Morgan Stanley Research Estimates, July 2011.
- 11 Kalorama. *Worldwide market for IVD tests*, 8th edition. New York: Kalorama, 2012.
- 12 Cowen & Company. *Cowen diagnostics kit – first edition*. New York: Cowen Med Tech Research Team, October 2012.
- 13 Coleman K. Companion diagnostics and personalized medicine. *Datamonitor Healthcare*, 2012.
- 14 Wood P et al. In-vitro diagnostics update 2014. New York: Morgan Stanley Research Estimates.
- 15 Olanow AE, Jungling MK, Bradshaw K. DiaSorin S.p.A: test results In: *~25% upside*. New York: Morgan Stanley Research Estimates, July 2011.
- 16 Cowen & Company. *Cowen diagnostics kit – first edition*. New York: Cowen Med Tech Research Team, October 2012.
- 17 Credit Suisse. *Life science tools and diagnostics initiation*. North America: Credit Suisse, 2011.
- 18 Ibid.
- 19 Coleman K. Companion diagnostics and personalized medicine. *Datamonitor Healthcare*, 2012.
- 20 Forbes Pharma & Healthcare. Congress is killing medical research, 14 January 2013 (<http://www.forbes.com/sites/stevensalzburg/2013/01/14/congress-is-killing-medical-research/>, accessed 25 January 2013).
- 21 Fact sheet: Impact of sequestration on the National Institutes of Health, 3 June 2013 (<http://www.nih.gov/news/health/jun2013/nih-03.htm>, accessed 13 April 2015).
- 22 European Research Council. Facts and figures. Brussels: European Research Council, 2015 (<http://erc.europa.eu/about-erc/facts-and-figures>, accessed 17 March 2015).
- 23 PhRMA. *Biomedical research industry 2014 profile*. Washington, DC: Pharmaceutical Research and Manufacturers of America (http://www.phrma.org/sites/default/files/pdf/2014_PhRMA_PROFILE.pdf, accessed 3 June 2014).
- 24 Olanow AE, Jungling MK, Bradshaw K. DiaSorin S.p.A: test results. In: *~25% upside*. New York: Morgan Stanley Research Estimates, July 2011.

- 25 EMDA. *European IVD market statistics report 2011*. Brussels: European Medical Devices Association (<http://www.edma-ivd.eu/library/504-2011-european-ivd-market-statistics>, accessed 10 January 2013).
- 26 Ibid.
- 27 Ibid.
- 28 Ibid.
- 29 Cowen & Company, *Cowen diagnostics kit – first edition*. New York: Cowen Med Tech Research Team, October 2012.
- 30 Interview with Simon Goldenberg, Consultant Microbiologist and Infection Control Doctor, Guy's and St Thomas' NHS Foundation Trust.
- 31 Cowen & Company. *Cowen diagnostics kit – first edition*. New York: Cowen Med Tech Research Team, October 2012.
- 32 Kalorama. *Worldwide market for IVD tests*, 8th edition. New York: Kalorama, 2012.
- 33 Olanow AE, Jungling MK, Bradshaw K. DiaSorin S.p.A: test results. In: *-25% upside*. New York: Morgan Stanley Research Estimates, July 2011.
- 34 Kalorama. *Worldwide market for IVD tests*, 8th edition. New York: Kalorama, 2012.
- 35 Olanow AE, Jungling MK, Bradshaw K. DiaSorin S.p.A: test results. In: *-25% upside*. New York: Morgan Stanley Research Estimates, July 2011.
- 36 Ibid.
- 37 Cowen & Company. *Cowen diagnostics kit – first edition*. New York: Cowen Med Tech Research Team, October 2012.
- 38 Olanow AE, Jungling MK, Bradshaw K. DiaSorin S.p.A: test results. In: *-25% upside*. New York: Morgan Stanley Research Estimates, July 2011.
- 39 Ibid.
- 40 Kalorama. *Worldwide market for IVD tests*, 8th edition. New York: Kalorama, 2012.
- 41 Cowen & Company. *Cowen diagnostics kit – first edition*. New York: Cowen Med Tech Research Team, October 2012.
- 42 Olanow AE, Jungling MK, Bradshaw K. DiaSorin S.p.A: test results. In: *-25% upside*. New York: Morgan Stanley Research Estimates, July 2011.
- 43 Interview with Anna Postulaka, Director, Medical and Economic Value Europe, Cepheid.
- 44 Weile J, Knabbe C. Current applications and future trends of molecular diagnostics in clinical bacteriology. *Analytical and Bioanalytical Chemistry*, 2009; 394(3):731–742.
- 45 Caliendo A et al. Better tests, better care: improved diagnostics for infectious diseases. *Clinical Infectious Diseases*, 2013; 57(S3):S139–179.
- 46 Credit Suisse. *Life science tools and diagnostics initiation*. North America: Credit Suisse, 2011.
- 47 Coleman K. Companion diagnostics and personalized medicine. *Datamonitor Healthcare*, 2012.
- 48 Credit Suisse. *Life science tools and diagnostics initiation*. North America: Credit Suisse, 2011.
- 49 Olanow AE, Jungling MK, Bradshaw K. DiaSorin S.p.A: test results. In: *-25% upside*. New York: Morgan Stanley Research Estimates, July 2011.
- 50 Olanow AE, Jungling MK, Bradshaw K. DiaSorin S.p.A: test results. In: *-25% upside*. New York: Morgan Stanley Research Estimates, July 2011.
- 51 Coleman K. Companion diagnostics and personalized medicine. *Datamonitor Healthcare*, 2012.
- 52 Credit Suisse. *Life science tools and diagnostics initiation*. North America: Credit Suisse, 2011.
- 53 Ibid.
- 54 PwC. *Diagnostics 2011: M&A surges, companion diagnostics accelerate, and early detection offers new prospects*. 2nd edn. US and Luxembourg: PwC.
- 55 Cowen & Company. *Cowen diagnostics kit – first edition*. New York: Cowen Med Tech Research Team, October 2012.
- 56 Coleman K. Companion diagnostics and personalized medicine. *Datamonitor Healthcare*, 2012.
- 57 EMDA. *European IVD market statistics report 2011*. Brussels: European Medical Devices Association (<http://www.edma-ivd.eu/library/504-2011-european-ivd-market-statistics>, accessed 10 January 2013).
- 58 Cowen & Company. *Cowen diagnostics kit – first edition*. New York: Cowen Med Tech Research Team, October 2012.
- 59 Interview with Martin Whitbread, CEO Proceur.
- 60 PwC. *Diagnostics 2011: M&A surges, companion diagnostics accelerate, and early detection offers new prospects*. 2nd edn. US and Luxembourg: PwC, December 2011.
- 61 EMDA. *European IVD market statistics report 2011*. Brussels: European Medical Devices Association (<http://www.edma-ivd.eu/library/504-2011-european-ivd-market-statistics>, accessed 10 January 2013).

- 62 PwC. *Diagnostics 2011: M&A surges, companion diagnostics accelerate, and early detection offers new prospects*. 2nd edn. US and Luxembourg: PwC.
- 63 Fierce Medical Devices. Biocartis bags \$44.5m Series D for molecular Dx commercialization. 12 December 2012 (<http://www.fiercemedicaldevices.com/story/biocartis-bags-445m-series-d-molecular-dx-commercialization/2012-12-12>, accessed 22 March 2013).
- 64 Fierce Medical Devices. Top developers VC investments of 2012. 1 February 2013 (<http://www.fiercemedicaldevices.com/special-reports/top-dx-vc-investments-2012>, 22 February 2013).
- 65 Cowen & Company. *Cowen diagnostics kit – first edition*. New York: Cowen Med Tech Research Team, October 2012.
- 66 Ibid.
- 67 Ibid.
- 68 Lord Carter of Coles, *Report of the review of NHS pathology services in England chaired by Lord Carter of Coles: an independent review for the Department of Health*. London: Department of Health, 2006.
- 69 Interview with Martin Whitbread, CEO Proceur.
- 70 Interview with James Collier, Director, Momentum Bioscience.
- 71 Ibid.
- 72 WHO. *Global Tuberculosis Report 2012*. Geneva: World Health Organization, 2012.
- 73 Millen SJ et al. The effect of diagnostic delays on the drop-out rate and the total delay to diagnosis of tuberculosis. *PLoS One*, 2008; 3(4):e1933.
- 74 Getahun H et al. Diagnosis of smear-negative pulmonary tuberculosis in people with HIV infection or AIDS in resource-constrained settings: informing urgent policy changes. *Lancet*, 2007; 369(9578):2042–2049.
- 75 Van Rie A et al. Xpert(®) MTB/RIF for point-of-care diagnosis of TB in high-HIV burden, resource-limited countries: hype or hope? *Expert Review of Molecular Diagnostics*, 2010; 10(7):937–946.
- 76 Getahun H et al. Diagnosis of smear-negative pulmonary tuberculosis in people with HIV infection or AIDS in resource-constrained settings: informing urgent policy changes. *Lancet*, 2007; 369(9578):2042–2049.
- 77 WHO. *Rapid implementation of the Xpert MTB/RIF diagnostic test: technical and operational “how-to”; practical considerations*. Geneva: World Health Organization, 2011.
- 78 Small PM, Pai M. Tuberculosis diagnosis: time for a game change. *New England Journal of Medicine*, 2010; 363(11):1070–1071.
- 79 Boehme CC et al. Rapid molecular detection of tuberculosis and rifampin resistance. *New England Journal of Medicine*, 2010; 363(11):1005–1015.
- 80 Clouse K et al. Implementation of Xpert MTB/RIF for routine point-of-care diagnosis of tuberculosis at the primary care level. *South African Medical Journal*, 2012; 102(10):805–807.
- 81 Meyer-Rath G et al. The impact and cost of scaling up GeneXpert MTB/RIF in South Africa. *PLoS One*, 2012; 7(5):e36966.
- 82 Abu-Raddad LJ et al. Epidemiological benefits of more-effective tuberculosis vaccines, drugs, and diagnostics. *Proceedings of the National Academy of Sciences of the United States of America*, 2009; 106(33):13980–13985.
- 83 WHO. Press release: WHO endorses new rapid tuberculosis test. Geneva: World Health Organization, 8 December 2010 (http://www.who.int/mediacentre/news/releases/2010/tb_test_20101208/en/index.html, 15 December 2012).
- 84 WHO. *Global tuberculosis report 2012*. Geneva: World Health Organization, 2012.
- 85 Pai NP, Pai M. Point-of-care diagnostics for HIV and tuberculosis: landscape, pipeline, and unmet needs. *Discovery Medicine*, 2012 Jan.; 13(68):35–45.
- 86 Batz H-G, Cooke GS, Reid SD. *Towards lab-free tuberculosis diagnosis*. New York/Geneva: Médecins Sans Frontières, TB/HIV Working Group, Treatment Action Group, Imperial College London, 2011.
- 87 CE-IVD tests. Cepheid International (<http://www.cephheidinternational.com/tests-and-reagents/ce-ivd-test>, accessed 27 November 2012).
- 88 WHO. *Prevalence and incidence of selected sexually transmitted infections: chlamydia trachomatis, Neisseria gonorrhoeae, syphilis and Trichomonas vaginalis. Methods and results used by WHO to generate 2005 estimates*. Geneva: World Health Organization, 2011.
- 89 WHO. *Advancing MDGs 4, 5 and 6: impact of congenital syphilis elimination – partner brief*. Geneva: World Health Organization, 2010.
- 90 Romoren M, Rahman M. Syphilis screening in the antenatal care: a cross-sectional study from Botswana. *BMC International Health and Human Rights*, 2006; 6:8.

- 91 Mabey D et al. Point-of-care tests to strengthen health systems and save newborn lives: the case of syphilis. *PLoS Med.*, 2012 Jun.;9(6):e1001233.
- 92 WHO/TDR. *The use of rapid syphilis tests*. Geneva: World Health Organization, Special Programme for Research & Training in Tropical Diseases, 2006.
- 93 Mabey D et al. Point-of-care tests to strengthen health systems and save newborn lives: the case of syphilis. *PLoS Med.*, 2012 Jun.; 9(6):e1001233.
- 94 Hawkes S et al. Effectiveness of interventions to improve screening for syphilis in pregnancy: a systematic review and meta-analysis. *Lancet Infectious Diseases*, 2011; 11(9):684–691.
- 95 Ibid.
- 96 Sabid M et al. Rapid point-of-care diagnostic test for syphilis in high-risk populations, Manaus, Brazil. *Emerging Infectious Diseases*, 2009; 15(4):647–649.
- 97 Statham V. Piloting the uptake of a rapid syphilis kit in Edinburgh. ROAM Outreach Edinburgh.
- 98 Mishra S et al. Syphilis screening among female sex workers in Bangalore, India: comparison of point-of-care testing and traditional serological approaches. *Sexually Transmitted Infections*, 2010; 86(3):193–198.
- 99 Klein E, Smith DL, Laxminarayan R. Hospitalizations and deaths caused by methicillin-resistant *Staphylococcus aureus*, United States, 1999–2005. *Emerging Infectious Diseases*, 2007 Dec.; 13(12):1840–1846.
- 100 Wassenberg M et al. Costs and benefits of rapid screening of methicillin-resistant *Staphylococcus aureus* carriage in intensive care units: a prospective multicentre study. *Critical Care*, 2012; 16(1):R22.
- 101 Davies J et al. Impact of results of a rapid *Staphylococcus aureus* diagnostic test on prescribing of antibiotics for patients with clustered gram-positive cocci in blood cultures. *Journal of Clinical Microbiology*, 2012 June; 50(6):2056–2058.
- 102 Bauer KA et al. An antimicrobial stewardship program's impact with rapid polymerase chain reaction methicillin-resistant *Staphylococcus aureus*/*S. aureus* blood culture test in patients with *S. aureus* bacteremia. *Clinical Infectious Diseases*, 2010; 51(9):1074–1080.
- 103 Brenwald NP, Baker N, Oppenheim B. Feasibility study of a real-time PCR test for methicillin-resistant *Staphylococcus aureus* in a point of care setting. *Journal of Hospital Infection*, 2010; 74(3):245–249.
- 104 Ibid.
- 105 Horn DL et al. Epidemiology and outcomes of candidemia in 2019 patients: data from the prospective antifungal therapy alliance registry. *Clinical Infectious Diseases*, 2009; 48(12):1695–1703.
- 106 Moran C et al. Comparison of costs, length of stay, and mortality associated with *Candida glabrata* and *Candida albicans* bloodstream infections. *American Journal of Infection Control*, 2010 Feb.; 38(1):78–80.
- 107 Taur Y et al. Effect of antifungal therapy timing on mortality in cancer patients with candidemia. *Antimicrobial Agents and Chemotherapy*, 2010; 54(1):184–190.
- 108 Berzaghi R et al. New approach for diagnosis of candidemia based on detection of a 65-kilodalton antigen. *Clinical and Vaccine Immunology*, 2009; 16(11):1538–1545.
- 109 Moran C et al. Comparison of costs, length of stay, and mortality associated with *Candida glabrata* and *Candida albicans* bloodstream infections. *American Journal of Infection Control*, 2010 Feb.; 38(1):78–80.
- 110 Pappas PG et al. Guidelines for treatment of candidiasis. *Clinical Infectious Diseases*, 2004; 38(2):161–189.
- 111 Ahmad S et al. Performance comparison of phenotypic and molecular methods for detection and differentiation of *Candida albicans* and *Candida dublimiensis*. *BMC Infectious Diseases*, 2012; 12(1):230.
- 112 T2 Biosystems. Press release: T2 Biosystems demonstrates first-ever ability to accurately and rapidly detect systemic candida infection directly in whole blood in single-process test (http://www.t2biosystems.com/site/Portals/0/MSG_FINAL_release_for_4-7-11_distribution.pdf, accessed 16 December 2012).
- 113 T2 Biosystems. Direct detection with T2 magnetic resonance: T2MR (<http://www.t2biosystems.com/Site/ScienceTechnology/tabid/54/Default.aspx>, accessed 16 December 2012).
- 114 T2 Biosystems. Press release: T2 Biosystems announces the presentation of data on direct detection with T2Candida (<http://www.t2biosystems.com/site/Portals/0/IDSA-FINAL-10-20-11.pdf>, accessed 16 December 2012).
- 115 Seiffert D. T2 biosystems gets two more patents for assay, *Boston Business Journal*, 14 November 2012 (<http://www.masshightech.com/stories/2012/11/12/daily30-T2-Biosystems-gets-two-more-patents-for-assay.html>, accessed 28 November 2012).
- 116 T2 Biosystems. Press release: T2 Biosystems announces the presentation of data on direct detection with T2Candida (<http://www.t2biosystems.com/site/Portals/0/IDSA-FINAL-10-20-11.pdf>, accessed 16 December 2012).
- 117 T2 Biosystems. Direct detection with T2 magnetic resonance: T2MR (<http://www.t2biosystems.com/Site/ScienceTechnology/tabid/54/Default.aspx>, accessed 16 December 2012).

- 118 Thews A. Health economic modeling of the impact of fast pneumonia testing. In: Thews A, ed. *ECCMID 2012 – Bacterial pneumonia and emerging antibiotic resistance. Curetis Symposia proceedings, April 1 2012 London, UK*. Holzgerlingen, Germany: Curetis, 2012.
- 119 Infectious Diseases Society of America. An unmet medical need: rapid molecular diagnostics tests for respiratory tract infections. *Clinical Infectious Diseases*, 2011; 52 Suppl. 4:S384–395.
- 120 Reddington K et al. Advances in multiparametric molecular diagnostics technologies for respiratory tract infections. *Current Opinion in Pulmonary Medicine*, 2013 Feb. 18 (Epub ahead of print).
- 121 Caliendo AM. Multiplex PCR and emerging technologies for the detection of respiratory pathogens. *Clinical Infectious Diseases*, 2011; 52 Suppl. 4:S326–330.
- 122 Curetis. Curetis AG Curetis: Corporate fact sheet. October 2012.
- 123 Curetis. Unyvero™ solution (<http://www.curetis.com/en/products/unyverotm-solution/>, accessed 8 February 2013).
- 124 Ibid.
- 125 Ibid.
- 126 Conference poster, European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) 2013, P1781.
- 127 Brittain-Long R et al. Access to a polymerase chain reaction assay method targeting 13 respiratory viruses can reduce antibiotics: a randomised, controlled trial. *BMC Medicine*, 2011; 9:44.
- 128 Gruteke P et al. Practical implementation of a multiplex PCR for acute respiratory tract infections in children. *Journal of Clinical Microbiology*, 2004; 42(12):5596–5603.
- 129 Thews A. Health economic modeling of the impact of fast pneumonia testing. In: Thews A (ed.) *ECCMID 2012 – Bacterial pneumonia and emerging antibiotic resistance. Curetis Symposia Proceedings, April 1 2012 London, UK*. Holzgerlingen, Germany: Curetis.
- 130 Devillé WL et al. The urine dipstick test useful to rule out infections. A meta-analysis of the accuracy. *BMC Urology*, 2004; 4:4.
- 131 Mach KE, Wong PK, Liao JC. Biosensor diagnosis of urinary tract infections: a path to better treatment? *Trends in Pharmacological Sciences*, 2011; 32(6):330–336.
- 132 Fahey T et al. Clinical management of urinary tract infection in women: a prospective cohort study. *Family Practice*, 2003; 20(1):1–6.
- 133 Little P et al. Dipsticks and diagnostic algorithms in urinary tract infection: development and validation, randomised trial, economic analysis, observational cohort and qualitative study. *Health Technology Assessment*, 2009; 13(19):iii–iv, ix–xi, 1–73.
- 134 Devillé WL et al. The urine dipstick test useful to rule out infections. A meta-analysis of the accuracy. *BMC Urology*, 2004; 4:4. Choose Destination
- 135 St John A et al. The use of urinary dipstick tests to exclude urinary tract infection: a systematic review of the literature. *American Journal of Clinical Pathology*, 2006; 126(3):428–436.
- 136 Devillé WL et al. The urine dipstick test useful to rule out infections. A meta-analysis of the accuracy. *BMC Urology*, 2004; 4:4.
- 137 Little P et al. Dipsticks and diagnostic algorithms in urinary tract infection: development and validation, randomised trial, economic analysis, observational cohort and qualitative study. *Health Technology Assessment*, 2009; 13(19):iii–iv, ix–xi, 1–73.
- 138 Fenwick EA, Briggs AH, Hawke CI. Management of urinary tract infection in general practice: a cost-effectiveness analysis. *British Journal of General Practice*, 2000; 50(457):635–639.
- 139 Mach KE, Wong PK, Liao JC. Biosensor diagnosis of urinary tract infections: a path to better treatment? *Trends in Pharmacological Sciences*, 2011; 32(6):330–336.
- 140 Mohan R et al. Clinical validation of integrated nucleic acid and protein detection on an electrochemical biosensor array for urinary tract infection diagnosis. *PLoS One*, 2011; 6(10):e26846.

4. Supply-side bottlenecks inhibiting development of priority diagnostics

- 1 Interview with Oliver Schacht, CEO, Curetis AG.
- 2 Interview with Anna Postulaka, Director, Medical and Economic Value Europe, Cepheid.
- 3 Interview with James Collier, Director, Momentum Bioscience.
- 4 Micklus A, Suprenant T. Device/diagnostic quarterly deal statistics, Q1. *Elsevier Business Intelligence*, 2012; 30(6).

