World Health Organization
REGIONAL OFFICE FOR Europe

PERSONALIZED MEDICINE AND GENOMICS

Opportunities for the Prevention and Control of Noncommunicable Diseases

"MEETING OF THE MINDS"

Saint Petersburg
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14 May 2018

Abstract

The World Health Organization, with support from the Russian Federation, organized a seminar to explore the role of personalized medicine (PM) in the prevention and control of noncommunicable diseases (NCDs) and its relevance to the Russian Federation. The seminar took place on 14 May 2018 at the Almazov National Medical Research Centre in Saint Petersburg, Russian Federation.

PM is "a medical model using characterisation of individuals' phenotypes and genotypes for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention". This approach can use genetic or other biological information about an individual to (for example) identify people at higher inherited risk of a disease or those who are most likely to respond to treatment and/or experience side effects.

There has been tremendous progress in this field in recent decades and there is exciting potential for PM approaches to be applied to prevention and control of NCDs across Europe in the future. However, a number of challenges to the integration of this model into health systems remain. Several strategies are proposed to help governments address these challenges and to ensure appropriate use of PM for NCD response in inclusive, sustainable health systems.

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Contents

Abbreviations

CVD	Cardiovascular disease
ICPerMed	International Consortium of Personalised Medicine
NCDs	Noncommunicable diseases
NMRC PM	National Medical Research Centre for Preventive Medicine
PM	Personalized medicine
WHO	World Health Organization

Executive summary

The World Health Organization (WHO) organized a seminar to explore the role of personalized medicine (PM) in the prevention and control of noncommunicable diseases (NCDs) and its relevance to the Russian Federation. The seminar, hosted by the Almazov National Medical Research Centre and with support from the Ministry of Health of the Russian Federation, took place on 14 May 2018 in Saint Petersburg. The 30 participants in this "meeting of the minds" included experts from the Russian Federation and from elsewhere in the WHO European Region and North America and WHO advisers.

PM is "a medical model using characterisation of individuals' phenotypes and genotypes for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention".[1] This approach – sometimes known as precision medicine or stratified medicine – can use genetic or other biological information about an individual to (for example) identify people at higher inherited risk of a disease or those who are most likely to respond to treatment and/or experience side effects.

There has been a great deal of encouraging progress in this field in recent decades, thanks to scientific advances accompanied by developments in information technology and investment from both public and private sectors. Some PM approaches are now well established in clinical practice; the meeting was given examples from Austria, Croatia, Finland, Italy and the Russian Federation. Gaps in the evidence to clarify whether PM can confer additional benefits over those achieved through existing approaches to NCD prevention and control were highlighted, and a large-scale trial of PM for NCDs was described. Different approaches to driving forward the development of PM were outlined: from an approach led by public research institutions in the Russian Federation to the public–private partnership models adopted in Austria and Finland.

It is clear that there is exciting potential for PM approaches to be applied in the future to prevention and control of NCDs across Europe. However, a number of challenges to the integration of this model into health systems remain. The key challenges highlighted by the meeting can be summarized as follows:

- difficulties in translating science into actual clinical practice, and poor understanding of these new techniques and their appropriate use among medical professionals, policy-makers, patient groups and the wider public;
- the need for a clear regulatory and governance framework to address the many complex issues involved, including privacy and protection of individuals' data, and patent law and its possible impact on access;

[1] Definition according to the "Council conclusions on personalised medicine for patients", Council of the European Union, 2015 (2015/C 421/03).

- the cost of personalized testing and treatment approaches, which can pose challenges for equitable access and sustainability of health systems.

A variety of possible responses available to help governments overcome these barriers were proposed. These included:

- preparing in advance for a smooth transition to integrate the new technologies;
- establishing a clear regulatory and governance system to ensure access is safe, affordable and equitable;
- conducting health technology assessments (including economic assessments) to evaluate whether and how specific techniques/processes should be integrated into health systems;
- producing national guidelines and protocols for appropriate use of these technologies;
- providing training for health professionals and policy-makers;
- ensuring a participatory approach to the scale-up of PM and promoting greater public awareness and better understanding of this model and its appropriate use and role in inclusive, sustainable health systems.

Background

Noncommunicable diseases (NCDs) present one of the biggest challenges of our time, not just in terms of health burden but also socially and economically. The causes and solutions are largely known, yet implementation of effective prevention and management can be a challenge and the treatment costs of chronic conditions are high. It has been suggested that personalized medicine (PM) could be part of the solution.

PM is "a medical model using characterisation of individuals' phenotypes and genotypes for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention".[2] This approach – sometimes known as precision medicine, or individualized or stratified medicine – can use genetic or other biological information about an individual to (for example) identify people at higher inherited risk of a disease or those who are most likely to respond to treatment and/or experience side effects. It is an approach to health care that puts the citizen at the centre in that it allows tailor-made strategies for diagnosis, treatment and prevention to be designed. As such, it should fit well with the World Health Organization (WHO)'s advocacy for more person-centred health care, which lies at the heart of its European health policy framework, Health 2020.

WHO organized a seminar to explore the role of PM in the prevention and control