- 5 Hollmer M. Medical device/developers VC funding has gotten “a little” better. Fierce Medical Devices, 2012 (<http://www.fiercemedicaldevices.com/story/bio-story-medical-devicedx-vc-funding-has-gotten-little-better/2012-06-18>, accessed 30 July 2012).
- 6 MODEdiagnostics. Press release: MODE Diagnostics attracts over £1,100,000 funding to develop health & wellness home diagnostic products. 2 July 2012 (<http://www.modedx.com/PDF/MODE%20Diagnostics-PressRelease-July2012-FINAL.pdf>, accessed 19 September 2012).
- 7 Lab21. Clydesdale Bank £5 million funding to support Lab21 international growth. 2012 (<http://www.lab21.com/Lab21Group/CorporateNewsEvents/CorporateNews/tabid/104/vw/1/ItemID/139/Default.aspx>, accessed 19 September 2012).
- 8 Marketwired. GeneWeave Biosciences attracts \$12 million in venture capital in round financed by Decheng Capital, Claremont Creek Ventures and X/Seed Capital. February 2012 (<http://www.marketwire.com/press-release/geneweave-biosciences-attracts-12-million-venture-capital-round-financed-decheng-capital-1625189.htm>, accessed 20 August 2012).
- 9 MaRS Innovation. Xagenic raises \$10 million in Series A financing. 3 February 2012 (<http://www.marsinnovation.com/2012/02/10-million-series-a-financing-in-xagenic/>, accessed 25 August 2012).
- 10 Health Technology Exchange (HTX). Xagenic receives \$300,000 from the Health Technology Exchange (HTX). 2010 (https://www.htx.ca/News/xagenic_receives_300000_from_the_health_technology_exchange_htx.htm, accessed 19 September 2012).
- 11 Xagenic. Xagenic Inc. closes \$10 million Series A financing. 2012 (<http://www.xagenic.com/news/>, accessed 19 September 2012).
- 12 MedMira. MedMira receives CAD\$6.0 million equity investment from Andurja Beteiligungen AG to bolster ongoing business development activities. 2012 (<http://www.medmira.com/default.asp?mn=1.85.132&csfield=content.id&search=402>, accessed on 30 September 2012).
- 13 National Venture Capital Association. FDA public meeting on strengthening the Center for Devices and Radiological Health’s 510(k) review process. 18 February 2010, Gaithersburg, MD.
- 14 Ibid.
- 15 Medical Devices and Diagnostics Industry. Venture capital is not dead ... just resting!, May 2012 (<http://www.mddionline.com/article/venture-capital-not-dead%E2%80%A6just-resting>, accessed 7 September 2012).
- 16 International Standards Organisation. Medical devices: quality management systems – requirements for regulatory purposes. ISO 13485:2003 (Abstract only: http://www.iso.org/iso/catalogue_detail?csnumber=36786, accessed 5 October 2012).
- 17 FDA. *Guidance for industry, third parties and Food and Drug Administration staff – medical device ISO 13485:2003 Voluntary Audit Report Submission Pilot Program*. Silver Spring, MD: Food and Drug Administration (<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm212795.htm>, accessed 5 October 2012).
- 18 Curetis AG. Press release: Curetis AG increases Series A Financing to €20 million and receives ISO 13485 certification (http://www.curetis.com/fileadmin/curetis/media/struktur/News_Media/Press_Releases/2010531CuretisPIAdditionofrenownedexpertsengl.pdf, accessed 7 September 2012).
- 19 Pant Pai N et al. Point-of-care testing for infectious diseases: diversity, complexity, and barriers in low- and middle-income countries. *PLoS Med.*, 2012 Sept.; 9(9):e1001306 (<http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1001306>, accessed October 2015).
- 20 Ibid.
- 21 *The Guardian*. Crowdsourcing reveals life-saving potential in global health research. 15 August 2012 (<http://www.guardian.co.uk/global-development/2012/aug/15/crowdsourcing-global-health-research>, accessed 27 February 2012).
- 22 Techmoola.com. CerViva test for cervical cancer. Inventor Funding & Technology Crowdfunding TechMoola.com (http://www.techmoola.com/project.php?project_id=152, accessed 27 February 2013).
- 23 *The Guardian*. Crowdsourcing reveals life-saving potential in global health research. 15 August 2012 (<http://www.guardian.co.uk/global-development/2012/aug/15/crowdsourcing-global-health-research>, accessed 27 February 2013).
- 24 Bogosian G, Bourneuf EV. A matter of bacterial life and death. *EMBO Reports*, 2001; 2(9):770–774.
- 25 *Report on the Joint EU–US Workshop: Challenges and solutions in the development of new diagnostic tests to combat antimicrobial resistance*, 28–29 September 2011. Brussels: European Commission.
- 26 Bissonnette L, Bergeron MG. Diagnosing infections – current and anticipated technologies for point-of-care diagnostics and home-based testing. *Clinical Microbiology and Infection* 2010; 16(8):1044–1053.

- 27 Kumar A et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Critical Care Medicine*, 2006; 34:1589–1596.
- 28 Weinstein MP. Current blood culture methods and systems: clinical concepts, technology, and interpretation of results. *Clinical Infectious Diseases*, 1996; 23(1):40–46.
- 29 Ibid.
- 30 Trotman-Grant A, Raney T, Dien Bard J. Evaluation of optimal storage temperature, time, and transport medium for detection of group B Streptococcus in StrepB carrot broth. *Journal of Clinical Microbiology*, 2012; 50(7):2446–2449.
- 31 Weinstein MP. Current blood culture methods and systems: clinical concepts, technology, and interpretation of results. *Clinical Infectious Diseases*, 1996; 23(1):40–46.
- 32 García-Vázquez E et al. Assessment of the usefulness of sputum culture for diagnosis of community-acquired pneumonia using the PORT predictive scoring system. *Archives of Internal Medicine*, 2004; 164(16):1807–1811.
- 33 Rex J. Diagnostics: a focus on use in development of drugs for MDR pathogens. Presented at the European Medicines Agency Workshop on the Addendum to the Guidance for the Development of Anti-Bacterial Drugs, London, 2012.
- 34 Weile J, Knabbe C. Current applications and future trends of molecular diagnostics in clinical bacteriology. *Analytical and Bioanalytical Chemistry*, 2009; 394(3):731–742.
- 35 Ibid.
- 36 Caliendo A et al. Better tests, better care: improved diagnostics for infectious diseases. *Clinical Infectious Diseases*, 2013; 57 Suppl. 3:S139–179.
- 37 Holland CA, Kiechle FL. Point-of-care molecular diagnostic systems – past, present and future. *Current Opinion in Microbiology*, 2005; 8(5):504–509.
- 38 Kang Y et al. Etiologic diagnosis of lower respiratory tract bacterial infections using sputum samples and quantitative loop-mediated isothermal amplification. *PLoS One*, 2012; 7(6):e38743.
- 39 Chawla K et al. PCR for M. tuberculosis in tissue samples. *Journal of Infection in Developing Countries*, 2009; 3(2):83–87.
- 40 Salian NV et al. Polymerase chain reaction to detect Mycobacterium tuberculosis in histologic specimens. *American Journal of Respiratory and Critical Care Medicine*, 1998; 158(4):1150–1155.
- 41 Dr Anna Zorzet, personal communication, April 2013.
- 42 Kobayashi H et al. Limiting false-positive polymerase chain reaction results: detection of DNA and mRNA to differentiate viable from dead bacteria. *Diagnostic Microbiology and Infectious Disease*, 2009; 64(4):445–447.
- 43 Ragoussis J et al. Matrix-assisted laser desorption/ionisation, time-of-flight mass spectrometry in genomics research. *PLoS Genetics*, 2006; 2(7):e100.
- 44 Ikryannikova LN et al. A MALDI TOF MS-based minisequencing method for rapid detection of TEM-type extended-spectrum beta-lactamases in clinical strains of Enterobacteriaceae. *Journal of Microbiological Methods*, 2008; 75(3):385–391.
- 45 Hortin GL. Can mass spectrometric protein profiling meet desired standards of clinical laboratory practice? *Clinical Chemistry*, 2005; 51(1):3–5.
- 46 Antti H et al. Metabolic profiling for detection of *Staphylococcus aureus* infection and antibiotic resistance. *PLoS ONE*, 2013; 8(2).
- 47 Wickremasinghe M et al. Non-tuberculous mycobacteria in patients with bronchiectasis. *Thorax*, 2005 Dec.; 60(12):1045–1051.
- 48 Robinson J. Colonization and infection of the respiratory tract: what do we know? *Paediatrics and Child Health*, 2004; 9(1):21–24.
- 49 Tenover FC. Developing molecular amplification methods for rapid diagnosis of respiratory tract infections caused by bacterial pathogens. *Clinical Infectious Diseases*, 2011 May; 52 Suppl. 4:S338–345.
- 50 Larsen HH et al. A prospective, blinded study of quantitative touch-down polymerase chain reaction using oral-wash samples for diagnosis of Pneumocystis pneumonia in HIV-infected patients. *Journal of Infectious Diseases*, 2004; 189(9):1679–1683.
- 51 Tenover FC. Developing molecular amplification methods for rapid diagnosis of respiratory tract infections caused by bacterial pathogens. *Clinical Infectious Diseases*, 2011 May; 52 Suppl. 4:S338–345.
- 52 Batz H-G, Cooke GS, Reid SD. *Towards lab-free tuberculosis diagnosis*. New York/Geneva: Médecins Sans Frontières, TB/HIV Working Group, Treatment Action Group, Imperial College London, 2011.
- 53 TDR Diagnostics Evaluation Expert Panel et al. Evaluation of diagnostic tests for infectious diseases: general principles. *Nature Reviews/Microbiology*, 2010; 8(12) Suppl.:S17–29.

- 54 Kozlakidis Z et al. How representative are research tissue biobanks of the local populations? Experience of the Infectious Diseases BioBank at King's College, London, UK. *Biopreservation and Biobanking*, 2011; 9(3):287–288.
- 55 TDR Diagnostics Evaluation Expert Panel et al. Evaluation of diagnostic tests for infectious diseases: general principles. *Nature Reviews/Microbiology*, 2010; 8(12) Suppl.:S17–29.
- 56 Caliendo AM. Multiplex PCR and emerging technologies for the detection of respiratory pathogens. *Clinical Infectious Diseases*, 2011; 52 Suppl. 4:S326–330.
- 57 Applied Biosystems. Application note: Factors influencing multiplex real-time PCR. Foster City, CA: Applied Biosystems, 2010.
- 58 Ibid.
- 59 Wilson JA et al. Verification and validation of multiplex nucleic acid assays: approved guideline. *Clinical and Laboratory Standards Institute*, 2008; 28(8).
- 60 Ibid.
- 61 Lin B et al. Application of broad-spectrum, sequence-based pathogen identification in an urban population. *PLoS One*, 2007; 2(5):e419.
- 62 Loens K et al. Optimal sampling sites and methods for detection of pathogens possibly causing community-acquired lower respiratory tract infections. *Journal of Clinical Microbiology*, 2009; 47(1):21–31.
- 63 Shata AM et al. Sputum induction for the diagnosis of tuberculosis. *Archives of Disease in Childhood*, 1996; 74(6):535–537.
- 64 Muzanye G et al. Impact of mouth rinsing before sputum collection on culture contamination. *African Health Sciences*, 2009; 9(3):200.
- 65 Urdea M et al. Requirements for high impact diagnostics in the developing world. *Nature*, 2006; 444 Suppl. 1:73–79.
- 66 Clouse K et al. Implementation of Xpert MTB/RIF for routine point-of-care diagnosis of tuberculosis at the primary care level. *South African Medical Journal*, 2012; 102(10):805–807.
- 67 ESP Central Ltd. *Sampling challenges for medical point of care diagnostics using microfluidic and lab-on-a-chip devices*. Horsham: ESP Knowledge Transfer Network– Electronics, Sensors, Photonics, 2012.
- 68 Paglia MG, Visca P. An improved PCR-based method for detection and differentiation of *Entamoeba histolytica* and *Entamoeba dispar* in formalin-fixed stools. *Acta Tropica*, 2004; 92(3):273–277.
- 69 Anna Zorzet, personal communication, April 2013.
- 70 Clouse K et al. Implementation of Xpert MTB/RIF for routine point-of-care diagnosis of tuberculosis at the primary care level. *South African Medical Journal*, 2012; 102(10):805–807.
- 71 *Report on the Joint EU–US Workshop: Challenges and solutions in the development of new diagnostic tests to combat antimicrobial resistance*, 28–29 September 2011. Brussels: European Commission.
- 72 Ibid.
- 73 Goossens H. Diagnostics: technical and scientific hurdles in the development of diagnostics for respiratory tract infections. Presented at the Joint EU–US Workshop on Challenges and Solutions in the Development of New Diagnostic Tests to Combat Antimicrobial Resistance, 28–29 September 2011, European Commission, Brussels.
- 74 Chin CD, Linder V, Sia SK. Commercialization of microfluidic point-of-care diagnostic devices. *Lab on a Chip*, 2012; 12(12):2118–2134.
- 75 ESP Central Ltd. *Sampling challenges for medical point of care diagnostics using microfluidic and lab-on-a-chip devices*. Horsham: ESP Knowledge Transfer Network – Electronics, Sensors, Photonics, 2012.
- 76 Lee WG et al. Nano/microfluidics for diagnosis of infectious diseases in developing countries. *Advanced Drug Delivery Reviews*, 2010; 62(4–5):449–457.
- 77 U Theuretzbacher, personal communication, June 2013.
- 78 CDC. *National ambulatory medical care survey: 2008 summary*. Atlanta, GA: Centers for Disease Control and Prevention, National Center for Health Statistics (http://www.cdc.gov/nchs/data/ahcd/namcs_summary/2008_namcs_web_tables.pdf, accessed September 2015).
- 79 Ebell MH et al. The rational clinical examination. Does this patient have strep throat? *JAMA: The Journal of the American Medical Association*, 2000; 284:2912–2918.
- 80 Krober MS, Bass JW, Michels GN. Streptococcal pharyngitis: placebo-controlled double-blind evaluation of clinical response to penicillin therapy. *JAMA: The Journal of the American Medical Association*, 1985; 253:1271–1274.
- 81 Randolph MF et al. Effect of antibiotic therapy on the clinical course of streptococcal pharyngitis. *Journal of Pediatrics*, 1985; 106:870–875.

- 82 Pfoh E et al. Burden and economic cost of group A streptococcal pharyngitis. *Pediatrics*, 2008; 121(2):229–234.
- 83 Mehrotra A et al. Comparing costs and quality of care at retail clinics with that of other medical settings for 3 common illnesses. *Annals of Internal Medicine*, 2009; 151:321–328.
- 84 Giraldez-Garcia C et al. Diagnosis and management of acute pharyngitis in a pediatric population: a cost–effectiveness analysis. *European Journal of Pediatrics*, 2011; 170:1059–1067.
- 85 American Academy of Pediatrics. *2010–2011 Medicaid reimbursement reports*. Elk Grove Village, IL: American Academy of Pediatrics (<http://www.aap.org/en-us/professional-resources/Research/research-resources/Pages/2010-2011-Medicaid-Reimbursement-Reports.aspx>, accessed 12 May 2015).
- 86 Ebell MH et al. The rational clinical examination. Does this patient have strep throat? *JAMA: The Journal of the American Medical Association*, 2000; 284:2912–2918.
- 87 McIsaac WJ et al. The validity of a sore throat score in family practice. *Canadian Medical Association Journal*, 2000; 163 (7):811–815.
- 88 McIsaac WJ et al. A clinical score to reduce unnecessary antibiotic use in patients with sore throat. *Canadian Medical Association Journal*, 1998; 158:75–83.
- 89 Donner-Banzhoff N et al. Clinical findings in patients presenting with sore throat: a study on inter-observer reliability. *Family Practice*, 2002; 19:466–468.
- 90 Redd SC et al. Rapid group A streptococcal antigen detection kit: effect on antimicrobial therapy for acute pharyngitis. *Pediatrics*, 1988; 82:576–581.
- 91 Schwartz B et al. Pediatricians' diagnostic approach to pharyngitis and impact of CLIA 1988 on office diagnostic tests. *JAMA: The Journal of the American Medical Association*, 1994; 271:234–238.
- 92 CMS. Clinical Laboratory Improvement Amendments, 1988. Baltimore, MD: Centers for Medicare and Medicaid Services (<http://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/index.html?redirect=clia>, accessed 3 December 2012).
- 93 Ferris DG, Fischer PM. Elementary school students' performance with two ELISA test systems. *JAMA: The Journal of the American Medical Association*, 1992; 268:766–770.
- 94 Lasseter GM et al. In vitro evaluation of five rapid antigen detection tests for group A beta-haemolytic streptococcal sore throat infections. *Family Practice*, 2009; 26:437–444.
- 95 Van Limbergen J et al. Streptococcus A in paediatric accident and emergency: are rapid streptococcal tests and clinical examination of any help? *Emergency Medicine Journal*, 2006; 23:32–34.
- 96 Nissinen A et al. Point-of-care testing of group A streptococcal antigen: performance evaluated by external quality assessment. *European Journal of Clinical Microbiology & Infectious Diseases*, 2009; 28:17–20.
- 97 Meier FA, Jones BA. Point of care testing error: sources and amplifiers, taxonomy, prevention strategies, and detection monitors. *Archives of Pathology & Laboratory Medicine*, 2005; 129:1262–1267.
- 98 Shulman ST et al. Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 update by the Infectious Diseases Society of America. *Clinical Infectious Diseases*, 2012; 55(10):e86–102.
- 99 Hoffmann S. The throat carrier rate of group A and other beta hemolytic streptococci among patients in general practice. *Acta Pathologica Microbiologica Scandinavica Series B: Microbiology*, 1985; 93B:347–351.
- 100 Martin JM et al. Group A streptococci among school-aged children: clinical characteristics and the carrier state. *Pediatrics*, 2004; 114:1212–1219.
- 101 Ayanruoh S et al. Impact of rapid streptococcal test on antibiotic use in a pediatric emergency department. *Pediatric Emergency Care*, 2009; 25:748–750.
- 102 Needham CA, McPherson KA, Webb KH. Streptococcal pharyngitis: impact of a high-sensitivity antigen test on physician outcome. *Journal of Clinical Microbiology*, 1998; 36:3468–3473.
- 103 Cooper RJ et al. Principles of appropriate antibiotic use for acute pharyngitis in adults: background. *Annals of Internal Medicine*, 2001; 1324:509–517.
- 104 Humair JP et al. Management of acute pharyngitis in adults: reliability of rapid streptococcal tests and clinical findings. *Archives of Internal Medicine*, 2006; 166(6):640–644.
- 105 Ehrlich JE et al. Cost–effectiveness of treatment options for prevention of rheumatic heart disease from group A streptococcal pharyngitis in a pediatric population. *Preventive Medicine*, 2002; 35:250–257.
- 106 Giraldez-Garcia C et al. Diagnosis and management of acute pharyngitis in a pediatric population: a cost–effectiveness analysis. *European Journal of Pediatrics*, 2011; 170:1059–1067.
- 107 Chiappini E et al. Analysis of different recommendations from international guidelines for the management of acute pharyngitis in adults and children. *Clinical Therapeutics*, 2011; 33:48–58.
- 108 Lieu TA, Fleisher GR, Schwartz JS. Cost–effectiveness of rapid latex agglutination testing and throat culture for streptococcal pharyngitis. *Pediatrics*, 1990; 85:246–256.

- 109 Giraldez-Garcia C et al. Diagnosis and management of acute pharyngitis in a pediatric population: a cost-effectiveness analysis. *European Journal of Pediatrics*, 2011; 170:1059–1067.
- 110 Van Howe RS, Kusnier LP. Diagnosis and management of pharyngitis in a pediatric population based on cost-effectiveness and projected health outcomes. *Pediatrics*, 2006; 117:609–619.
- 111 Veasy LG et al. Resurgence of acute rheumatic fever in the intermountain area of the United States. *New England Journal of Medicine*, 1987; 316:421–427.
- 112 Jackson SJ, Steer AC, Campbell H. Systematic review: estimation of global burden of non-suppurative sequelae of upper respiratory tract infection: rheumatic fever and post-streptococcal glomerulonephritis. *Tropical Medicine and International Health*, 2011; 16:2–11.
- 113 Dajani A et al. Treatment of acute streptococcal pharyngitis and prevention of rheumatic fever: a statement for health professionals. *Pediatrics*, 1995; 96: 758–764.
- 114 Shulman ST et al. Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 update by the Infectious Diseases Society of America. *Clinical Infectious Diseases*, 2012; 55(10):e86–102.
- 115 Stone S et al. Antibiotic prescribing for patients with colds, upper respiratory infections, and bronchitis: a national study of hospital-based emergency departments. *Annals of Emergency Medicine*, 2000; 36:320–327.
- 116 Gonzales R, Steiner JF, Sande MA. Antibiotic prescribing for adults with colds, upper respiratory tract infections, and bronchitis by ambulatory care physicians. *JAMA: The Journal of the American Medical Association*, 1997;278:901–904.
- 117 Grijalva CG, Nuorti JB, Griffin MR. Antibiotic prescription rates for acute respiratory tract infections in US ambulatory settings. *JAMA: The Journal of the American Medical Association*, 2009; 302(7):758–766.
- 118 Adriasenssens N et al. European surveillance of antimicrobial consumption (ESAS): outpatient antibiotic use in Europe (1992–2009). *Journal of Antimicrobial Chemotherapy*, 2011; 66 Suppl. 6:vi3–vi12.
- 119 Lindbaek M. Prescribing antibiotics to patients with acute cough and otitis media. *British Journal of General Practice*, 2006; 56:164–166.
- 120 Little P et al. Reattendance and complications in a randomised trial of prescribing strategies for sore throat: the medicalising effect of prescribing antibiotics. *British Medical Journal*, 1997; 315:350–352.
- 121 True BL et al. Effect of a rapid diagnostic method on prescribing patterns and ordering of throat cultures for streptococcal pharyngitis. *Journal of Family Practice*, 1986; 23:215–219.
- 122 Meier FA et al. Effects of a rapid antigen test for group A streptococcal pharyngitis on physician prescribing and antibiotic costs. *Archives of Internal Medicine*, 1990; 150:1696–1700.
- 123 Hong SY et al. Antimicrobial prescribing in the US for adult acute pharyngitis in relation to treatment guidelines. *Journal of Evaluation in Clinical Practice*, 2011;17:1176–1183.
- 124 Ubukata K et al. Expression and inducibility in *Staphylococcus aureus* of the *mecA* gene, which encodes a methicillin-resistant *S. aureus*-specific penicillin-binding protein. *Journal of Bacteriology*, 1989; 171: 2882–2885.
- 125 Chalfine A et al. Ten-year decrease of acquired methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia at a single institution: the result of a multifaceted program combining cross-transmission prevention and antimicrobial stewardship. *Antimicrobial Resistance and Infection Control*, 2012; 1:18.
- 126 Dancer SJ et al. Approaching zero: temporal effects of a restrictive antibiotic policy on hospital-acquired *Clostridium difficile*, extended-spectrum β -lactamase-producing coliforms and methicillin-resistant *Staphylococcus aureus*. *International Journal of Antimicrobial Agents*, 2013 Feb.; 41(2):137–142.
- 127 Schweizer ML et al. Clinical utility of infection control documentation of prior methicillin-resistant *Staphylococcus aureus* colonization or infection for optimization of empirical antibiotic therapy. *Infection Control and Hospital Epidemiology*, 2008; 29: 972.
- 128 Wolk DM et al. Multicentre evaluation of the Cepheid Xpert methicillin-resistant *Staphylococcus aureus* (MRSA) test as a rapid screening method for detection of MRSA in nares. *Journal of Clinical Microbiology*, 2009; 47:758–764.
- 129 Cunningham R et al. Effect on MRSA transmission of rapid PCR testing of patients admitted to critical care. *Journal of Hospital Infection*, 2007; 65(1):24–28.
- 130 Lever A, Mackenzie I. Sepsis: definition, epidemiology, and diagnosis. *British Medical Journal*, 2007; 335:879–883.
- 131 Angus DC et al. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Critical Care Medicine*, 2001; 29:1303–1310.
- 132 Lever A, Mackenzie I. Sepsis: definition, epidemiology, and diagnosis. *British Medical Journal*, 2007; 335:879–883.

- 133 Martin GS et al. The epidemiology of sepsis in the United States from 1979 through 2000. *New England Journal of Medicine*, 2003; 348:1546–1554.
- 134 Padkin A et al. Epidemiology of severe sepsis occurring in the first 24 hrs in intensive care units in England, Wales, and Northern Ireland. *Critical Care Medicine*, 2003; 31:2232–2238.
- 135 Angus DC et al. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Critical Care Medicine*, 2001; 29:1303–1310.
- 136 Talmor D et al. The costs and cost-effectiveness of an integrated sepsis treatment protocol. *Critical Care Medicine*, 2008; 36: 168–1174.
- 137 Moerer O et al. Direct costs of severe sepsis in three German intensive care units based on retrospective electronic record analysis of resource use. *Intensive Care Medicine*, 2002; 28:1440–1446.
- 138 Ibid.
- 139 Martin GS et al. The epidemiology of sepsis in the United States from 1979 through 2000. *New England Journal of Medicine*, 2003; 348: 1546–1554.
- 140 Letarte J et al. Patient characteristics and cost of severe sepsis and septic shock in Quebec. *Journal of Critical Care*, 2002; 17:39–49.
- 141 Lucioni C, Mazzi S, Currado I. Sepsis costs in Italy. *Intensive Care Medicine*, 2001; 27(S2):284.
- 142 Burchardi H, Schneider H. Economic aspects of severe sepsis: a review of intensive care unit costs, cost of illness and cost effectiveness of therapy. *Pharmacoeconomics*, 2004; 22:793–813.
- 143 Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. *New England Journal of Medicine*, 2003; 348(2):138.
- 144 Ibrahim EH et al. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. *Chest*, 2000; 118:146–155.
- 145 Garnacho-Montero J et al. Impact of adequate empirical antibiotic therapy on the outcome of patients admitted to the intensive care unit with sepsis. *Critical Care Medicine*, 2003; 31:2742–2751.
- 146 Gaieski DF et al. Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. *Critical Care Medicine*, 2010; 38:1045–1053.
- 147 Dellinger RP et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and shock: 2012. *Critical Care Medicine*, 2013; 41:580–637.
- 148 Sands KE et al. Epidemiology of sepsis syndrome in 8 academic medical centres. *JAMA: The Journal of the American Medical Association*, 1997; 278:234–240.
- 149 Castellanos-Ortega Á et al. Impact of the Surviving Sepsis Campaign protocols on hospital length of stay and mortality in septic shock patients: results of a three-year follow-up quasi-experimental study. *Critical Care Medicine*, 2010; 38:1036–1043.
- 150 Adrie C et al. Epidemiology and economic evaluation of severe sepsis in France: age, severity, infection site, and place of acquisition (community, hospital, or intensive care unit) as determinants of workload and cost. *Journal of Critical Care*, 2005; 20:46–58.
- 151 Puskarich MA et al. Association between timing of antibiotic administration and mortality from septic shock in patients treated with a quantitative resuscitation protocol. *Critical Care Medicine*, 2011; 39:2066–2071.
- 152 Martin GS et al. The epidemiology of sepsis in the United States from 1979 through 2000. *New England Journal of Medicine*, 2003; 348:1546–1554.
- 153 Alberti C et al. Epidemiology of sepsis and infection in ICU patients from an international multicenter cohort study. *Intensive Care Medicine*, 2002; 28:108–121.
- 154 Sands KE et al. Epidemiology of sepsis syndrome in 8 academic medical centres. *JAMA: The Journal of the American Medical Association*, 1997; 278:234–240.
- 155 Engel C et al. Epidemiology of sepsis in Germany: results from a national prospective multicentre study. *Intensive Care Medicine*, 2007; 33:606–618.
- 156 Dellinger RP et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and shock: 2012. *Critical Care Medicine*, 2013; 41:580–637.
- 157 Lever A, Mackenzie I. Sepsis: definition, epidemiology, and diagnosis. *British Medical Journal*, 2007; 335:879–883.
- 158 Tang BM et al. Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: systematic review and meta-analysis. *Lancet Infectious Diseases*, 2007;7:210–217.
- 159 Müller B, Schuetz P, Trampuz A. Circulating biomarkers as surrogates for bloodstream infections. *International Journal of Antimicrobial Agents*, 2007; 30 Suppl. 1:S16–23.
- 160 Carrigan S et al. Toward resolving the challenge of sepsis diagnosis. *Clinical Chemistry*, 2004; 50(4) :1301–1314.

- 161 Castelli GP et al. Procalcitonin and C-reactive protein during systemic inflammatory response syndrome, sepsis and organ dysfunction. *Critical Care*, 2004; 8:R234–R242.
- 162 Livaditi O et al. Neutrophil CD64 expression and serum IL-8: sensitive early markers of severity and outcome in sepsis. *Cytokine*, 2006; 36:283–290.
- 163 Harbath S et al. Diagnostic value of procalcitonin, interleukin-6, and interleukin-8 in critically ill patients admitted with suspected sepsis. *American Journal of Respiratory Critical Care Medicine*, 2001; 164(3):396–402.
- 164 Brunkhorst FM et al. Procalcitonin for early diagnosis and differentiation of SIRS, sepsis, severe sepsis, and septic shock. *Intensive Care Medicine*, 2000; 26 Suppl. 2:S148–152.
- 165 Müller B, Schuetz P, Trampuz A. Circulating biomarkers as surrogates for bloodstream infections. *International Journal of Antimicrobial Agents*, 2007; 30 Suppl. 1:16–23.
- 166 Li H et al. Meta-analysis and systematic review of procalcitonin-guided therapy in respiratory tract infections. *Antimicrobial Agents and Chemotherapy*, 2011; 55(12):5900–5906.
- 167 BRAHMS Diagnostics. BRAHMS Procalcitonin sensitive KRYPTOR. Instructions for use. Publication No. D 13988, Ver. R10en. Henningsdorf, Germany: BRAHMS, 2008:1–6.
- 168 Llorente E et al. Umbilical cord blood serum procalcitonin by Time-Resolved Amplified Cryptate Emission (TRACE) technology: reference values of a potential marker of vertically transmitted neonatal sepsis. *Clinical Chemistry and Laboratory Medicine*, 2007; 45(11):1531–1535.
- 169 Smith EY et al. Biphasic activated partial thromboplastin time waveform and adverse events in non-intensive care unit patients. *American Journal of Clinical Pathology*, 2004; 121:138–141.
- 170 Pasqualini L et al. Diagnostic performance of a multiple real-time PCR assay in patients with suspected sepsis in an internal medicine ward. *Journal of Clinical Microbiology*, 2012; 50(4):1285–1288.
- 171 Lucignano B et al. Multiplex PCR allows rapid and accurate diagnosis of bloodstream infections in newborns and children with suspected sepsis. *Journal of Clinical Microbiology*, 2011; 49(6):2252–2258.
- 172 Rowther FB et al. Prospective comparison of eubacterial PCR and measurement of procalcitonin levels with blood culture for diagnosing septicemia in intensive care unit patients. *Journal of Clinical Microbiology*, 2009; 47:2964–2969.
- 173 FDA. FDA allows marketing of first test to identify certain bacteria associated with bloodstream infections. FDA News Release, 2012 (<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm309950.htm>, accessed 12 May 2015).
- 174 Weinstein MP et al. The clinical significance of positive blood cultures in the 1990s: a prospective comprehensive evaluation of the microbiology, epidemiology, and outcome of bacteremia and fungemia in adults. *Clinical Infectious Diseases*, 1997; 24(4):584–602.
- 175 Mancini N et al. The era of molecular and other non-culture-based methods in diagnosis of sepsis. *Clinical Microbiology Reviews*, 2010; 23:235–251.
- 176 Dagan R et al. Epidemiology and laboratory diagnosis of infection with viral and bacterial pathogens in infants hospitalized for suspected sepsis. *Journal of Pediatrics*, 1989; 115:351–356.
- 177 Watson RS et al. The epidemiology of severe sepsis in children in the United States. *American Journal of Respiratory Critical Care Medicine*, 2003; 167:695–701.
- 178 Engel C et al. Epidemiology of sepsis in Germany: results from a national prospective multicentre study. *Intensive Care Medicine*, 2007; 33:606–618.
- 179 Martin GS et al. The epidemiology of sepsis in the United States from 1979 through 2000. *New England Journal of Medicine*, 2003; 348:1546–1554.
- 180 Garnacho-Montero J et al. Impact of adequate empirical antibiotic therapy on the outcome of patients admitted to the intensive care unit with sepsis. *Critical Care Medicine*, 2003; 31:2742–2751.
- 181 Schorr A et al. Economic implications of an evidence-based sepsis protocol: can we improve outcomes and lower costs? *Critical Care Medicine*, 2007; 35:1257–1262.
- 182 Jones AE, Troyer JL, Kline JA. Cost-effectiveness of an emergency department based early sepsis resuscitation protocol. *Critical Care Medicine*, 2011; 39:1306–1312.
- 183 Ibid.
- 184 Talmor D et al. The costs and cost-effectiveness of an integrated sepsis treatment protocol. *Critical Care Medicine*, 2008; 36:1168–1174.
- 185 Burchardi H, Schneider H. Economic aspects of severe sepsis: a review of intensive care unit costs, cost of illness and cost effectiveness of therapy. *Pharmacoeconomics*, 2004; 22:793–813.
- 186 Talmor D et al. The costs and cost-effectiveness of an integrated sepsis treatment protocol. *Critical Care Medicine*, 2008; 36:1168–1174.

- 187 Dineva MA, Mahilum-Tapay L, Lee H. Sample preparation: a challenge in the development of point-of-care nucleic acid-based assays for resource-limited settings. *Analyst*, 2007; 132:1193–1199.

5. Reimbursement-related signals received from procurement and reimbursement agencies

- 1 Kaiser Family Foundation. Medicare fact sheet. November 2012 (<http://www.kff.org/medicare/upload/1066-15.pdf>, accessed 27 February 2013).
- 2 MEDpac. Clinical laboratory services payment system. October 2012 (http://www.medpac.gov/documents/MedPAC_briefs_Payment_Basics_12_clinical_lab.pdf, accessed 27 Feb. 2013).
- 3 CMS. *Innovators' guide to navigating Medicare*, version 2.0, 2010. Baltimore, MD: Centers for Medicare and Medicaid Services (https://www.cms.gov/Medicare/Coverage/CouncilonTechInnov/downloads/InnovatorsGuide5_10_10.pdf, accessed 27 Feb. 2013).
- 4 Neuman PJ, Chambers JD. Medicare's enduring struggle to define "reasonable and necessary" care. *New England Journal of Medicine*, 2012; 367:1775–1777.
- 5 AHRQ. Evidence-based practice centers reports. Rockville, MD: Agency for Healthcare Research and Quality (<http://www.ahrq.gov/research/findings/evidence-based-reports/a-z/index.html>, accessed 6 March 2013).
- 6 United States Preventative Services Task Force. *A–Z topic guide*. (<http://www.uspreventiveservicestaskforce.org/uspsttopics.htm>, accessed 6 March 2013).
- 7 United States Preventative Services Task Force. Grade definitions after July 2012 (<http://www.uspreventiveservicestaskforce.org/uspstf/grades.htm>, accessed 27 Feb. 2013).
- 8 CMS. Decision memo for screening for STIs and high-intensity behavioral counseling to prevent STIs (CAG-00426N) ([http://cms.hhs.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAlid=250&NcaName=Screening+for+Sexually+Transmitted+Infections+\(STIs\)+and+High-Intensity+Behavioral+Counseling+\(HIBC\)+to+prevent+STIs&year=2011&DocType=All&bc=AQAAAAIAAAAA%3d%3d&](http://cms.hhs.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAlid=250&NcaName=Screening+for+Sexually+Transmitted+Infections+(STIs)+and+High-Intensity+Behavioral+Counseling+(HIBC)+to+prevent+STIs&year=2011&DocType=All&bc=AQAAAAIAAAAA%3d%3d&), accessed 27 February 2013).
- 9 ECRI Institute. Health Technology Assessment Information Service (<https://www.ecri.org/Products/Pages/htais.aspx>, accessed 10 March 2013).
- 10 BlueCross BlueShield Association. Technology Evaluation Center assessment topics (<http://www.bcbs.com/bluesources/tec/topic.html>, accessed 27 February 2013).
- 11 Ibid.
- 12 Cook DJ et al. Rules of evidence and clinical recommendations on the use of antithrombotic agents. *Chest*, 1999; 4:205S–311S.
- 13 California Technology Assessment Forum. Assessments (<http://www.ctaf.org/assessments>, accessed 27 Feb. 2013).
- 14 Hayes Rating system (http://www.hayesinc.com/hayes/products_and_services/hayes-rating/, accessed 5 March 2013).
- 15 Gustavsen G, Philips K, Pothier K. The reimbursement landscape for novel diagnostics. *Health Advances*, 2010 (http://www.healthadvances.com/pdf/novel_diag_reimbursement.pdf, accessed 27 Feb. 2013).
- 16 FDA, Center for Devices and Radiologic Health. Public meeting: Oversight of laboratory developed tests (LDTs). U.S. Department of Health and Human Services, July 2010 (<http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm212830.htm>, accessed 30 July 2012).
- 17 CMS. Coverage with evidence development. Baltimore, MD: Centers for Medicare and Medicaid Services (<http://www.cms.gov/Medicare/Coverage/Coverage-with-Evidence-Development/index.html>, accessed 10 March 2013).
- 18 CMS.gov. CED public solicitation, 2011 (, accessed 4 March 2013).
- 19 CMS.gov. View public comments for CED public solicitation (<http://www.cms.gov/medicare-coverage-database/details/mcd-view-public-comments.aspx?MCDId=8&ExpandComments=y&McdName=CED+Public+Solicitation&mcdtypename=Guidance+Documents&MCDIndexType=1&bc=AgAEAAAAAiAA&>, accessed 4 March 2013).
- 20 CMS.gov. Draft guidance for the public, industry, and CMS staff. Coverage with evidence development in the context of coverage decisions (<http://www.cms.gov/medicare-coverage-database/details/medicare-coverage-document-details.aspx?MCDId=27>, accessed 7 March 2013).
- 21 CMS.gov. Public comments for draft guidance for the public, industry and CMS staff. Evidence development in the context of coverage decisions (<http://www.cms.gov/medicare-coverage-database/>

- details/mcd-view-public-comments.aspx?MCDId=23&ExpandComments=n&bc=AAAAAAAAAIAA AA%3d%3d&, accessed 6 March 2013).
- 22 CMS. Medicare contracting reform, A/B MAC jurisdictions. Baltimore, MD: Centers for Medicare and Medicaid (<http://www.cms.gov/Medicare/Medicare-Contracting/MedicareContractingReform/PartAandPartBMACJurisdictions.html>, accessed 27 February 2013).
 - 23 CMS. Guidance on section 4106 of the Affordable Care Act. Baltimore, MD: Centers for Medicare and Medicaid Services, 1 February 2013 (<http://www.medicaid.gov/Federal-Policy-Guidance/downloads/SMD-13-002.pdf>, accessed 27 February 2013).
 - 24 AMA. Resources, CPT. Chicago: American Medical Association (<http://www.ama-assn.org/ama/pub/physician-resources/solutions-managing-your-practice/coding-billing-insurance/cpt/applying-cpt-codes.page>, accessed 27 February 2013).
 - 25 MedPAC. Clinical laboratory service payment system (revised Oct. 2012). Washington, DC: Medicare Payment Advisory Committee (http://www.medpac.gov/documents/MedPAC_briefs_Payment_Basics_12_clinical_lab.pdf, accessed 27 February 2013).
 - 26 CMS.gov. Clinical laboratory fee schedule: laboratory public meetings (http://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ClinicalLabFeeSched/Laboratory_Public_Meetings.html, accessed 10 March 2013).
 - 27 Comments from Biotechnology Industry Organization on the CY2013 CMS new and reconsidered CLFS test codes and preliminary payment determinations (<http://www.bio.org/sites/default/files/BIO%20Comments%20on%20CY2013%20CLFS%20Payment%20Determinations.pdf>, accessed 13 March 2013).
 - 28 Wolman DM, Kalfoglou AL, LeRoy L, eds. Medicare laboratory payment policy: now and in the future. Washington, DC: Institute of Medicine, National Academy Press, 2000 (<http://iom.edu/Reports/2000/Medicare-Laboratory-Payment-Policy-Now-and-in-the-Future.aspx>, accessed 10 March 2013)
 - 29 Quinn B, Hoag F. Current issues and options: coverage and reimbursement for complex molecular diagnostics. DHSS policy analysis document, 2010 (<http://aspe.hhs.gov/health/reports/2010/CovReimCMD/index.shtml>, accessed on 10 March 2013).
 - 30 MedPac. Payment basics: hospital acute inpatient services payment system 2012. Washington, DC: Medicare Payment Advisory Committee (http://www.medpac.gov/documents/MedPAC_Payment_Basics_12_hospital.pdf, accessed on 13 February 2013).
 - 31 Lord Darzi of Denham. *High quality care for all: NHS next stage review*. London: Department of Health (www.sdh.gov.uk/en/publication-andstatistics/publications/publicationspolicy-andguidance/dh_085825, accessed on 30 June 2008).
 - 32 Russo T. *UK healthcare reimbursement: a market report from the U.S. Commercial Service*. Washington, DC, 2005 ([commercecanc.ic.gc.ca/scdb/bizmap/interface2.nsf/vdownload/ISA_2805/\\$file/X_8252893.doc](http://commercecanc.ic.gc.ca/scdb/bizmap/interface2.nsf/vdownload/ISA_2805/$file/X_8252893.doc), accessed 2 July 2012).
 - 33 Fitzgibbon F, Huckle D, Meenan BJ. Market access for cardiac POC testing in the National Health Service. *IVD Technology*, July–August 2011 (<http://www.ivdtechnology.com/article/market-access-cardiac-point-care-testing-uk-national-health-service>, accessed September 2015).
 - 34 Quotec Ltd. *Commercialising medical devices: a guide for UK based small companies*. London: Quotec Ltd, January 2010. (<http://www.quotec.co.uk/attachments/article/37/Commercialising%20Medical%20Devices.pdf>, accessed September 2015).
 - 35 Ibid.
 - 36 National Innovation Centre. Selling to the NHS: a guide to suppliers. 2012 (<http://knowledge.nic.nhs.uk/documentDetails.aspx?docId=10#section2>, accessed 26 November 2007).
 - 37 Olanow AE, Jungling MK, Bradshaw K, DiaSorin S.p.A. test results. In: *-25% upside*. New York: Morgan Stanley Research Estimates.
 - 38 Fitzgibbon F, Huckle D, Meenan BJ. Market access for cardiac POC testing in the National Health Service. *IVD Technology*, July–August 2011 (<http://www.ivdtechnology.com/article/market-access-cardiac-point-care-testing-uk-national-health-service>, September 2015).
 - 39 Ibid.
 - 40 FitzGibbon F, D Huckle D, Meenan BJ. Barriers affecting the adoption of point-of-care technologies used in chest pain diagnosis within the UK National Health Service: Part 2 – Manufacturer pricing and reimbursement policy issues. *Point of Care: The Journal of Near Patient Testing and Technology*, 2010; 9(2):80–90.
 - 41 Beastall GH. The modernization of pathology and laboratory medicine in the UK: networking into the future. *Clinical Biochemistry Review*, 2008; 29:3–10.

- 42 Charny M. Reimbursement for point-of-care diagnostics: opportunities and barriers. Paper presented to the Informa Market Access for Point-of-Care conference, Amsterdam (www.informa-ls.com/POCT/docs, accessed on 20 May 2008).
- 43 Galloway M. Making sense of the pathology tariff: how will it work in practice? Paper presented to the Health Service Journal Pathology Modernization Conference, London, 19 June 2008 (www.hsj-pathology.co.uk/homepage.asp, accessed 19 June 2008).
- 44 Department of Health. *A simple guide to payment by results*. London: Department of Health, July 2011 (http://www.ncvo-vol.org.uk/sites/default/files/DH_PBR.pdf, accessed 4 December 2012).
- 45 Department of Health, Update to best practice tariffs (news story), 13 December 2011 (<http://www.dh.gov.uk/health/2011/12/bpt-update/>, accessed 17 February 2013).
- 46 NHS Institute for Innovation and Improvement. Commissioning for Quality and Innovation (CQUIN) payment framework (http://www.institute.nhs.uk/world_class_commissioning/pct_portal/cquin.html, accessed 21 February 2013).
- 47 Lord Carter of Coles, *Report of the review of NHS pathology services in England Chaired by Lord Carter of Coles: an independent review for the Department of Health*. London: Department of Health, 2006.
- 48 Fitzgibbon F, Huckle D, Meenan BJ. Market access for cardiac POC testing in the National Health Service. *IVD Technology*, July–August 2011 (<http://www.ivdtechnology.com/article/market-access-cardiac-point-care-testing-uk-national-health-service>, accessed September 2015).
- 49 Beastall GH. The modernization of pathology and laboratory medicine in the UK: networking into the future. *Clinical Biochemistry Review*, 2008; 29:3–10.
- 50 Galloway M. Making sense of the pathology tariff: how will it work in practice? Paper presented to the Health Service Journal Pathology Modernization Conference, London, 19 June 2008 (www.hsj-pathology.co.uk/homepage.asp, accessed 19 June 2008).
- 51 Fitzgibbon F, Huckle D, Meenan BJ. Market access for cardiac POC testing in the National Health Service. *IVD Technology*, July–August 2011 (<http://www.ivdtechnology.com/article/market-access-cardiac-point-care-testing-uk-national-health-service>, accessed September 2015).
- 52 Quotec Ltd. *Commercialising medical devices: a guide for UK based small companies*. London: Quotec Ltd, January 2010. (<http://www.quotec.co.uk/attachments/article/37/Commercialising%20Medical%20Devices.pdf>, accessed September 2015).
- 53 MHRA. Devices evaluations. London: Medicines and Healthcare products Regulatory Agency (<http://webarchive.nationalarchives.gov.uk/20141205150130/http://www.mhra.gov.uk/Publications/Safetyguidance/Otherdevicesafetyguidance/Deviceevaluations/index.htm>, accessed 14 May 2015).
- 54 NICE medical technologies guidance (<http://www.nice.org.uk/mt>, accessed 14 May 2015).
- 55 Department of Trade and Industry. *UK sector competitive analysis of six healthcare equipment segments*. London: Department of Trade and Industry, 2005 (<http://www.dti.gov.uk/files/file10462.pdf>, accessed 10 November 2012).
- 56 Department of Health. *Pathology commissioning toolkit: supporting effective commissioning of laboratory medicine*. London: Department of Health, 2012 (<http://www.dh.gov.uk/health/2012/05/pathology-toolkit/>, accessed 22 February 2013).
- 57 PwC. *International review of pathology funding arrangements*. PricewaterhouseCoopers, March 2012 (<http://www.hirc.health.gov.au>, accessed 20 February 2013).
- 58 Lord Carter of Coles. *Report of the second phase of the review of NHS pathology services in England*. London: Department of Health, 2008.
- 59 Department of Health. *Pathology commissioning toolkit: supporting effective commissioning of laboratory medicine*. London: Department of Health, 2012 (<http://www.dh.gov.uk/health/2012/05/pathology-toolkit/>, accessed 22 February 2013).
- 60 Ibid.
- 61 Chris Price, Oxford, personal communication 2013.
- 62 Department of Health. *Pathology commissioning toolkit: supporting effective commissioning of laboratory medicine*. London: Department of Health, 2012 (<http://www.dh.gov.uk/health/2012/05/pathology-toolkit/>, accessed 22 February 2013).
- 63 EMDA. *European IVD market statistics report 2011*. Brussels: European Medical Devices Association, 2012 (<http://www.edma-ivd.eu/library/504-2011-european-ivd-market-statistics>, accessed 10 January 2013).
- 64 PwC. *International review of pathology funding arrangements*. PricewaterhouseCoopers, March 2012 (<http://www.hirc.health.gov.au/>, accessed 20 February 2013).

- 65 EMDA. *European IVD market statistics report 2011*. Brussels: European Medical Devices Association, 2012 (<http://www.edma-ivd.eu/library/504-2011-european-ivd-market-statistics>, accessed 10 January 2013).
- 66 Ibid.
- 67 Ibid.
- 68 Miller I et al. Market access challenges in the EU for high medical value diagnostic tests. *Personalized Medicine*, 2011; 8(2):137–148.
- 69 Ibid.
- 70 Ibid.
- 71 PwC. *International review of pathology funding arrangements*. PricewaterhouseCoopers, March 2012 (<http://www.hirc.health.gov.au/>, accessed on 20 February 2013).
- 72 Ibid.
- 73 Garfield S, *Advancing access to personalized medicine: a comparative assessment of European reimbursement systems*. Washington, DC: Personalized Medicine Coalition, 2011 (www.personalizedmedicinecoalition.org, accessed February 2012).
- 74 European Diagnostic Manufacturers' Association workshop, Brussels, 29 June 2010.
- 75 BioHealth EpiMed 2011 (<http://www.business-meets-research.lu>, accessed July 2013).

6. Regulation

- 1 WHO. *Medical devices: managing the mismatch. An outcome of the Priority Medical Devices project*. Geneva: World Health Organization, 2010 (http://whqlibdoc.who.int/publications/2010/9789241564045_eng.pdf, accessed February 2012).
- 2 Ibid.
- 3 DHHS, Centers for Medicare and Medicaid Services organizational chart. Washington, DC: Department of Health and Human Services (http://www.cms.gov/About-CMS/Agency-Information/CMSLeadership/Downloads/CMS_Organizational_Chart.pdf, accessed September 2012).
- 4 Ibid.
- 5 Office of Clinical Standards and Quality. *CMS* http://www.cms.gov/About-CMS/Agency-Information/CMSLeadership/Office_OCSQ.html, accessed September 2012).
- 6 FDA, *FDA organization overview*. Silver Spring, MD: Food and Drugs Administration, 2015 (<http://www.fda.gov/AboutFDA/CentersOffices/OrganizationCharts/ucm393155.htm>, accessed 14 May 2015).
- 7 FDA, Office of Medical Products and Tobacco. Silver Spring, MD: Food and Drugs Administration, 2015 (<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/>, accessed 15 May 2015).
- 8 Boone DJ. A history of the QC gap in the clinical laboratory. *Lab Medicine*, October 2005 (<http://labmed.ascpjournals.org/content/36/10/611.full.pdf>, accessed 14 May 2015).
- 9 Baker EL et al. *Regulations for implementing the Clinical Laboratory Improvement Amendments of 1988: a summary*. Atlanta, GA: Centers for Disease Control, 1992 (<http://www.cdc.gov/mmwr/preview/mmwrhtml/00016177.htm>, accessed 14 May 2015).
- 10 CMS, Clinical Laboratory Improvement Amendments (CLIA). Baltimore, MD: Centers for Medicare and Medicaid Services, 2015 (<http://www.cms.gov/clia/>, accessed 14 May 2015).
- 11 FDA. *IVD regulatory assistance. Device regulation and guidance 2012*. Silver Spring, MD: Food and Drug Administration (<http://www.fda.gov/medicaldevices/deviceregulationandguidance/ivdregulatoryassistance/ucm124269.htm>, accessed February 2012).
- 12 MaRS. Pathway to commercialization for an *in vitro* diagnostic (IVD) in the US. 2010 (<http://www.marsdd.com/wp-content/uploads/2012/09/Pathway-to-Commercialization-for-an-In-Vitro-Diagnostic-in-the-US.pdf>, accessed 14 May 2015).
- 13 FDA. *IVD regulatory assistance. Device regulation and guidance 2012*. Silver Spring, MD: Food and Drug Administration (<http://www.fda.gov/medicaldevices/deviceregulationandguidance/ivdregulatoryassistance/ucm124269.htm>, accessed February 2012).
- 14 Gitterman S. The US approach to the regulation of diagnostic tests for bacterial bloodstream and respiratory tract infections. FDA, 29 September 2011 (http://ecdc.europa.eu/en/activities/diseaseprogrammes/TATFAR/Documents/TATFAR_EU-US_workshop_US_approach.pdf, accessed 14 May 2015).
- 15 Murillo FM. Regulation of POCt and LDts: an FDA's perspective: Slide 22. Silver Spring, MD: Food and Drug Administration, 2011 (http://www.nibsc.ac.uk/PDF/Francisco_Martinez-Murillo.pdf, accessed September 2012).

- 16 FDA. General controls for medical devices. Silver Spring, MD: Food and Drug Administration, 26 June 2014 (<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/GeneralandSpecialControls/ucm055910.htm>, accessed 14 May 2015).
- 17 Lamph S. Regulation of medical devices outside the European Union. *Journal of the Royal Society of Medicine*, 2012; 105:S12–S21.
- 18 FDA, 510(k) Clearances. Silver Spring, MD: Food and Drug Administration, 2015 (<http://www.fda.gov/medicaldevices/productsandmedicalprocedures/deviceapprovalsandclearances/510kclearances/default.htm>, accessed 14 May 2015).
- 19 FDA. Premarket notification [5010(k)] review fees. Silver Spring, MD: Food and Drug Administration, 2015 (<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/ucm134566.htm>, accessed 14 May 2015).
- 20 FDA, Priority review of premarket submissions for devices. Washington, DC: Department of Health and Human Services, Food and Drug Administration (<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089698.pdf>, accessed 3 September 2012).
- 21 Law Offices of Michael A Swift. The De Novo petition: is there hope at FDA for lower risk, innovative devices? FX Conferences, 15 February 2012 (<http://www.slideshare.net/mswit/the-de-novo-510k-process>, accessed 14 May 2015).
- 22 FDA. Medical device appeals and complaints: guidance on dispute resolution. Silver Spring, MD: Food and Drug Administration, 1998 (<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094523.pdf>, accessed 30 January 2013).
- 23 FDA. Medical devices and flu emergencies. Silver Spring, MD: Food and Drug Administration 2012 (<http://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm>, accessed 30 January 2013).
- 24 FDA. H1N1 approved diagnostic devices (in vitro diagnostics product database). Silver Spring, MD: Food and Drug Administration, 2014 (<http://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm>, accessed 2 June 2014).
- 25 FDA. *Medical devices: PMA special considerations*. Silver Spring, MD: Food and Drug Administration, 2013 (<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm050490.htm>, accessed 18 January 2013).
- 26 European Commission. Dialogue between interested parties. (http://ec.europa.eu/growth/sectors/medical-devices/dialogues-parties/index_en.htm#taskforces, accessed on 14 May 2015).
- 27 Castle G, Blaney R. European Union regulation of in vitro diagnostic medical devices. Brussels, 2012 (<http://www.cov.com/files/Publication/5529cdda-e7c3-4ac8-b613-7e945a92ce44/Presentation/PublicationAttachment/9f2d9b63-f46d-4103-bf27-8d603abaeaf8/European%20Union%20Regulation%20of%20In%20Vitro%20Diagnostic%20Medical%20Devices.pdf>, accessed September 2015).
- 28 French-Mowat E, Burnett J. How are medical devices regulated in the European Union? *Journal of the Royal Society of Medicine*, 2012; 105:S22–S28.
- 29 MHRA. Register as a manufacturer to sell medical devices. London: Medicines and Healthcare Products Regulatory Agency, 2014 (<http://www.mhra.gov.uk/Howweregulate/Devices/Registrationofmedicaldevices/index.htm>, accessed 17 May 2015).
- 30 BSI. Medical devices: in vitro diagnostics. Milton Keynes: BSI Medical Devices, 2015 (<http://medicaldevices.bsigroup.com/en-GB/technologies/ivd/>, accessed 17 May 2015).
- 31 Polley R. The future of European regulation: the proposed changes to the IVD Directive. London: Medicines and Healthcare Products Regulatory Agency, 2005 (http://ecdc.europa.eu/en/activities/diseaseprogrammes/TATFAR/Documents/TATFAR_EU-US_workshop_future_European_Regulation.pdf, accessed September 2015).
- 32 Castle G, Blaney R. European Union regulation of in vitro diagnostic medical devices. Brussels, 2012 (<http://www.cov.com/files/Publication/5529cdda-e7c3-4ac8-b613-7e945a92ce44/Presentation/PublicationAttachment/9f2d9b63-f46d-4103-bf27-8d603abaeaf8/European%20Union%20Regulation%20of%20In%20Vitro%20Diagnostic%20Medical%20Devices.pdf>, accessed September 2015).
- 33 UK Medical Devices Notified Body Group. The responsibilities of the Notified Body under Medical Device Directive 93/42/EEC. April 2001 (http://ec.europa.eu/health/medical-devices/files/meddev/2_10-2annex3_04-2001_en.pdf, accessed 17 May 2015).
- 34 FDASIA (S. 3187). (<http://www.gpo.gov/fdsys/pkg/BILLS-112s3187enr/pdf/BILLS-112s3187enr.pdf>, accessed September 2015).

- 35 Thompson H. FDASIA is more than just user fees. *Medical Device and Diagnostic Industry*, 2012 (<http://www.mddionline.com/article/fdasia-more-just-user-fees>, accessed September 2015).
- 36 Okie S. Reviving the FDA. *New England Journal of Medicine*, 2010; 363:1492–1494.
- 37 PwC. Health industries registration. PricewaterhouseCoopers, 2014 (<http://pwchealth.com/cgi-local/hregister.cgi/reg/2012-Food-and-Drug-Administration-Safety-and-Innovation-Act.pdf>, accessed September 2015).
- 38 FDA. Background on MDUFMA. Silver Spring, MD: Food and Drug Administration, 2015 (<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFMA/ucm109149.htm>, accessed 17 May 2015).
- 39 PwC. Health industries registration. PricewaterhouseCoopers, 2014 (<http://pwchealth.com/cgi-local/hregister.cgi/reg/2012-Food-and-Drug-Administration-Safety-and-Innovation-Act.pdf>, accessed September 2015).
- 40 Hyman, Phelps & McNamara. PC, Food and Drug Administration Safety and Innovation Act. July 2012 (<http://www.hpm.com/pdf/blog/FDASIA-HP&MSummary&Analysis.pdf>, accessed 17 May 2015).
- 41 D'Orazio P. Improving health care accessibility through point-of-care technologies: issues from the IVD industry perspective. Paper presented at workshop on Improving Health Care Accessibility through Point-of-Care Technologies, 2006, report, p. 31 (http://www.nibib.nih.gov/sites/default/files/FINAL%20book%20for%20NIBIB_after.pdf, accessed September 2015).
- 42 James Nichols, 2011 interview with *Technological and Regulatory Developments in Point of Care*.
- 43 Ibid.
- 44 *National Action Plan for Combating Antibiotic Resistant Bacteria*. Washington, DC: The White House, 2015.
- 45 Ibid.
- 46 Ibid.
- 47 Proposal for a Regulation of the European Parliament and of the Council concerning medical devices and repealing Directives 90/385/EEC and 93/42/EEC (http://ec.europa.eu/governance/impact/planned_ia/docs/2008_sanco_081_proposal_medical_devices_en.pdf, accessed September 2015).
- 48 EC. Regulatory framework for medical devices. Brussels: European Commission, 2012 (http://ec.europa.eu/health/medical-devices/regulatory-framework/index_en.htm, accessed September 2015).
- 49 Medical Device Blog. Upcoming IVD changes for EU market will increase costs for medical device companies. AptivSolutions, 2012 (<http://www.aptivsolutions.com/blog/medical-device/2012/02/upcoming-ivd-changes-for-eu-market-will-increase-costs-for-medical-device-companies/>
<http://xavierhealth.org/>
- 50 <http://xavierhealth.org/>
- 51 EC. Revision of Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on *in vitro* diagnostic medical devices: summary of responses to the public consultation. Brussels: European Commission, Health and Consumers Directorate-General, 23 February 2011 (http://ec.europa.eu/growth/sectors/medical-devices/dialogues-parties/index_en.htm, accessed July 2015).
- 52 EC. Dialogue parties: working groups. Brussels: European Commission (http://ec.europa.eu/growth/sectors/medical-devices/dialogues-parties/index_en.htm, accessed July 2015).
- 53 Thompson M et al. Medical device recalls and transparency in the UK. *British Medical Journal*, 2011; 342:d2973.
- 54 O'Connor AB. The need for improved access to FDA reviews. *JAMA: The Journal of the American Medical Association*, 2009; 302:191–193
- 55 FDA. About: FDA Transparency Initiative. Silver Spring, MD: Food and Drug Administration. 2009 (<http://www.fda.gov/AboutFDA/Transparency/TransparencyInitiative/default.htm>, September 2015).
- 56 Ibid.
- 57 FDA. Device regulation and guidance. Silver Spring, MD: Food and Drug Administration, 2012 (<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089643.htm>, accessed February 2012).
- 58 Titus K. Two for the road with companion diagnostics. *CAP [College of American Pathologists] Today*, April 2012 (http://www.captodayonline.com/Archives/0412/0412b_diagnostics.html, accessed 4 February 2013).
- 59 Ibid.
- 60 Infectious Disease Society. Limited Population Antibacterial (LPAD) Approval Mechanism. 30 March 2012 (http://www.idsociety.org/uploadedFiles/IDSA/Policy_and_Advocacy/Current_Topics_and_Issues/Advancing_Product_Research_and_Development/Bad_Bugs_No_Drugs/Press_Releases/LPAD%20one%20pager.pdf, accessed 1 February 2013).

- 61 Shlaes D. FDA reboot! Antibiotics: the perfect storm, 2012 (<http://antibiotics-theperfectstorm.blogspot.co.uk/2012/05/fda-reboot.html>, accessed 15 January 13).
- 62 Janet Woodcock presentation at Brookings Workshop, Facilitating Antibacterial Drug Development, 9 May 2012.
- 63 EC. IVD guidance: research use only products: a guide for manufacturers and Notified Bodies. *Guidelines on Medical Devices 2004* (http://ec.europa.eu/health/medical-devices/files/meddev/2_14_2_research_only_product_en.pdf, accessed 18 May 2015).
- 64 European IVD Directive (http://ec.europa.eu/growth/single-market/european-standards/harmonised-standards/iv-diagnostic-medical-devices/index_en.htm, accessed October 2015).
- 65 Basu S, Hassenplug JC. Patient access to medical device: a comparison of US and European review processes. *New England Journal of Medicine*, 2012; 367:485–488.
- 66 Ibid.
- 67 IMDRF. IMDRF Presentation. International Medical Device Regulators Forum (<http://www.imdrf.org/docs/imdrf/final/meetings/imdrf-meet-120228-singapore-outcome-statement.pdf>, accessed October 2015).
- 68 EDMA. Media statement – EU free trade agreement negotiations with Japan, 2012 (http://www.eucomed.org/newsroom/95/19/Media-Statement-EU-Free-Trade-Agreement-negotiations-with-Japan?cntnt01template=display_details, accessed 10 February 2013).
- 69 PwC. 2012 Food and Drug Administration Safety and Innovation Act. August 2012 (<http://www.pwc.fr/the-2012-food-and-drug-administration-safety-and-innovation-act.html>, accessed 25 February 2013).

7. Intellectual property challenges

- 1 U.S. Supreme Court. *Diamond v. Chakrabarty*, 447 U.S.303 (1980).
- 2 Robinson D et al. *Diamond v. Chakrabarty*. A retrospective on 25 years of biotech patents. *Intellectual Property & Technology Law Journal*, 2005; 17(10):12–15.
- 3 Ibid.
- 4 Ibid.
- 5 Stix G. Owning the stuff of life. *Scientific American*, 2006; 294(2):76–83.
- 6 Notices. *Federal Register*, 2001; 66(4):1092–1099 – see comment #2 (www.gpo.gov).
- 7 Cho MK et al. Effects of patents and licenses on the provision of clinical testing services. *Journal of Molecular Diagnostics*, 2003; 5:3–8.
- 8 Gaisser S, Hokins MM. The phantom menace of gene patents. *Nature*, 2009; 458:407–408.
- 9 Hopkins MM et al. *The patenting of human DNA: global trends in the granting, filing and exploitation of DNA patents*. Report for the European Commission Sixth Framework Programme. Brighton: Science and Technology Policy Research, University of Sussex, 2006 (www.wipo.int/patentscope/en/programs/patent_landscapes/documents/patgen_finalreport.pdf, accessed September 2015).
- 10 European Patent Office. G-2/06: Use of embryos/WARE. *Official Journal of the European Patent Office*, 2009; 5:306–332.
- 11 Saul DJ, Gibbs MD, Berquist PL. Biocatalysis: industrial enzymes and the exploitation of microorganisms. Christchurch: Publication of the New Zealand Institute of Chemistry (<http://nzic.org.nz/ChemProcesses/biotech/12H.pdf>, accessed September 2015).
- 12 Aymé S, Matthijs G, Soini S. Patenting and licensing in genetic testing. *European Journal of Human Genetics*, 2008; 16:S3–S9.
- 13 Gaisser S et al. The phantom menace of gene patents. *Nature*, 2009; 458:407–408.
- 14 Ibid.
- 15 Andrews LB. Genes and patent policy: rethinking intellectual property rights. *Nature Reviews/Genetics*, 2002; 3: 803–808.
- 16 Utility Examination Guidelines. *Federal Register*, 2001; 66:1092–2002.
- 17 Wei T. Patenting genomic technology – 2001 Utility Examination Guidelines: an incomplete remedy in need of prompt reform. *Santa Clara Law Review*, 2003; 44(1):306–333.
- 18 Merz J et al. Diagnostic testing fails the test. *Nature*, 2002; 415:577–579.
- 19 Andrews LB. Genes and patent policy: rethinking intellectual property rights. *Nature Reviews/Genetics*, 2002; 3:803–808.
- 20 SACGHS. *Gene patents and licensing practices and their impact on patient access to genetics test*. Report of the SACGH, April 2010, Bethesda, MD: Secretary's Advisory Committee on Genetics, Health and Society (http://oba.od.nih.gov/oba/SACGHS/reports/SACGHS_patents_report_2010.pdf, accessed September 2015).

- 21 Hopkins M, Hogarth S. *Intellectual property and DNA diagnostics*. Report of a Seminar on the Impact of DNA Patents on Diagnostic Innovation. London: Human Genetics Commission Publications, 2010.
- 22 Andrews LB. Genes and patent policy: rethinking intellectual property rights. *Nature Reviews/Genetics*, 2002; 3:803–808.
- 23 Ibid.
- 24 Ibid.
- 25 Gaisser S et al. The phantom menace of gene patents. *Nature*, 2009; 458:407–408.
- 26 Human Genetics Commission. Powerbase (www.spinprofiles.org/index.php/Human_Genetics_Commission, accessed September 2015).
- 27 Hopkins M, Hogarth S. *Intellectual property and DNA diagnostics*. Report of a Seminar on the Impact of DNA Patents on Diagnostic Innovation. London: Human Genetics Commission Publications, 2010.
- 28 Hill R. Human Genetics Commission publishes Final Report. *BioNews*, 2012 June; 660.
- 29 SACGH. *Gene patents and licensing practices and their impact on patient access to genetics test*. Report of the SACGH, April 2010. Bethesda, MD: Secretary's Advisory Committee on Genetics, Health and Society (http://oba.od.nih.gov/oba/SACGHS/reports/SACGHS_patents_report_2010.pdf, accessed September 2015).
- 30 H.R. 3966 (107th). Genome Science and Technology Innovation Act of 2002 (<http://www.govtrack.us/congress/bills/107/hr3966>, accessed September 2015).
- 31 Andrews LB. Genes and patent policy: rethinking intellectual property rights. *Nature Reviews/Genetics*, 2002; 3:803–808.
- 32 *Association for Molecular Pathology et al. v. Myriad Genetics, Inc. et al.* (<http://www.patentdocs.typepad.com/files/brief-for-the-u.s.-as-amicus-curiae.pdf>, accessed September 2015).
- 33 Liptak A. Justices, 9–0, bar patenting human genes. *The New York Times*, 13 June 2013.
- 34 Skolnick MH et al. *17Q-linked breast and ovarian cancer susceptibility*. US 5747282 (<http://www.google.com/patents/US5747282>, accessed)
- 35 Tavtigian SV et al. *Chromosome 13-linked breast cancer susceptibility gene*. US 5837492A (<http://www.google.com/patents/US5837492>, accessed September 2015).
- 36 Butler D, Goodman S. French researchers take a stand against cancer gene patent. *Nature*, 2001; 413:95–96.
- 37 Andrews LB. Genes and patent policy: rethinking intellectual property rights. *Nature Reviews/Genetics*, 2002; 3:803–808.
- 38 Benowitz S. French challenge to BRCA1 patent underlies European discontent. *Journal of the National Cancer Institute*, 2002; 94:80–81.
- 39 Gad S et al. Identification of a large rearrangement of the BCRA1 gene using colour bar code on combed DNA in an American breast/ovarian cancer family previously studied by direct sequencing. *Journal of Medical Genetics*, 2001; 38:388–392.
- 40 Conley J, Vorhaus D. Supreme Court to rule on patentability of human gene. *Genomics Law Report. A publication of the Law Firm Robinson Bradshaw and Hinson*, 30 November 2012 (www.genomicslawreport.com/index.php/2012/11/30/supreme-court-to-rule-on-patentability-of-human-genes/#more-6923, accessed September 2015).
- 41 See: *Association for Molecular Pathology et al. v. Myriad Genetics, Inc., et al.*, October 2012 (http://www.supremecourt.gov/opinions/12pdf/12-398_1b7d.pdf, accessed September 2015).
- 42 Conley J. Myriad, finally: Supreme Court surprises by not surprising. *Genomics Law Report*, 18 June 2013 (www.genomicslawreport.com/index.php/2013/06/18/myriad-finally-supreme-court-surprises-by-not-surprising/, accessed September 2015).
- 43 Liptak A. Supreme Court rules human genes may not be patentable. *The New York Times*, 14 June 2013 (www.nytimes.com/2013/06/14/supreme-court-rules-human-genes-may-not-be-patentable.html, accessed September 2015).
- 44 Conley J. Myriad, finally: Supreme Court surprises by not surprising. *Genomics Law Report*, 18 June 2013 (www.genomicslawreport.com/index.php/2013/06/18/myriad-finally-supreme-court-surprises-by-not-surprising/, accessed September 2015).

8. Demand-side issues

- 1 Serra-Sastre V, McGuire A. Diffusion of health technologies: evidence from the pharmaceutical sector. In: Costa-Font J, Courbage C, McGuire A. *The economics of new health technologies: incentives, organization, and financing*, ch. 4. Oxford: Oxford University Press, 2009.

- 2 Chilukuri S et al. *Design to value in medical devices*. McKinsey & Co., 2009.
- 3 Parvin CA et al. Impact of point-of-care testing on patients' length of stay in a large emergency department. *Clinical Chemistry*, 1996 May; 42(5):711–717.
- 4 Hsieh YH et al. Perceptions on point-of-care tests for sexually transmitted infections - comparison between frontline clinicians and professionals in industry. *Point of Care*, 2012; 11(2):126–129.
- 5 Hsieh YH et al. What qualities are most important to making a point of care test desirable for clinicians and others offering sexually transmitted infection testing? *PLoS One*, 2011 Apr.; 6(4):e19263.
- 6 Thompson M et al. *Innovation in diagnostics and healthcare: improving bench to bedside processes for diagnostic testing*. Centre for Monitoring and Diagnosis, University of Oxford Department of Primary Care Health Sciences, 2011.
- 7 Ibid.
- 8 Pai NP et al. Point-of-care testing for infectious diseases: diversity, complexity, and barriers in low- and middle-income countries. *PLoS Medicine*, 2012; 9(9):e1001306.
- 9 West D. David Nicholson seeks NHS “nature and culture” change to innovate. *Health Service Journal*, 5 December 2011 (<http://www.hsj.co.uk/david-nicholson-seeks-nhs-nature-and-culture-change-to-innovate/5038823.article>, accessed 25 February 2013).
- 10 Huppert J, Hesse E, Gaydos CA. What's the point? How point-of-care STI tests can impact infected patients. *Point of Care*, 2010; 9(1):36–46.
- 11 Banda CI et al. Evaluation of the rapid BioStar optical immunoassay for detection of Chlamydia trachomatis in adolescent women. *Journal of Clinical Microbiology*, 2009; 47(1):215–216.
- 12 Price CP, Kricka LJ. Improving healthcare accessibility through point-of-care technologies. National Institute of Biomedical Imaging and Bioengineering/National Heart, Lung, and Blood Institute/National Science Foundation Workshop Faculty. *Clinical Chemistry*, 2007; 53(9):1665–1675.
- 13 National Institute of Biomedical Imaging and Bioengineering. Point-of-Care Technologies Research Network, October 2012 (<http://www.nibib.nih.gov/Research/POCTRN>, accessed 29 November 2012).
- 14 National Research Council. *Crossing the quality chasm – a new health system for the 21st century*. Washington, DC: National Academy Press, 2001, p. 2.
- 15 Balas EA, Boren SA. Managing clinical knowledge for health care improvement. In: *Yearbook of Medical Informatics*. Bethesda, MD: National Library of Medicine, 2000, pp. 65–70.
- 16 Wanless D. *Securing our future health: taking a long-term view*. London: HMSO, 2002.
- 17 Department of Health, *Innovation, health and wealth: accelerating adoption and diffusion in the NHS*. London: HMSO, 2011.
- 18 Booth-Clibborn N, Packer C, Stevens A. Health technology diffusion rates. Statins, coronary stents, and MRI in England. *International Journal of Technology Assessment in Health Care*, 2000; 16(3):781–786.
- 19 Thompson M et al. *Innovation in diagnostics and healthcare: improving bench to bedside processes for diagnostic testing*. Centre for Monitoring and Diagnosis, University of Oxford Department of Primary Care Health Sciences, 2011.
- 20 Simon Kimber, personal communication, 22 December 2012.
- 21 O’Kane MJ et al. Quality error rates in point-of-care testing. *Clinical Chemistry*, 2011; 57(9):1267–1271.
- 22 CDC. CLIA Certificate of Waiver Fact Sheet. Atlanta, GA: Centers for Disease Control and Prevention. (<http://www.cdc.gov/hiv/topics/testing/resources/factsheets/roltclia.htm>, accessed on 17 January 2013).
- 23 Washington State Clinical Laboratory Advisory Council. *Point-of-care testing guidelines*, March 2009 (<http://www.doh.wa.gov/portals/1/Documents/2700/POCT.pdf>, accessed September 2015).
- 24 Howerton D et al. Good laboratory practices for waived testing sites: survey findings from testing sites holding a certificate of waiver under the clinical laboratory improvement amendments of 1988 and recommendations for promoting quality testing. *Morbidity and Mortality Weekly Report. Recommendations and Reports/Centers for Disease Control*, 2005; 54(RR-13):1–25; quiz CE1–4.
- 25 Knapp H et al. Interactive internet-based clinical education: an efficient and cost-savings approach to point-of-care test training. *Telemedicine Journal and e-health: The Official Journal of the American Telemedicine Association*, 2011; 17(5):335–340.
- 26 Lewandrowski K, Gregory K, Macmillan D. Assuring quality in point-of-care testing: evolution of technologies, informatics, and program management. *Archives of Pathology & Laboratory Medicine*, 2012. Special section on Quality (<http://www.archivesofpathology.org/doi/full/10.5858/arpa.2011-0157-RA>, accessed September 2015).
- 27 Nichols JH. IVD interview, personal communication.
- 28 Ibid.
- 29 Ibid.

- 30 Ibid.
- 31 Ibid.
- 32 Ibid.
- 33 Belanger AC. Point-of-care testing: the JCAHO perspective. *Medical Laboratory Observer*, 1994; 26(6):46–49.
- 34 BIVDA. *Point of care testing: the difference diagnostics can make*. London: BIVDA, 2003.
- 35 Miller K, Miller N. Benefits of a joint nursing and laboratory point-of-care program: nursing and laboratory working together. *Critical Care Nursing Quarterly*, 2001; 24(1):15–20.
- 36 Geyer SJ. Implementing an effective point-of-care testing program. *Critical Care Nursing Quarterly*, 2001; 24(1):7–14.
- 37 Blattner K et al. Introducing point-of-care testing into a rural hospital setting: thematic analysis of interviews with providers. *Journal of Primary Health Care*, 2010; 2(1):54–60.
- 38 Lord Carter of Coles. *Report of the review of NHS pathology services in England chaired by Lord Carter of Coles: an independent review for the Department of Health*. London: Department of Health, 2006.
- 39 Broughton R, Rathbone B. What makes a good clinical guideline? (<http://www.medicine.ox.ac.uk/bandolier/painres/download/whatis/whatareclinguide.pdf>, accessed 20 February 2013).
- 40 Audit Commission. Best practice tariffs and their impact. February 2013 (<http://www.dh.gov.uk/health/2013/02/bpt-impact/>, accessed 20 February 2013).
- 41 Rotter T et al. Clinical pathways: effects on professional practice, patient outcomes, length of stay and hospital costs. *Cochrane Database of Systematic Reviews*, 2010; Issue 3; Art. No. CD006632.
- 42 Cabana MD et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA: The Journal of the American Medical Association*, 1999; 282(15):1458–1465.
- 43 CDC. Summary of notifiable diseases – United States, 2010. *Centres for Disease Control and Prevention Morbidity and Mortality Weekly Report*, 2012; 59(53):25.
- 44 CDC. *Special populations. Sexually transmitted diseases treatment guidelines 2010*. Atlanta, GA: Centers for Disease Control and Prevention, 2010.
- 45 Trepka MJ et al. Inadequate syphilis screening among women with prenatal care in a community with a high syphilis incidence. *Sexually Transmitted Diseases*, 2006; 33(11):670–674.
- 46 Bandea CI et al. Evaluation of the rapid BioStar optical immunoassay for detection of Chlamydia trachomatis in adolescent women. *Journal of Clinical Microbiology*, 2009; 47(1):215–216.
- 47 Björkman I et al. Awareness of antibiotic resistance and antibiotic prescribing in UTI treatment: a qualitative study among primary care physicians in Sweden. *Scandinavian Journal of Primary Health Care*, 2013; 31(1):50–55.
- 48 Cabana MD et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA: The Journal of the American Medical Association*, 1999; 282(15):1458–1465.
- 49 McDonnell Norms Group. Antibiotic overuse: the influence of social norms. *Journal of the American College of Surgeons*, 2008; 207(2):265–275.
- 50 Department of Health. *Innovation, health and wealth: accelerating adoption and diffusion in the NHS*. London: HMSO, 2011.
- 51 U.S Prevention Services Task Force. *USPSTF A–Z topic guide* (<http://www.uspreventiveservicestaskforce.org/uspstops.htm>, accessed 9 March 2013).
- 52 USPSTF. Screening for Chlamydial infection, clinical summary of recommendations (<http://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/chlamydia-and-gonorrhea-screening>, accessed 10 March 2013).
- 53 UnitedHealth, Centre for Health Reform and Modernization. Personalized medicine: trends and prospects for the new science of genetic testing and molecular diagnostics. Working Paper 7. Minneapolis, MN, 2012 (http://www.unitedhealthgroup.com/hrm/UNH_WorkingPaper7.pdf, accessed 14 February 2013).
- 54 American Medical Association. Acute respiratory tract infection guideline summaries (<http://www.ama-assn.org/ama/pub/physician-resources/medical-science/infectious-diseases/topics-interest/other-infectious-diseases/acute-respiratory-tract.page>, accessed on 10 March 2013).
- 55 CDC. *Report of expert consultations on rapid molecular testing to detect drug-resistant tuberculosis in the United States*. Atlanta, GA: Centers for Disease Control and Prevention (<http://www.cdc.gov/tb/topic/Laboratory/rapidmoleculartesting/MolDSTreport.pdf>, accessed 4 March 2013).
- 56 CDC. Molecular detection of drug resistance (MDDR). Atlanta, GA: Centers for Disease Control and Prevention, June 2012 (<http://www.cdc.gov/>, accessed 4 March 2013).
- 57 NICE Diagnostics Assessment Program. 2013 (<http://www.nice.org.uk/aboutnice/whatwedo/aboutdiagnosticsassessment/diagnosticsassessmentprogramme.jsp>, accessed 23 February 2013).

- 58 Map of Medicine (www.mapofmedicine.com, accessed 15 February 2013).
- 59 Price CP, St John A. *Point-of-care testing. Making innovation work for patient centred care*. Washington, DC: AACC Press.
- 60 O'Connor S, Freedman D, Kimber W. Working smarter. Putting the "path" in patient pathways – a collaboration between the College and the Map of Medicine. *Bulletin of the Royal College of Pathologists*, 2012; 158:101–103.
- 61 Hurwitz B. Legal and political considerations of clinical guidelines. *British Medical Journal*, 1999; 318.
- 62 Maisonneuve H et al. The French clinical guidelines and medical references program: development of 48 guidelines for private practice over a period of 18 months. *Journal of Evaluation in Clinical Practice*, 1997; 3:3–13.
- 63 Boissinot M, Bergeron M. Toward rapid real-time molecular diagnostic to guide smart use of antimicrobials. *Current Opinion in Microbiology*, 2002; 5:478–482.
- 64 Cals JW et al. Point-of-care C-reactive protein testing and antibiotic prescribing for respiratory tract infections: a randomized controlled trial. *Annals of Family Medicine* 2010; 8(2):124–133.
- 65 Sande MA, Gwaltney JM. Acute community-acquired bacterial sinusitis: continuing challenges and current management. *Clinical Infectious Diseases*, 2004; 39 Suppl. 3:S151–158.
- 66 Wang EE et al. Antibiotic prescribing for Canadian preschool children: evidence of overprescribing for viral respiratory infections. *Clinical Infectious Diseases*, 1999; 29(1):155–160.
- 67 Vanden Eng J et al. Consumer attitudes and use of antibiotics. *Emerging Infectious Diseases*, 2003; 9(9):1128–1135.
- 68 Macfarlane J et al. Prospective case-control study of role of infection in patients who reconsult after initial antibiotic treatment for lower respiratory tract infection in primary care. *British Medical Journal*, 1997; 315(7117):1206–1210.
- 69 Macfarlane J et al. Influence of patients' expectations on antibiotic management of acute lower respiratory tract illness in general practice: questionnaire study. *British Medical Journal*, 1997; 315(7117):1211–1214.
- 70 Cockburn J, Pit S. Prescribing behaviour in clinical practice: patients' expectations and doctors' perceptions of patients' expectations – a questionnaire study. *British Medical Journal*, 1997; 315(7107):520–523.
- 71 Mangione-Smith R et al. The relationship between perceived parental expectations and pediatrician antimicrobial prescribing behavior. *Pediatrics*, 1999; 103(4 Pt 1):711–718.
- 72 Butler CC et al. Understanding the culture of prescribing: qualitative study of general practitioners' and patients' perceptions of antibiotics for sore throats. *British Medical Journal*, 1998; 317(7159):637–642.
- 73 Kai J. Parents' difficulties and information needs in coping with acute illness in preschool children: a qualitative study. *British Medical Journal*, 1996; 313(7063):987–990.
- 74 De Sutter AI et al. Antibiotic prescribing in acute infections of the nose or sinuses: a matter of personal habit? *Family Practice*, 2001; 18(2):209–213.
- 75 O'Leary KJ et al. Medical students' and residents' clinical and educational experiences with defensive medicine. *Academic Medicine*, 2012; 87(2):142–148.
- 76 Grol R et al. Attitudes to risk taking in medical decision making among British, Dutch and Belgian general practitioners. *British Journal of General Practice*, 1990; 40(333):134–136.
- 77 McDonnell Norms Group. Antibiotic overuse: the influence of social norms. *Journal of the American College of Surgeons*, 2008; 207(2):265–275.
- 78 Perz JF et al. Changes in antibiotic prescribing for children after a community-wide campaign. *JAMA: The Journal of the American Medical Association*, 2002; 287(23):3103–3109.
- 79 Wood F et al. A multi-country qualitative study of clinicians' and patients' views on point of care tests for lower respiratory tract infection. *Family Practice*, 2011; 28(6):661–669.
- 80 Kessler D, McClellan M. Do doctors practice defensive medicine? *Quarterly Journal of Economics*, 1996; 111(2):353–390.
- 81 Rothstein MA. Currents in contemporary bioethics. Health care reform and medical malpractice claims. *Journal of Law and Medical Ethics*, 2010; 38(4):871–874.
- 82 Seabury SA et al. On average, physicians spend nearly 11 percent of their 40-year careers with an open, unresolved malpractice claim. *Health Affairs*, 2013; 32(1):111–119.
- 83 RAND Institute for Civil Justice and RAND Health. *Research brief: Malpractice risk, by physician specialty*. Santa Monica, CA: RAND Corporation.
- 84 Diederich Healthcare. 2012 medical malpractice payout analysis. Carbondale, IL (<http://www.diederichhealthcare.com/medical-malpractice-insurance/wp-content/uploads/2012/03/infographic.jpg>, accessed 6 March 2013).
- 85 Mello MM et al. National costs of the medical liability. *Health Affairs*, 2010; 29(9):1569–1577.

- 86 Ibid.
- 87 McClellan F. *Medical malpractice: law, tactics, and ethics*. Philadelphia, PA; Temple University Press, 1993, p. 192.
- 88 Jackson Healthcare. Physicians on medical liability reform options – an online quantitative research study. Alpharetta, GA: Jackson Healthcare (http://www.jacksonhealthcare.com/media/162770/phys_on_med_liability_reform_11.26.12_weighted_by_specialty.pdf, accessed 15 February 2013).
- 89 Studdert DM et al. Defensive medicine among high-risk specialist physicians in a volatile malpractice environment. *JAMA: The Journal of the American Medical Association* 2005; 293(21):2609–2617.
- 90 Jackson Healthcare. A costly defense: physicians sound off on the high price of defensive medicine in the U.S. 2011. Alpharetta, GA: Jackson Healthcare (http://www.jacksonhealthcare.com/media/8968/defensivemedicine_ebook_final.pdf, accessed 15 February 2013).
- 91 Ibid.
- 92 Gallegos A. Massachusetts hospitals launch patient apology program. *American Medical News*, 21 May 2012 (<http://www.ama-assn.org/amednews/2012/05/21/prsa0521.htm>, accessed 15 February 2013).
- 93 Jackson Healthcare. Physicians on medical liability reform options – an online quantitative research study. Alpharetta, GA: Jackson Healthcare (http://www.jacksonhealthcare.com/media/162770/phys_on_med_liability_reform_11.26.12_weighted_by_specialty.pdf, accessed February 2013).
- 94 WHO. Priority research topics. Geneva: World Health Organization, 2013 (<http://www.who.int/drugresistance/informationsharing/en/priorityresearchtopics.pdf>, accessed 21 November 2013).
- 95 Theuretzbacher U. Personal communication, June 2013.
- 96 Bandea CI et al. Evaluation of the rapid BioStar optical immunoassay for detection of Chlamydia trachomatis in adolescent women. *Journal of Clinical Microbiology*, 2009; 47(1):215–216.
- 97 Huppert J, Hesse E, Gaydos CA. What's the point? How point-of-care STI tests can impact infected patients. *Point of Care*, 2010; 9(1):36–46.

9. Economic evaluation: the limited evidence base affecting both supply and demand for new diagnostics

- 1 Briggs AH, O'Brien BJ. The death of cost-minimization analysis? *Health Economics*, 2001; 10:179–184.
- 2 Krupnick AJ. *Valuing health outcomes: policy choices and technical issues*, RFF Report. Washington, DC: Resources for the Future (<http://www.rff.org/rff/Documents/RFF-RPT-ValuingHealthOutcomes.pdf>, accessed 27 February 2013).
- 3 Center for the Evaluation of Value and Risk in Health. Cost effectiveness analysis registry. Boston, MA: Tufts Medical Center (<https://research.tufts-nemc.org/cear4/default.aspx#>, accessed 4 March 2013).
- 4 Braithwaite RS et al. What does the value of modern medicine say about the \$50,000 per Quality-Adjusted Life-Year decision rule? *Medical Care*, 2008; 46:343–345.
- 5 Garber AM. Cost-effectiveness and evidence evaluation as criteria for coverage policy. *Health Affairs (Millwood)*, 2004; Suppl. Web Exclusives: W4-284-96.
- 6 Murthy A, De Angelis G, Pittet D. Cost-effectiveness of universal MRSA screening on admission to surgery. *Clinical Microbiological Infections*, 2010; 16:1747–1753.
- 7 De Angelis G, Allignol A, Murthy A. Multistate modeling to estimate the excess length of stay associated with methicillin-resistant *Staphylococcus aureus* colonization and infection in surgical patients. *Journal of Hospital Infection* 2011; 78:86–91.
- 8 Schwegman D. Prevention of cross transmission of microorganisms is essential to preventing outbreaks of hospital-acquired infections. Nosocomial containment products, 2013 (<http://intl.welchalln.com/documents/Blood%20Pressure%20Management/FlexiPort%20Blood%20Pressure%20Cuffs/MC5032WHP%20White%20PaperHR.pdf>, accessed 27 February 2013).
- 9 Umscheid CA et al. Estimating the proportion of healthcare-associated infections that are reasonably preventable and the related mortality and costs. *Infection Control and Hospital Epidemiology*, 2011; 32:101–114.
- 10 Harbarth S, Sax H, Gastmeier P. The preventable proportion of nosocomial infections: an overview of published reports. *Journal of Hospital Infections*, 2003; 54:258–266.
- 11 Scott RD. The direct medical costs of healthcare-associated infections in U.S. hospitals and the benefits of prevention. Atlanta, GA: Centers for Disease Control and Prevention, 2009 (http://www.cdc.gov/hai/pdfs/hai/scott_costpaper.pdf, accessed 27 February 2013).

- 12 Anderson DJ, Kirkland KB, Kaye KS. Under resourced hospital infection control and prevention programs: penny wise, pound foolish? *Infection Control and Hospital Epidemiology*, 2007; 28:767–773.
- 13 Stone PW, Braccia D, Larson E. Systematic review of economic analyses of health care-associated infections. *American Journal of Infection Control*, 2005; 33:501–509.
- 14 Hu K et al. Use of maximal sterile barriers during central venous catheter insertion: clinical and economic outcomes. *Clinical Infectious Diseases*, 2004; 39:1441–1445.
- 15 Warren DK et al. Outcome and attributable cost of ventilator-associated pneumonia among intensive care unit patients in a suburban medical centre. *Critical Care Medical Journal*, 2003; 31:1312–1317.
- 16 Anderson DJ, Kirkland KB, Kaye KS. Under-resourced hospital infection control and prevention programs: penny wise, pound foolish? *Infection Control and Hospital Epidemiology*, 2007; 28:767–773.
- 17 Ibid.
- 18 Tambyah PA, Knasinski V, Maki DG. The direct costs of nosocomial catheter-associated urinary tract infection in the era of managed care. *Infection Control and Hospital Epidemiology*, 2002; 23:27–31.
- 19 Dubberke ER et al. Short- and long-term attributable costs of *Clostridium difficile*-associated disease in nonsurgical inpatients. *Clinical Infectious Diseases*, 2008; 46:497–504.
- 20 Institute of Medicine. *To err is human: building a safer health system*, edited by Kohn L, Corrigan J, Donaldson M. Washington, DC: National Academy Press, 2000.
- 21 Navarrete-Navarro S, Armengol-Sanchez G. Secondary costs due to nosocomial infections in 2 pediatric intensive care units. *Salud Publica Mex*, 1999; 41:S51–8.
- 22 Plowman R et al. The rate and cost of hospital-acquired infections occurring in patients admitted to selected specialties of a district general hospitals in England and the national burden imposed. *Journal of Hospital Infection*, 2001; 47:198–209.
- 23 Ibid.
- 24 Ibid.
- 25 Klevens R et al. Changes in the epidemiology of methicillin-resistant *Staphylococcus aureus* in intensive care units in US hospitals, 1992–2003. *Clinical Infectious Diseases*, 2006; 42:389–391.
- 26 Harbarth S. Control of endemic methicillin-resistant *Staphylococcus aureus* – recent advances and future challenges. *Clinical Microbiology and Infection*, 2006; 12:11554–11562.
- 27 Murthy A, De Angelis G, Pittet D. Cost–effectiveness of universal MRSA screening on admission to surgery. *Clinical Microbiological Infections*, 2010; 16:1747–1753.
- 28 Lehmann L et al. Cost and mortality prediction using polymerase chain reaction pathogen detection in sepsis: evidence from three observational trials. *Critical Care*, 2010; 14: R186.
- 29 Martin G et al. The epidemiology of sepsis in the United States from 1979 through 2000. *New England Journal of Medicine*, 2003; 348:1546–1554.
- 30 Byl B et al. Impact of infectious diseases specialists and microbiological data on the appropriateness of antimicrobial therapy for bacteremia. *Clinical Infectious Diseases*, 1999; 29:60–66.
- 31 Ibrahim EH et al. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. *Chest*, 2000; 118:146–155.
- 32 Kumar A et al. Duration of hypotension before initiation of effective antimicrobial therapy is the crucial determinant of survival in human septic shock. *Critical Care Medicine*, 2006; 34:1589–1596.
- 33 Kumar A et al. Initiation of inappropriate antimicrobial therapy results in a fivefold reduction of survival in human septic shock. *Chest*, 2009; 136:1237–1248
- 34 Alvarez J et al. Cost analysis of real-time polymerase chain reaction microbiological diagnosis in patients with septic shock. *Anaesthesia and Intensive Care*, 2012; 40:958–963.
- 35 Garnacho-Montero J et al. Mortality and morbidity attributable to inadequate empirical antimicrobial therapy in patients admitted to ICU with sepsis: a matched cohort study. *Journal of Antimicrobial Chemotherapy*, 2008; 61:436–441.
- 36 Afshari A. Bench-to-bedside review: rapid molecular diagnostics for bloodstream infections – a new frontier? *Critical Care*, 2012; 16:222.
- 37 Lehmann LE et al. Potential clinical utility of polymerase chain reaction in microbiological testing for sepsis. *Critical Care Medicine*, 2009; 37:2985–2990.
- 38 Lehmann L et al. Cost and mortality prediction using polymerase chain reaction pathogen detection in sepsis: evidence from three observational trials. *Critical Care*, 2010; 14: R186.
- 39 Alvarez J et al. Cost analysis of real-time polymerase chain reaction microbiological diagnosis in patients with septic shock. *Anaesthesia and Intensive Care*, 2012; 40:958–963.
- 40 Haley RW et al. Nosocomial infections in U.S. hospitals, 1975–1976: estimated frequency by selected characteristics of patients. *American Journal of Medicine*, 1981; 70:947–959.

- 41 Haley RW et al. The nationwide nosocomial infection rate. A new need for vital statistics. *American Journal of Epidemiology*, 1985; 121:159–167.
- 42 Downs SM. Technical report: urinary tract infections in febrile infants and young children. The Urinary Tract Subcommittee of the American Academy of Pediatrics Committee on Quality Improvement. *Pediatrics*, 1999; 103:e54
- 43 Little P et al. Dipsticks and diagnostic algorithms in urinary tract infection: development and validation, randomized trial, economic analysis, observational cohort and qualitative study. *Health Technology Assessment*, 2009; 13:1–73.
- 44 Shaw KN et al. Screening for urinary tract infection in infants in the emergency department: which test is best? *Pediatrics*, 1998; 101:E1.
- 45 Fowles GA, Waters J, Williams G. The cost–effectiveness of combined rapid tests (Multistix) in screening for urinary tract infections. *Journal of the Royal Society of Medicine*, 1994; 87:681–682.
- 46 Wong HF, Lee LC, Han HC. Cost–effective screening for urinary tract infections in urogynaecological patients. *International Urogynecological Journal*, 2008; 19:671–676.
- 47 Fowles GA, Waters J, Williams G. The cost–effectiveness of combined rapid tests (Multistix) in screening for urinary tract infections. *Journal of the Royal Society of Medicine*, 1994; 87:681–682.
- 48 Awonuga DO et al. Asymptomatic bacteriuria in pregnancy: evaluation of reagent strips in comparison to microbiological culture. *Global Advances in Health and Medicine*, 2011; 40:377–383.
- 49 Wong HF, Lee LC, Han HC. Cost–effective screening for urinary tract infections in urogynaecological patients. *International Urogynecological Journal*, 2008; 19:671–676.
- 50 Little P et al. Dipsticks and diagnostic algorithms in urinary tract infection: development and validation, randomized trial, economic analysis, observational cohort and qualitative study. *Health Technology Assessment*, 2009; 13:1–73.
- 51 Whiting P et al. Clinical effectiveness and cost–effectiveness of tests for the diagnosis and investigation of urinary tract infection in children: a systematic review and economic model. *Health Technology Assessment*, 2006; 36:1–154.
- 52 Linder JA, Stafford RS. Antibiotic treatment of adults with sore throat by community primary care physicians: a national survey, 1989–1999. *JAMA: The Journal of the American Medical Association*, 2001; 286:1181–1186.
- 53 Butler CC et al. Understanding the culture of prescribing: qualitative study of general practitioners' and patients' perceptions of antibiotics for sore throats. *British Medical Journal*, 1998; 317:637–642.
- 54 Humair JP, Revaz SA, Bovier P. Management of acute pharyngitis in adults: reliability of rapid streptococcal tests and clinical findings. *Archives of Internal Medicine* 2006; 166:640–644.
- 55 Giraldez-García C et al. Diagnosis and management of acute pharyngitis in a paediatric population: a cost–effectiveness analysis. *European Journal of Pediatrics*, 2011; 170:1059–1067.
- 56 Ehrlich JE, Demopoulos BP, Daniel KR. Cost–effectiveness of treatment options for prevention of rheumatic heart disease from Group A streptococcal pharyngitis in a pediatric population. *Preventative Medicine*, 2002; 35:250–257.
- 57 Neuner JM et al. Diagnosis and management of adults with pharyngitis. A cost–effectiveness analysis. *Annals of Internal Medicine*, 2003; 139:113–122.
- 58 Tsevat J, Kotagal UR. Management of sore throats in children: a cost–effectiveness analysis. *Archives of Pediatrics and Adolescent Medicine*, 1999; 153:681–688.
- 59 Kaplan SL. The emergence of resistant pneumococcus as a pathogen in childhood upper respiratory tract infections. *Seminars in Respiratory Infections*, 1995; 10:31–36.
- 60 Woo PC et al. Cost–effectiveness of rapid diagnosis of viral respiratory tract infections in pediatric patients. *Journal of Clinical Microbiology*, 1997; 35:1579–1581.
- 61 Barenfanger J et al. Clinical and financial benefits of rapid detection of respiratory viruses: an outcomes study. *Journal of Clinical Microbiology*, 2000; 38:2824–2828.
- 62 Symis MW et al. A sensitive, specific, and cost–effective multiplex reverse transcriptase-PCR assay for the detection of seven common respiratory viruses in respiratory samples. *Journal of Molecular Diagnostics*, 2004; 6:125–131.
- 63 Meropol SB. Valuing reduced antibiotic use for pediatric acute otitis media. *Pediatrics* 2008; 121:669–673.
- 64 Aral S, Douglas JM (Jr), Douglas JM. *Behavioral Interventions for Prevention and Control of Sexually Transmitted Diseases*. New York: Springer, 2007.
- 65 Abimbola TO et al. Cost–effectiveness of tuberculosis diagnostic strategies to reduce early mortality among persons with advanced HIV infection initiating antiretroviral therapy. *Journal of Acquired Immune Deficiency Syndrome*, 2012; 60:e1–7.

- 66 Meropol SB. Valuing reduced antibiotic use for pediatric acute otitis media. *Pediatrics* 2008; 121: 669–673.
- 67 White AR. Effective antibacterials: at what cost? The economics of antibacterial resistance and its control. *Journal of Antimicrobial Chemotherapy*, 2011; 66:1948–1953.
- 68 Jönsson B. Ten arguments for a societal perspective in the economic evaluation of medical innovations. *European Journal of Health Economics*, 2009; 10:357–359.
- 69 Council on Health Care Technology, Institute of Medicine. Costs and sources of funding. In: *Assessment of Diagnostic Technology in Health Care: Rationale, Methods, Problems, and Directions*. Washington, DC: The National Academies Press, 1989, ch. 5.
- 70 Thompson M et al. *Innovation in diagnostics and healthcare: improving bench to bedside processes for diagnostic testing*. Centre for Monitoring and Diagnosis, University of Oxford Department of Primary Care Health Sciences, 2011.
- 71 Innovate UK: Technology Strategy Board (<https://www.gov.uk/government/organisations/innovate-uk>, accessed 7 April 2014).
- 72 Thompson M et al. *Innovation in diagnostics and healthcare: improving bench to bedside processes for diagnostic testing*. Centre for Monitoring and Diagnosis, University of Oxford Department of Primary Care Health Sciences, 2011.
- 73 Alvarez J et al. Cost analysis of real-time polymerase chain reaction microbiological diagnosis in patients with septic shock. *Anaesthesia Intensive Care*, 2012; 40(6):958–963.
- 74 Royal College of Pathologists. *The future provision of molecular diagnostic services for acquired disease in the UK*. London, Royal College of Pathologists, October 2010.
- 75 Lord Carter of Coles, *Report of the review of NHS pathology services in England chaired by Lord Carter of Coles: an independent review for the Department of Health*. London: Department of Health, 2006.
- 76 Advanced Product Development for Multiplex Infectious Disease Diagnostics: Summary of a NIAID Workshop held on 27 June 2005 (https://www.niaid.nih.gov/topics/diagnostics/Documents/adv_prod.pdf, accessed 13 Oct. 2015).
- 77 Nichols JH. IVD interview, personal communication.
- 78 Hornberger J, Cosler LE, Lyman GH. Economic analysis of targeting chemotherapy using a 21-gene RT-PCR assay in lymph-node-negative, estrogen-receptor-positive, early-stage breast cancer. *American Journal of Managed Care*, 2005; 11:313–324.
- 79 Evans RW et al. The economic implications of noninvasive molecular testing for cardiac allograft rejection. *American Journal of Transplant*, 2005; 5:1553–1558.
- 80 Gustavsen G, Philips K, Pothier K. *The reimbursement landscape for novel diagnostics*. Weston, MA: Health Advances, 2010 (http://www.healthadvances.com/pdf/novel_diag_reimbursement.pdf, accessed 27 February 2013).
- 81 Garber AM. Cost–effectiveness and evidence evaluation as criteria for coverage policy. *Health Affairs (Millwood)*, 2004; Suppl. Web Exclusives: W4-284-96.
- 82 Lord Carter of Coles, *Report of the review of NHS pathology services in England chaired by Lord Carter of Coles: an independent review for the Department of Health*. London: Department of Health, 2006.
- 83 Ibid.
- 84 Ibid.
- 85 Ibid.
- 86 Crabb N. The NICE Diagnostics Assessment Programme. Paper presented at the Evidence for Diagnostic Tests – How Can We Improve “Bench to Bedside Process”? Conference, Oxford, 2011.
- 87 Department of Health. *Innovation, health and wealth: accelerating adoption and diffusion in the NHS*. London: HMSO, 2011.
- 88 Ibid.
- 89 NIHR. Diagnostic evidence co-operatives: invitation to submit pre-qualifying questionnaire, London: National Institute for Health Research, 2012 (<http://www.ccf.nihr.ac.uk/Documents/NIHR%20DECs%20-%20invitation%20to%20submit%20PQQ%20guidance.pdf>, accessed 26 November 2013).
- 90 Stafinski T et al. Health technology funding decision-making processes around the world: the same, yet different. *Pharmacoeconomics*, 2011; 29(6):475–495.
- 91 Stafinski T, McCabe CJ, Menon D. Funding the unfundable: mechanisms for managing uncertainty in decisions on the introduction of new and innovative technologies into healthcare systems. *Pharmacoeconomics*, 2010; 28(2):113–142.
- 92 Mushlin AI, Ruchlin HS, Callahan MA. Costeffectiveness of diagnostic tests. *Lancet*, 2001; 358(9290):1353–1355.

- 93 UK Technology Strategy Board (SBRI). Assessing the impact of near-patient testing. SBRI Competition for development contracts, September 2011 (http://www.scottishlifesciencesassociation.org.uk/userfiles/Comp_SBRI_DIIA_FINAL.pdf, 16 November 2012).
- 94 Severens JL, van der Wilt GJ. Economic evaluation of diagnostic tests. A review of published studies. *International Journal of Technology Assessment in Health Care*, 1999; 15(3):480–496.
- 95 Lord Carter of Coles, *Report of the review of NHS pathology services in England chaired by Lord Carter of Coles: an independent review for the Department of Health*. London: Department of Health, 2006.
- 96 Keffer J. Health economic aspects of point-of-care testing. In: Price C, St John A, Hicks J, eds. *Point-of-Care Testing*, 2nd edn. Washington, DC: American Association for Clinical Chemistry, 2004.
- 97 Moayyedi P, Mason J. Cost–utility and cost–benefit analyses: how did we get here and where are we going? *European Journal of Gastroenterology and Hepatology*, 2004; 16(6):527–534.
- 98 Mason J, Drummond M, Torrance G. Some guidelines on the use of cost–effectiveness league tables. *British Medical Journal*, 1993; 306(6877):570–572.
- 99 Teutsch SM, Harris JR. Introduction. In: Haddix AC, Teutsch SM, Corso PS, eds. *Prevention effectiveness: a guide to decision analysis and economic evaluation*, 2nd edn. New York: Oxford University Press, 2003.
- 100 Mooney GH. Cost–benefit analysis and medical ethics. *Journal of Medical Ethics*, 1980; 6(4):177–179.
- 101 Mauskopf JA et al. The role of cost–consequence analysis in healthcare decision-making. *Pharmacoeconomics*, 1998; 13(3):277–288.
- 102 Van Howe RS, Kusnier LP 2nd. Diagnosis and management of pharyngitis in a pediatric population based on cost–effectiveness and projected health outcomes. *Pediatrics*, 2006; 117(3):609–619.
- 103 Lehmann LE et al. Cost and mortality prediction using polymerase chain reaction pathogen detection in sepsis: evidence from three observational trials. *Critical Care*, 2010; 14(5):R186.
- 104 Alvarez J et al. Cost analysis of real-time polymerase chain reaction microbiological diagnosis in patients with septic shock. *Anaesthesia Intensive Care*, 2012; 40(6):958–963
- 105 Wong HF, Lee LC, Han HC. Cost–effective screening for urinary tract infections in urogynaecological patients. *International Urogynecological Journal*, 2008; 19:671–676.
- 106 Jönsson B. Ten arguments for a societal perspective in the economic evaluation of medical innovations. *European Journal of Health Economics*, 2009; 10(4):357–359.
- 107 Kassler WJ et al. On-site, rapid HIV testing with same-day results and counseling. *AIDS*, 1997; 11(8):1045–1051.
- 108 Meropol SB. Valuing reduced antibiotic use for pediatric acute otitis media. *Pediatrics*, 2008; 121(4):669–673.
- 109 White AR on behalf of the BSAC Working Party on the Urgent Need: Regenerating Antibacterial Drug Discovery and Development. Effective antibacterials: at what cost? The economics of antibacterial resistance and its control. *Journal of Antimicrobial Chemotherapy*, 2011; 66(9):1948–1953.
- 110 Mossialos A et al. *Policies and incentives for promoting innovation in antibiotic research*. London: European Observatory on Health Systems and Policy, 2010, p. 24.
- 111 Cosgrove SE, Carmeli Y. The impact of antimicrobial resistance on health and economic outcomes. *Clinical Infectious Diseases*, 2003; 36(11):1433–1437.
- 112 Howard DH et al. The global impact of drug resistance. *Clinical Infectious Diseases*, 2003; 36 Suppl. 1:S4–10.
- 113 Okeke IN et al. Diagnostics as essential tools for containing antibacterial resistance. *Drug Resistance Updates*, 2011; 14(2):95–106.
- 114 Keffer J. Health economic aspects of point-of-care testing. In: Price C, St John A, Hicks J, eds. *Point-of-care testing*, 2nd edn. Washington, DC: American Association for Clinical Chemistry, 2004.
- 115 Lewandrowski EL, Lewandrowski K. Implementing point-of-care testing to improve outcomes. *Journal of Hospital Administration*, 2013; 2(2):125–132.
- 116 Baer DM. Point-of-care testing versus central lab costs. *Medical Laboratory Observer*, 1 September 1998.
- 117 Keffer J. Health economic aspects of point-of-care testing. In: Price C, St John A, Hicks J eds. *Point-of-care testing*, 2nd edn. Washington, DC: American Association for Clinical Chemistry, 2004.
- 118 Baer DM. Point-of-care testing versus central lab costs. *Medical Laboratory Observer*, September 1 1998.
- 119 Ibid.
- 120 De Angelis G, Allignol A, Murthy A. Multistate modeling to estimate the excess length of stay associated with methicillin-resistant *Staphylococcus aureus* colonization and infection in surgical patients. *Journal of Hospital Infection*, 2011; 78:86–91.
- 121 Lehmann L et al. Cost and mortality prediction using polymerase chain reaction pathogen detection in sepsis: evidence from three observational trials. *Critical Care*, 2010, 14: R186.

- 122 Murthy A, De Angelis G, Pittet D. Cost–effectiveness of universal MRSA screening on admission to surgery. *Clinical Microbiological Infections*, 2010; 16:1747–1753.
- 123 Afshari A et al. Bench-to-bedside review: rapid molecular diagnostics for bloodstream infections – a new frontier? *Critical Care*, 2012; 16:222.
- 124 Lehmann L et al. Cost and mortality prediction using polymerase chain reaction pathogen detection in sepsis: evidence from three observational trials. *Critical Care*, 2010, 14: R186.
- 125 Dierkes C et al. Clinical impact of a commercially available multiplex PCR system for rapid detection of pathogens in patients with presumed sepsis. *BMC Infectious diseases*, 2009; 9:126.
- 126 Fischer JE et al. Quantifying uncertainty: physicians’ estimates of infection in critically ill neonates and children. *Clinical Infectious Diseases*, 2004; 38:1383–1390.
- 127 Innovate UK/Technology Strategy Board. ‘Medical innovations backed by £18million fund’. Press release, 24 January 2012, Swindon.
- 128 Keffer J. Health economic aspects of point-of-care testing. In: Price C, St John A, Hicks J, eds. *Point-of-care testing*, 2nd edn. Washington, DC: American Association for Clinical Chemistry, 2004.
- 129 Van Howe RS, Kusnier LP 2nd. Diagnosis and management of pharyngitis in a pediatric population based on cost–effectiveness and projected health outcomes. *Pediatrics*, 2006 Mar.; 117(3):609–619.
- 130 Fleisher M, Schwartz MK. Automated approaches to rapid-response testing. A comparative evaluation of point-of-care and centralized laboratory testing. *American Journal of Clinical Pathology*, 1995; 104(4) Suppl. 1:S18–25.
- 131 Tsevat J, Kotagal UR. Management of sore throats in children: a cost–effectiveness analysis. *Archives of Pediatric and Adolescent Medicine*, 1999; 153:681–688.
- 132 Lieu TA, Fleisher GR, Schwartz JS. Cost–effectiveness of rapid latex agglutination testing and throat culture for streptococcal pharyngitis. *Pediatrics*, 1990; 85(3):246–256.
- 133 Tsevat J, Kotagal UR. Management of sore throats in children: a cost–effectiveness analysis. *Archives of Pediatric and Adolescent Medicine*, 1999; 153:681–688.
- 134 Lieu TA, Fleisher GR, Schwartz JS. Cost–effectiveness of rapid latex agglutination testing and throat culture for streptococcal pharyngitis. *Pediatrics*, 1990; 85(3):246–256.
- 135 Neuner JM et al. Diagnosis and management of adults with pharyngitis: a costeffectiveness analysis. *Annals of Internal Medicine*, 2003; 139:113–122.

10. Underlying and purpose-driven health system incentives affecting demand for diagnostics

- 1 Langenbrunner J, Cashin C, O’Dougherty S. *Designing and implementing health care provider payment systems*. Washington DC, World Bank, 2009.
- 2 Kwon S. Payment system reform for health care providers in Korea. *Health Policy and Planning*, 2003; 18(1):84–92.
- 3 Institute of Medicine, Committee on Quality of Health Care in America. *Crossing the quality chasm; a new health system for the 21st century*. Washington, DC: National Academy Press, 2001.
- 4 Office of Technology Assessment. *Diagnosis-related groups (DRGs) and the Medicare program: implications for medical technology – a technical memorandum*. Washington, DC: US Congress, Office of Technology Assessment, July 1983(<http://digital.library.unt.edu/ark:/67531/metadc39505/>, accessed 23 February 2013).
- 5 Busse R et al. *Diagnosis-related groups in Europe*. Buckingham: Open University Press, 2011.
- 6 Miller I et al. Market access challenges in the EU for high medical value diagnostic tests. *Personalized Medicine*, 2011; 8(2):137–148.
- 7 Office of Technology Assessment. *Diagnosis-related groups (DRGs) and the Medicare program: implications for medical technology – a technical memorandum*. Washington, DC: US Congress, Office of Technology Assessment, July 1983(<http://digital.library.unt.edu/ark:/67531/metadc39505/>, accessed 23 February 2013).
- 8 Thompson M et al. *Innovation in diagnostics and healthcare: improving bench to bedside processes for testing*. Oxford: Centre for Monitoring and Diagnosis, University of Oxford Department of Primary Health Care Science, 2011.
- 9 Miller I et al. Market access challenges in the EU for high-value diagnostic tests. *Personalized Medicine*, 2011; 8(2):137–148(<http://www.futuremedicine.com/doi/pdf/10.2217/pme.11.2>, accessed 18 February 2013)

- 10 Ibid.
- 11 Department of Health. *Health reform in England: update and commissioning framework. Annex: The commissioning framework*. London: Department of Health (http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4137230.pdf, accessed 23 February 2013).
- 12 Department of Health. *Commissioning a patient-led NHS*. London: Department of Health, 2005 (http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4116716, accessed 23 February 2013).
- 13 Price C, Jones R. The challenges in commissioning laboratory medicine (pathology) services. *Journal of Management & Marketing in Healthcare*, 2008; 1(2):166–178.
- 14 Department of Trade and Industry. *UK sector competitive analysis of six healthcare equipment segments*. London: Department of Trade and Industry (<http://www.dti.gov.uk/files/file10462.pdf>, accessed 10 November 2012).
- 15 House of Commons Select Committee Report. *The use of new medical technology within the NHS*. London: Stationery Office, 2005 (www.publications.parliament.uk/pa/cm200405/cmselect/cmhealth/398/39802.htm, accessed 23 February 2013).
- 16 Healthcare Industries Task Force. *Better health through partnership: a programme for action*. London: Department of Health, 2004 (<http://www.abhi.org.uk/multimedia/downloads/2004/hitf/coi-hitf-report.pdf>, accessed 23 February 2013).
- 17 Price C, Jones R. The challenges in commissioning laboratory medicine (pathology) services. *Journal of Management & Marketing in Healthcare*, 2008; 1(2):166–178.
- 18 Ibid.
- 19 Audit Commission for Local Authorities and the National Health Service in England and Wales. *Critical path: an analysis of the pathology services (NHS Report)*. London: Department of Health, 1993.
- 20 Great Britain NHS Executive. *Strategic review of pathology services*. London: Department of Health, 1995.
- 21 Lord Carter of Coles. *Report of the review of pathology services in England chaired by Lord Carter of Coles: an independent review for the Department of Health*. London: Department of Health, 2006.
- 22 MHRA. *Management of in vitro medical devices*. London: Medicines and Healthcare products Regulatory Agency, 2013 (<http://www.mhra.gov.uk/home/groups/dts-bs/documents/publication/con007336.pdf>, accessed September 2015).
- 23 Healthcare Industries Task Force. *Better health through partnership: a programme for action*. London: Department of Health, 2004 (<http://www.abhi.org.uk/multimedia/downloads/2004/hitf/coi-hitf-report.pdf>, accessed 23 February 2013).
- 24 Price C, Jones R. The challenges in commissioning laboratory medicine (pathology) services. *Journal of Management & Marketing in Healthcare*, 2008; 1(2):166–178.
- 25 Ibid.
- 26 Lord Carter of Coles. *Report of the review of pathology services in England chaired by Lord Carter of Coles: an independent review for the Department of Health*. London: Department of Health, 2006.
- 27 Lord Carter of Coles. *Report of the second phase of the review of NHS pathology services in England*. London: Department of Health, 2008.
- 28 Interview with Martin Whitbread, CEO Proceur.
- 29 EMDA. *European IVD market statistics report 2011*. Brussels: European Medical Devices Association (<http://www.edma-ivd.eu/library/504-2011-european-ivd-market-statistics>, accessed 10 January 2013).
- 30 Price C, Jones R. The challenges in commissioning laboratory medicine (pathology) services. *Journal of Management & Marketing in Healthcare*, 2008; 1(2):166–178.
- 31 Department of Health. *Innovation, Health and Wealth: accelerating adoption and diffusion in the NHS*. London: HMSO, 2011 (http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_134597.pdf, accessed on 15 February 2013).
- 32 Premier. Group purchasing code of conduct. Washington, DC: Premier (<https://www.premierinc.com/wps/wcm/connect/627c9e41-e175-4d16-bc46-a9a9fb851a03/GPO6292012.pdf?MOD=AJPERES>, accessed 20 February 2013).
- 33 United States Government Accountability Office. *Group Purchasing Organizations: Services provided to customers and initiatives regarding their business practices*. Washington, DC: GAO, 2010 (<http://www.gao.gov/products/GAO-10-738>, accessed 24 February 2013).
- 34 Kanavos P, Seeley L, Vadoros S. Tender systems for outpatient pharmaceuticals in the European Union: evidence from the Netherlands, Germany and Belgium. EmiNet, LSE Health, London School

- of Economics, 2009 (http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/study_pricing_2007/rendering_systems_en.pdf, accessed 24 February 2013).
- 35 Litan RE, Singer HJ, Birkenbach A. An empirical analysis of aftermarket transactions. *Journal of Contemporary Health Law Policy*, 2011; 28:23–38.
- 36 Price C, Jones R. The challenges in commissioning laboratory medicine (pathology) services. *Journal of Management & Marketing in Healthcare*, 2008; 1(2):166–178.
- 37 Kilpatrick ES, Holding S. Use of computer terminals on wards to access emergency test results: a retrospective audit. *British Medical Journal*, 2001; 322(7294):1101–1103.
- 38 Khunti K et al. Randomised controlled trial of near-patient testing for glycated haemoglobin in people with type 2 diabetes mellitus. *British Journal of General Practice*, 2006; 56(528): 511–517.
- 39 Price CP, Christenson RH, eds. *Evidence-based laboratory medicine: principles, practice and outcomes*, 2nd edn. Washington, DC: AACC Press, 2007.
- 40 National Audit Office. *The management and control of hospital acquired infection in acute trusts in England*. London: National Audit Office, 2000 (HC 230 Session 1999–2000).
- 41 National Audit Office. *Improving patient care by reducing the risks of hospital acquired infection: a progress report*. London: National Audit Office, 2004 (HC 876 Session 2003–2004).
- 42 National Audit Office. *Reducing healthcare associated infections in hospitals in England*. Report by the Comptroller and Auditor General. London: National Audit Office, 2009 (HC 560 Session 2008–2009).
- 43 Ibid.
- 44 Ibid.
- 45 Ibid.
- 46 Ibid.
- 47 Dellinger RP et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and shock: 2012. *Critical Care Medicine*, 2013; 41:580–637.
- 48 Price CP, St John A. *Point-of-care testing. Making innovation work for patient centred care*. Washington, DC: AACC Press.
- 49 Ibid., p. 23.
- 50 Price CP, St John A. *Point-of-care testing. Making innovation work for patient centred care*. Washington, DC: AACC Press.
- 51 Price CP. Evidence-based laboratory medicine: is it working in practice? *The Clinical Biochemist Reviews*, 2012; 33:13–19.
- 52 National Audit Office. *Reducing healthcare associated infections in hospitals in England*. Report by the Comptroller and Auditor General. London: National Audit Office, 2009 (HC 560 Session 2008–2009).
- 53 Map of Medicine, Map of Medicine Supporting the QIPP Challenge, 2012 (<http://www.mapofmedicine.com/>, accessed 22 February 2013).
- 54 CMS. Hospital-acquired conditions (HAC) in acute inpatient prospective payment system (IPPS) hospitals. Centers for Medicare and Medicaid Services, Oct. 2012 (<http://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/HospitalAcqCond/downloads/hacfactsheet.pdf>, accessed 25 February 2013).
- 55 CMS. Hospital-acquired conditions (HAC) in acute inpatient prospective payment system (IPPS) hospitals. Baltimore, MD: Centers for Medicare and Medicaid Services, Oct. 2012 (<http://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/HospitalAcqCond/downloads/hacfactsheet.pdf>, accessed 25 February 2013).
- 56 CMS. Readmissions reduction program. Baltimore, MD: Centers for Medicare and Medicaid Services, 2012 (<http://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/AcuteInpatientPPS/Readmissions-Reduction-Program.html>, accessed 25 February 2013).
- 57 HealthCare.gov. About the health insurance marketplace (<http://www.healthcare.gov/marketplace/about/index.html>, accessed 25 February 2013).
- 58 HealthCare.gov. Hospital value-based purchasing: measure explanations (<http://www.healthcare.gov/news/factsheets/2011/04/valuebasedpurchasing04292011b.html>, accessed 25 February 2013).
- 59 How hospitals' quality bonuses and penalties were determined and how to use the data. *Kaiser Health News*, December 2012 (<http://www.kaiserhealthnews.org/Stories/2012/December/21/value-based-purchasing-methodology.aspx>, accessed 25 February 2013).
- 60 CDC. Eliminating healthcare-associated infections. State policy options. Atlanta, GA: Centers for Disease Control and Prevention, 2012 (http://www.cdc.gov/hai/pdfs/toolkits/toolkit-hai-policy-final_01-2012.pdf, accessed 12 March 2013).

11. Co-development of antibiotics and diagnostics for bacterial infection

- 1 Davis J, Ma P, Sutaria S. The microeconomics of personalized personalized medicine. *McKinsey Quarterly*, February 2012 (http://www.mckinsey.com/insights/health_systems_and_services/the_microeconomics_of_personalized_medicine, accessed 3 April 15)
- 2 Davis J, Ma P, Sutaria S. The microeconomics of personalized personalized medicine. *McKinsey Quarterly*, February 2012 (http://www.mckinsey.com/insights/health_systems_and_services/the_microeconomics_of_personalized_medicine, accessed 3 April 2015)
- 3 Interview with David Payne, GSK. *Telegraph* 2012 (<http://www.telegraph.co.uk/finance/newsbysector/pharmaceuticalsandchemicals/9010738/The-battle-to-discover-new-antibiotics.html>, accessed 27 January 2013).
- 4 Glaxo press release on launch of IMI program “NewDrugs4BadBugs”. 2012. (<http://us.gsk.com/html/media-news/pressreleases/2012/2012-pressrelease-1104300.htm>, accessed 27 January 2013).
- 5 Antibiotic resistance 2012: The antibiotics development pipeline and strategies to combat antibiotic resistance. BioPharm, 2012 (<http://www.prnewswire.com/news-releases/antibiotic-resistance-2012-the-antibiotics-development-pipeline-and-strategies-to-combat-antibiotic-resistance-171228621.html>, accessed September 2015).
- 6 Titus K. Two for the road with companion diagnostics. *CAP [College of American Pathologists] Today*, April 2012 (http://www.captodayonline.com/Archives/0412/0412b_diagnostics.html, accessed 4 February 2013).
- 7 Mossialos A et al. *Policies and incentives for promoting innovation in antibiotic research*. London: The European Observatory on Health Systems and Policy, 2010, p. 24.
- 8 Morel C, Mossialos A. Stoking the antibiotic pipeline. *British Medical Journal*, 2010; 340.
- 9 Sharma P, Towse A. Incentives for R&D for new antimicrobial drugs. Research Paper 11/02. London: Office of Health Economics, 2011.
- 10 Shlaes D et al. Commentary: the FDA reboot of antibiotic development. *American Society for Microbiology*, 2013 (<http://aac.asm.org/content/early/2013/07/23/AAC.01277-13.full.pdf>, accessed 30 May 2014).
- 11 Roche Diagnostics. Presentation to Medicines and Healthcare products Regulatory Agency, 2011. (<http://webarchive.nationalarchives.gov.uk/20141205150130/http://www.mhra.gov.uk/home/groups/es-policy/documents/websitesresources/con065601.pdf>, accessed September 2015).
- 12 Kolodziej E. Regulatory and technical challenges for sequencing. Presentation to FDA public meeting, 23 June 2011. Roche Diagnostics (<http://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM261813.pdf>, accessed 30 January 2013).
- 13 Davis J, Ma P, Sutaria S. The microeconomics of personalized personalized medicine. *McKinsey Quarterly*, February 2012 (http://www.mckinsey.com/insights/health_systems_and_services/the_microeconomics_of_personalized_medicine, accessed 3 April 2015).
- 14 Coleman K. Companion diagnostics and personalized medicine. *Datamonitor Healthcare*, 2012.
- 15 Moore M, Babu D, Cotter P. Challenges in the co-development of companion diagnostics. *Personalized Medicine*, 2012; 9(5).
- 16 PwC. *Diagnostics 2011: M&A surges, companion diagnostics accelerate, and early detection offers new prospects*. 2nd edn. US and Luxembourg: PwC, December 2011.
- 17 Moore M, Babu D, Cotter P. Challenges in the co-development of companion diagnostics. *Personalized Medicine*, 2012; 9(5).
- 18 Roche Diagnostics 2011 presentation to MHRA. Medicines and Healthcare products Regulatory Agency <http://webarchive.nationalarchives.gov.uk/20141205150130/http://www.mhra.gov.uk/home/groups/es-policy/documents/websitesresources/con065601.pdf>
- 19 Coleman K. Companion diagnostics and personalized medicine. *Datamonitor Healthcare*. 2012.
- 20 Roche Diagnostics PHC Investor Day (<http://www.roche.com/irp110921.pdf>, accessed on 31 January 2013).
- 21 PwC. *Diagnostics 2011: M&A surges, companion diagnostics accelerate, and early detection offers new prospects*. 2nd edn. US and Luxembourg: PwC.
- 22 Coleman K. Companion diagnostics and personalized medicine. *Datamonitor Healthcare*, 2012.
- 23 Ibid.
- 24 Ibid.
- 25 AstraZeneca. Press release: AstraZeneca and Dako sign agreement to develop companion diagnostics for cancer treatments. 19 January 2010 (<http://www.astrazeneca.se/pressrum/pressmeddelanden-och-nyheter/Article/astrazeneca-and-dako-sign-agreement-to-develop-companion-diagnos>, accessed 2 February 2013).

- 26 RAPP-ID: Development of point-of-care test platforms for infectious disease. Innovative Medicines Initiative (<http://www.imi.europa.eu/content/rapp-id>, accessed September 2015).
- 27 Titus K. Two for the road with companion diagnostics. *CAP [College of American Pathologists] Today*, April 2012 (http://www.captodayonline.com/Archives/0412/0412b_diagnostics.html, accessed 4 February 2013).
- 28 Theuretzbacher U. Future antibiotics scenarios: is the tide starting to turn? *International Journal of Microbial Agents*, 2009 Jul.; 34(1):15–20.
- 29 Rex J. Diagnostics: a focus on use in development of drugs for MDR pathogens. European Federation of Pharmaceutical Industries and Associations (EFPIA), Brussels, 25–26 Oct. 2012.
- 30 Rex J. Personal communication, 6 November 2012.
- 31 Rex J. Diagnostics: a focus on use in development of drugs for MDR pathogens. European Federation of Pharmaceutical Industries and Associations (EFPIA), Brussels, 25–26 Oct. 2012.
- 32 Ibid.
- 33 Rex J. The importance of rapid diagnostics for advancing antibacterial development. Paper presented at TATFAR workshop Challenges and Solutions in the Development of New Diagnostic Tests to Combat Antimicrobial Resistance, 28–29 September 2011 (http://ecdc.europa.eu/en/activities/diseaseprogrammes/TATFAR/news/Pages/TATFAR_Workshop.aspx, accessed September 2015).
- 34 Ibid.
- 35 Rex J. Diagnostics: a focus on use in development of drugs for MDR pathogens. European Federation of Pharmaceutical Industries and Associations (EFPIA), Brussels, 25–26 Oct. 2012.
- 36 Theuretzbacher U. Future antibiotics scenarios: is the tide starting to turn? *International Journal of Microbial Agents*, 2009 Jul.; 34(1):15–20.
- 37 Titus K. Two for the road with companion diagnostics. *CAP [College of American Pathologists] Today*, April 2012 (http://www.captodayonline.com/Archives/0412/0412b_diagnostics.html, accessed 4 February 2013).
- 38 Roche Diagnostics PHC Investor Day presentation (<http://www.roche.com/irp110921.pdf>, accessed 31 January 2013).
- 39 Ibid.
- 40 Titus K. Two for the road with companion diagnostics. *CAP [College of American Pathologists] Today*, April 2012 (http://www.captodayonline.com/Archives/0412/0412b_diagnostics.html, accessed 4 February 2013).
- 41 Koberstein W. Can rapid mobile diagnostics speed up clinical trials and regulatory reviews? *Life Science Leader*, 30 August 2012 (<http://lifescienceleader.com/magazine/past-issues3/item/4268-can-rapid-mobile-diagnostics-speed-up-clinical-trials-and-regulatory-reviews>, accessed 3 February 2013).
- 42 Trushheim MR, Berndt ER, Douglas FL. Stratified medicine: strategic and economic implications of combining drugs and clinical biomarkers. *Nature Reviews/Drug Discovery*, 2007; 6:287–293.
- 43 Agarwal A. Overlooked opportunities. 1 January 2009 (<http://www.pharmexec.com/overlooked-opportunities>, accessed 3 February 2013).
- 44 Theuretzbacher U. Future antibiotics scenarios: is the tide starting to turn? *International Journal of Microbial Agents*, 2009; 34(1):15–20.
- 45 Coleman K. Companion diagnostics and personalized medicine. *Datamonitor Healthcare*. 2012.
- 46 Moore MW, Babu D, Cotter PD. Challenges in the development of companion diagnostics. *Future Medicine*, 2012; 9(5):485–496 (<http://www.futuremedicine.com/doi/pdf/10.2217/pme.12.60>, accessed September 2015).
- 47 Ibid.
- 48 PwC. *Diagnostics 2011: M&A surges, companion diagnostics accelerate, and early detection offers new prospects*. 2nd edn. US and Luxembourg: PwC.
- 49 Marketwatch.com. Pfizer to invest \$25m in Monogram Biosciences. 2006. (<http://www.marketwatch.com/story/pfizer-to-invest-25m-in-monogram-biosciences>, accessed 30 May 2014).
- 50 PwC. *Diagnostics 2011: M&A surges, companion diagnostics accelerate, and early detection offers new prospects*. 2nd edn. US and Luxembourg: PwC.
- 51 Titus K. Two for the road with companion diagnostics. *CAP [College of American Pathologists] Today*, April 2012 (http://www.captodayonline.com/Archives/0412/0412b_diagnostics.html, accessed 4 February 2013).
- 52 EBD Group. Gene multiplex assays key to companion diagnostics. January 2012 (<http://ebdgroup.com/partneringnews/2012/01/seegene-multiplex-assays-key-to-companion-diagnostics/>, accessed January 2012).

- 53 PwC. *Diagnostics 2011: M&A surges, companion diagnostics accelerate, and early detection offers new prospects*. 2nd edn. US and Luxembourg: PwC.
- 54 Genentech. Herceptin (Trastuzumab) development timeline (<http://www.gene.com/media/product-information/herceptin-development-timeline>, accessed 22 May 2015).
- 55 Miller I et al. Market access challenges in the EU for high-value diagnostic tests. *Personalized Medicine*, 2011;8(2):137–148 (<http://www.futuremedicine.com/doi/pdf/10.2217/pme.11.2>, accessed 18 February 2013).
- 56 Roche Diagnostics PHC Investor Day presentation (<http://www.roche.com/irp110921.pdf>, accessed 31 January 2013).
- 57 Davis J, Ma P, Sutaria S. The microeconomics of personalized personalized medicine. *McKinsey Quarterly*, 2012 (http://blog.ykalantzakis.eu/wp-content/uploads/2010/03/2010Feb_The-microeconomics-of-personalized-medicine-miof10.pdf, accessed on 25 February 2013).
- 58 Fugel H-J, Nuijten M, Postma M. Stratified medicine and reimbursement issues. *Frontiers in Pharmacology*, 2012; 3: 181.
- 59 FDA. FDA news release: FDA approves Xalkori with companion diagnostic for a type of late-stage lung cancer. Silver Spring, NH: Food and Drugs Administration, 2011.
- 60 Lehr M. The summer of companion diagnostics. 2011 (<http://www.blogoup.com/blog/2011/9/5/the-summer-of-companion-diagnostics.html>, accessed 14 February 2013).
- 61 Trosman J, Van Bebber B, Phillips K. Coverage policy development for personalized medicine: private payer perspectives on developing policy for the 21-gene assay. *Journal of Oncology Practice*, 2010; 6(5):238–242.
- 62 Theuretzbacher U. Personal communication, June 2013.

12. Policy response

- 1 Adapted from Morel CM, Mossialos EM. Stoking the antibiotic pipeline. *British Medical Journal*, 2011; 340:1115–1118.
- 2 Dorsey ER et al. Funding of US biomedical research, 2003–2008. *JAMA: The Journal of the American Medical Association*, 2010; 303(2):137–143.
- 3 NIAID. About NIAID. Bethesda, MD: National Institute of Allergy and Infectious Diseases (<http://www.niaid.nih.gov/about/Pages/default.aspx>, accessed 14 January 2013).
- 4 NIAID. New investigator guide to NIH funding –NIAID research funding. Bethesda, MD: National Institute of Allergy and Infectious Diseases (<http://www.niaid.nih.gov/researchfunding/grant/Pages/newpiguide.aspx#new11>, accessed 14 January 2013).
- 5 NIAID. Should you apply for an R21? Bethesda, MD: National Institute of Allergy and Infectious Diseases (<http://www.niaid.nih.gov/researchfunding/grant/strategy/Pages/r21decide.aspx>, accessed 15 January 2013).
- 6 Cepheid. Cepheid cares about tuberculosis (<http://www.cephheidcares.com/tb/cephheid-vision.html>, accessed 11 January 2013).
- 7 NIAID. Should you apply for an R21? Bethesda, MD: National Institute of Allergy and Infectious Diseases (<http://www.niaid.nih.gov/researchfunding/grant/strategy/Pages/r21decide.aspx>, accessed 15 January 2013).
- 8 NIAID. Small business awards – NIAID research funding. Bethesda, MD: National Institute of Allergy and Infectious Diseases (<http://www.niaid.nih.gov/researchfunding/sb/pages/default.aspx>, accessed 11 January 2013).
- 9 NIAID. Small business high-priority areas of interest; small business awards, SBIR and STTR; NIAID research funding. Bethesda, MD: National Institute of Allergy and Infectious Diseases (<http://www.niaid.nih.gov/researchfunding/sb/pages/sbirareas.aspx>, accessed 14 January 2013).
- 10 NIH. RFA-AI-06-036 Partnerships to improve diagnosis and treatment of selected drug-resistant healthcare-associated infections (U01). Bethesda, MD: National Institutes of Health (<http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-06-036.html>, accessed 14 January 2013).
- 11 NIH. RFA-AI-08-003 Partnerships for point of care (POC) diagnostic technologies for nontraditional health care settings (U01). Bethesda, MD: National Institutes of Health (<http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-08-003.html>, accessed on 14 January 2013).
- 12 NIH. RFA-AI-09-029 Partnerships for development of therapeutics and diagnostics for drug-resistant bacteria and eukaryotic parasites (SBIR [R43-R44]). Bethesda, MD: National Institutes of Health (<http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-09-029.html>, accessed on 14 January 2013).

- 13 NIH. RFA-AI-10-003 Partnerships for biodefense (R01). Bethesda, MD: National Institutes of Health (<http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-10-003.html>, accessed 14 January 2013).
- 14 NIAID. Advisory Council; NIAID research funding. Bethesda, MD: National Institute of Allergy and Infectious Diseases (<http://www.niaid.nih.gov/researchfunding/council/Pages/default.aspx>, accessed 15 January 2013).
- 15 US Department of Health and Human Services. Biomedical Advanced Research and Development Authority (BARDA) (<https://www.medicalcountermeasures.gov/barda.aspx>, accessed 6 February 2013).
- 16 US Department of Health and Human Services. Influenza antivirals, diagnostics and devices. (<https://www.medicalcountermeasures.gov/barda.aspx>, accessed 6 February 2013).
- 17 *National Action Plan for Combating Antibiotic Resistant Bacteria*. Washington, DC: The White House, 2015.
- 18 DARPA. About. Arlington, VA: Defense Advanced Research Projects Agency (<http://www.darpa.mil/About.aspx>, accessed on 1 February 2013).
- 19 DARPA. Autonomous Diagnostics to Enable Prevention and Therapeutics (ADEPT). Arlington, VA: Defense Advanced Research Projects Agency. ([http://www.darpa.mil/Our_Work/DSO/Programs/Autonomous_Diagnostics_to_Enable_Prevention_and_Therapeutics_\(ADEPT\).aspx](http://www.darpa.mil/Our_Work/DSO/Programs/Autonomous_Diagnostics_to_Enable_Prevention_and_Therapeutics_(ADEPT).aspx), accessed 1 February 2013).
- 20 Federal Business Opportunities. Enabling remote clinical trials and point-of-need diagnostics: preserved and stabilized self-collected biospecimens request for information. RFI DARPA-SN-12-10 (<https://www.fbo.gov/utills/view?id=b56ed75fb91ec10c62d681ba8b5949af>, accessed 1 February 2013)
- 21 Federal Business Opportunities. SPECIAL NOTICE DARPA-SN-11-15: Working with DARPA to develop novel platform molecular diagnostics, face-to-face and information sessions. Arlington, VA: Defense Advanced Research Projects Agency, 2011 (<https://www.fbo.gov/utills/view?id=972800cc02baea784f5089764dfe21eb>, accessed 1 February 2013).
- 22 DARPA. Doing business with DARPA. Arlington, VA: Defense Advanced Research Projects Agency, 2011 (www.darpa.mil/WorkArea/DownloadAsset.aspx?id=2147484492, accessed 5 February 2013).
- 23 Forum on Drug Discovery, Development, and Translation, Board on Health Sciences Policy, Institute of Medicine. *Application of flexible research authority. Accelerating the development of new drugs and diagnostics: maximizing the impact of the Cures Acceleration Network: Workshop Summary*. Washington, DC: National Academies Press, 2012.
- 24 Ibid.
- 25 Ibid.
- 26 Ibid.
- 27 Gates Foundation. Information for grant seekers. Seattle, WA: Gates Foundation (<http://www.gatesfoundation.org/grantseeker/Pages/information-for-grant-seekers.aspx>, Accessed 15 January 2013).
- 28 Gates Foundation. What we do not fund. Seattle, WA: Gates Foundation (<http://www.gatesfoundation.org/grantseeker/Pages/what-we-do-not-fund.aspx>, accessed 15 January 2013).
- 29 Gates Foundation. Search past grants. Seattle, WA: Gates Foundation (<http://www.gatesfoundation.org/grants/Pages/search.aspx>, accessed 15 January 2013).
- 30 EC. Research and innovation, FP7, health. Brussels: European Commission (http://ec.europa.eu/research/fp7/index_en.cfm?pg=health, accessed 18 February 2013).
- 31 EC. Research and innovation, FP7, budgets. Brussels: European Commission (http://ec.europa.eu/research/fp7/index_en.cfm?pg=budget, accessed 18 February 2013).
- 32 Ibid.
- 33 EC. FP7 in brief: how to get involved in the EU 7th Framework Programme for Research. Luxembourg: Office for Official Publications of the European Communities, 2007.
- 34 TheraEDGE. Factsheet: An integrated platform enabling Theranostic applications at the point of primary care, pushing point of care Theranostics to the EDGE. Brussels: European Commission (http://cordis.europa.eu/project/rcn/85784_en.html, accessed 22 January 2013).
- 35 EC. Tempotest QC (http://cordis.europa.eu/projects/rcn/93642_en.html, accessed 18 February 2013).
- 36 EC. Horizon 2020, EU Framework Programme for Research and Innovation. Brussels: European Commission (http://ec.europa.eu/research/horizon2020/index_en.cfm?pg=h2020, accessed 18 February 2013).
- 37 Grand Challenges Canada/Grand Défis Canada. What is Grand Challenges Canada? Toronto: Grand Challenges Canada/Grand Défis Canada (<http://www.grandchallenges.ca/who-we-are/>, accessed 21 January 2013).

- 38 Grand Challenges Canada/Grand Défis Canada. The Grand Challenges approach. Toronto: Grand Challenges Canada/Grand Défis Canada, 2011.
- 39 Grand Challenges Canada/Grand Défis Canada. World researchers embark on historic grand challenge: invent and deliver low-cost devices to rapidly diagnose diseases in developing countries. Toronto: Grand Challenges Canada/Grand Défis Canada, 16 December 2001 (http://www.grandchallenges.ca/wordpress/wp-content/uploads/pointofcare_newsrelease_2011Dec16_EN.pdf, accessed 21 January 2013).
- 40 Grand Challenges Canada. Point-of-Care Diagnostics program information. Toronto: Grand Challenges Canada/Grand Défis Canada (<http://www.grandchallenges.ca/grand-challenges/gc2-point-of-care-diagnostics/point-of-care-diagnostics-program-information/>, accessed 21 January 2013).
- 41 Grand Challenges Canada/Grand Défis Canada. Integrated innovation, September 2010. Toronto: Grand Challenges Canada/Grand Défis Canada.
- 42 Global Health Diagnostics. Affordable access project (<http://globalhealthdiagnostics.tghn.org/affordableaccess/>, accessed 26 January 2013).
- 43 Grand Challenges Canada/Grand Défis Canada. Global access policy, 4 April 2012. Toronto: Grand Challenges Canada/Grand Défis Canada (http://www.grandchallenges.ca/wordpress/wp-content/uploads/globalaccesspolicy_2012Apr04_EN.pdf, accessed on 26 January 2013).
- 44 TSB. About us. Swindon: Technology Strategy Board (<http://www.innovateuk.org/aboutus.ashx>, accessed 16 January 2013).
- 45 Barker I et al. *Foresight. Infectious diseases: preparing for the future. A vision of future detection, identification and monitoring systems*. London: Office of Science and Innovation, 2006.
- 46 TSB. Fighting infection through detection. Competition for funding: feasibility studies, fast-track and larger R&D projects. Swindon: Technology Strategy Board, 2010.
- 47 TSB. Technology Strategy Board competitions. Competition guidance for applicants, funding rules, applicant type, size and activity. Swindon: Technology Strategy Board (<http://www.innovateuk.org/competitions/guidance-for-applicants/funding-rules/applicant-type-size.ashx>, accessed 18 February 2013).
- 48 TSB. Fighting infection through detection. Competition for funding: feasibility studies, fast-track and larger R&D projects. Swindon: Technology Strategy Board, 2010.
- 49 TSB. Press release: New research will target threat caused by sepsis. Swindon: Technology Strategy Board, 2012.
- 50 TSB. Press release: New development projects will improve the assessment of point-of-care tests for infectious agents. Swindon: Technology Strategy Board, 2012.
- 51 TSB. Technology Strategy Board competitions Rapid diagnostics for human and bovine tuberculosis. Swindon: Technology Strategy Board (<http://www.innovateuk.org/content/competition/rapid-diagnostics-for-human-and-bovine-tuberculosisi.ashx>, accessed 16 January 2013).
- 52 NIHR. Invention for innovation (i4i): guidance for applicants version 1.5.1. London: National Institute for Health Research, 2012.
- 53 NIHR. Invention for innovation (i4i): funded research. London: National Institute for Health Research (<http://www.ccf.nihr.ac.uk/i4i/about/Pages/FundedProjects.aspx>, accessed 22 January 2013).
- 54 Wellcome Trust. What is translational research? London: Wellcome Trust (<http://www.wellcome.ac.uk/Funding/Technology-transfer/WTD027704.htm>, accessed 22 January 2013).
- 55 Wellcome Trust. Translation fund – frequently asked questions (<http://www.wellcome.ac.uk/Funding/Technology-transfer/Application-information/WTVM056272.htm>, accessed 22 January 2013).
- 56 University of the West of England. Research showcase | The diarrhea diagnostic device: from bench to bedside. Bristol (<http://www1.uwe.ac.uk/hls/as/research/researchshowcase.aspx>, accessed 12 February 2013).
- 57 Wellcome Trust. Health Innovation Challenge Fund. London: Wellcome Fund at (<http://www.isis-innovation.com/researchers/wellcometrust.html>, accessed 12 February 2013).
- 58 Finance Wales. About us. Cardiff: Finance Wales (http://www.financewales.co.uk/about_us.aspx, accessed 11 February 2013).
- 59 Finance Wales. Technology ventures. Cardiff: Finance Wales (http://www.financewales.co.uk/what_we_do/how_we_invest/early_stage.aspx, accessed 11 February 2013).
- 60 Wei M. Should prizes replace patents? A critique of the Medical Innovation Prize Act of 2005. *Boston University Journal of Science and Technology*, Working paper, 2007.
- 61 WHO. *Research and development to meet health needs in developing countries; strengthening global financing and coordination*. Report of the Consultative Expert Working Group on Research and Development, Financing and Coordination. Geneva: World Health Organization, 2012.

- 62 Médecins Sans Frontières. Looking for alternative models. Geneva: Médecins Sans Frontières (<http://www.msfaccess.org/content/looking-alternative-models>, accessed 27 February 2013)
- 63 Love J, Hubbard T. The big idea: prizes to stimulate R&D for new medicines. *Chicago-Kent Law Review*, 2007; 82(3):1519–1554.
- 64 Bio Ventures for Global Health (BVGH). Global Health Innovation Quotient Prize (IQ Prize) (<http://www.bvgh.org/What-We-Do/Incentives/IQ-Prize.aspx>, accessed 11 February 2013).
- 65 Bio Ventures for Global Health (BVGH). The Global Health Innovation Quotient Prize: a milestone-based prize to stimulate R&D for point-of-care fever diagnostics. Proposal submitted by BIO Ventures for Global Health for consideration by the WHO/CEW, 16 June 2011.
- 66 Médecins Sans Frontières. Submission to the Expert Working Group on Research and Development Financing. Geneva: Médecins Sans Frontières – Campaign for Access to Essential Medicines April 2009.
- 67 Longitude Prize 2014 (<http://www.nesta.org.uk/project/longitude-prize-2014>, accessed 7 April 2015).
- 68 Longitude Prize (<https://longitudeprize.org/>, accessed 7 April 2015).
- 69 Fact sheet: Obama administration takes actions to combat antibiotic-resistant bacteria. Washington, DC: The White House, 18 September 2014 (<https://www.whitehouse.gov/the-press-office/2014/09/18/fact-sheet-obama-administration-takes-actions-combat-antibiotic-resistan>, accessed 7 April 2015).
- 70 Barbados, Bolivia, Bangladesh, Surinam. Proposal by Bangladesh, Barbados Bolivia, and Suriname – Prize fund for development of low-cost rapid diagnostic test for tuberculosis, 15 April 2009 (http://www.who.int/phi/Bangladesh_Barbados_Bolivia_Surinam_TBPrize.pdf, accessed 27 February 2013).
- 71 X-Prize Foundation. TB Diagnostics X PRIZE (<http://www.xprize.org/prize/tb-diagnostics-x-prize>, accessed 19 February 2013).
- 72 InnoCentive. Case study: Prize4Life: a deadly disease with no cure (www.innocentive.com/files/node/casestudy/case-study-prize4life.pdf, accessed 27 February 2013).
- 73 Venkataraman B. \$1 Million to inventor of tracker for A.L.S. *The New York Times*, 3 February 2011 (http://www.nytimes.com/2011/02/08/health/08als.html?_r=1&, accessed 27 February 2013).
- 74 Birkinshaw J, Crainer S. Combine harvesting. *London Business School Labnotes*, 2009; 12:15–18.
- 75 Ibid.
- 76 Kalil, T. Prizes for technological innovation. Discussion paper 2006–08. Washington, DC: The Hamilton Project, Brookings Institution, 2006.
- 77 Knowledge Ecology International. Selected innovation prizes and reward program. *KEI Research Note*, 2008: 1 (http://www.keionline.org/misc-docs/research_notes/kei_rn_2008_1.pdf, accessed 1 March 2013).
- 78 Kalil, T. Prizes for technological innovation. Discussion paper 2006–08. Washington, DC: The Hamilton Project, Brookings Institution, 2006.
- 79 Médecins Sans Frontières. Submission to the expert working group on research and development financing. Geneva: Médecins Sans Frontières – Campaign for Access to Essential Medicines, April 2009.
- 80 Betsou F, Parida SK, Guillerm M. Infectious diseases biobanking as a catalyst towards personalized medicine: Mycobacterium tuberculosis paradigm. *Tuberculosis* (Edinburgh, Scotland), 2011; 91(6):524–532.
- 81 Riegman PH et al. Biobanking for better healthcare. *Molecular Oncology*, 2008; 2(3):213–222.
- 82 Williams R, Mant C, Cason J. The Infectious Diseases BioBank at King's College London: archiving samples from patients infected with HIV to facilitate translational research. *Retrovirology*, 2009; 6:98.
- 83 Ibid.
- 84 Park A. 10 ideas changing the world right now. *Time Magazine*, 12 March 2009 (http://www.time.com/time/specials/packages/article/0,28804,1884779_1884782_1884766,00.html, accessed 20 January 2013).
- 85 Batz HG, Cooke GS, Reid SD. Towards lab-free tuberculosis diagnosis. New York/Geneva: Médecins Sans Frontières, TB/HIV Working Group, Treatment Action Group, Imperial College London, 2011.
- 86 IDSA. Promoting Anti-infective development and antimicrobial stewardship through the U.S. Food and Drug Administration Prescription Drug User Fee Act (PDUFA) Reauthorization. Statement of the Infectious Diseases Society of America (IDSA) before the House Committee on Energy and Commerce's Subcommittee on Health, 8 March 2012.
- 87 Kozlakidis Z et al. How representative are research tissue biobanks of the local populations? experience of the Infectious Diseases BioBank at King's College, London, UK. *Biopreservation and Biobanking*, 2011; 9(3):287–288.
- 88 Batz HG, Cooke GS, Reid SD. *Towards lab-free tuberculosis diagnosis*. New York/Geneva: Médecins Sans Frontières, TB/HIV Working Group, Treatment Action Group, Imperial College London, 2011.

- 89 Franco JR et al. The Human African trypanosomiasis specimen biobank: a necessary tool to support research of new diagnostics. *PLoS Neglected Tropical Diseases*, 2012 Jun; 6(6):e1571.
- 90 Mather S. Human Tissue Authority: regulating tissues and cells in the UK. Biobanks Conference, 7–8 July 2008, Rome, Italy (http://www.hta.gov.uk/contentdisplay.cfm?widCall1=customWidgets.content_view_1&cit_id=436, accessed 21 January).
- 91 Ibid.
- 92 NIAID. Clinical laboratory diagnostics for invasive aspergillosis. Bethesda, MD: NIAID (<http://www.niaid.nih.gov/labsandresources/resources/dmid/clinasper/Pages/default.aspx>, accessed 15 January 2013).
- 93 Riegman PH et al. Biobanking for better healthcare. *Molecular Oncology*, 2008; 2(3):213–222.
- 94 Ibid.
- 95 Franco JR et al. The Human African trypanosomiasis specimen biobank: a necessary tool to support research of new diagnostics. *PLoS Neglected Tropical Diseases*, 2012 Jun; 6(6):e1571.
- 96 BBMRI. BBMRI during the transition phase. Graz: European Biobanking and Biomolecular Resources Infrastructure (<http://www.bbMRI.eu>, accessed 21 January 2013).
- 97 Yuille M et al. Biobanking for Europe. *Briefings in Bioinformatics*, 2008; 9(1):14–24.
- 98 Kryl D et al. *Healthcare technology co-operatives: filling a niche in the English R&D landscape*. Report prepared by Rand Europe at the request of the Department of Health (England), 2011.
- 99 National Institute of Biomedical Imaging and Bioengineering. Point-of-Care Technologies Research Network. Bethesda, MD: National Institute of Biomedical Imaging and Bioengineering (<http://www.nibib.nih.gov/Research/POCTRN>, accessed 10 January 2013)
- 100 IMI. Mission IMI – Innovative Medicines Initiative (<http://www.imi.europa.eu/content/mission>, accessed 19 February 2013).
- 101 Goosens H. RAPP-ID- Development of RApid Point-of-Care. Presented at the Innovative Medicines Initiative press briefing to announce a new total of 23 unique projects to boost drug innovation. Test Platforms for Infectious Diseases, Brussels, 2011.
- 102 PF. Personal communication, April 2013
- 103 Theuretzbacher U. Personal communication, June 2013.

Appendix A

- 1 Personal communication from the study's corresponding author.
- 2 Ibid.
- 3 Ibid.
- 4 Ibid.

Appendix B

- 1 Ibid.

The inappropriate use of antibiotics is a primary cause of the ongoing increase in drug resistance amongst pathogenic bacteria. The resulting decrease in the efficacy of antibiotics threatens the ability to combat infectious diseases. Rapid, point-of-care tests to identify pathogens and better target the appropriate treatment could greatly improve the use of antibiotics, yet few such tests are available or being developed, despite the rapid pace of medical innovation. Clearly, something is inhibiting the much-needed development of new and more convenient diagnostic tools.

This study delineates priorities for developing diagnostics to improve antibiotic prescription and use, in order to manage and curb the expansion of drug resistance. It calls for new approaches, particularly in the provision of diagnostic devices, and, in doing so, outlines some of the inadequacies in health, science and policy initiatives that have led to the dearth of such devices. The authors make the case that innovation is clearly and urgently needed, not only in the technology of diagnosis but also in public policy and medical practice to support the availability and use of better diagnostic tools.

This book explores the complexities of the diagnostics market from the perspective of both supply and demand, unearthing interesting bottlenecks: some obvious, some more subtle. It calls for a broad, multifaceted policy response, and an overhaul of current practice, so that the growth of bacterial resistance can be stemmed.

The editors

Chantal Morel, Research Officer, LSE Health (London School of Economics and Political Science), Faculty of Medicine, University of Geneva

Lindsay McClure, Research Associate, LSE Health

Suzanne Edwards, Research Associate, LSE Health

Victoria Goodfellow, Research Associate, LSE Health

Dale Sandberg, Research Associate, LSE Health

Joseph Thomas, Research Assistant, LSE Health

Elias Mossialos, Professor of Health Policy, LSE Health

Observatory Studies Series No. 44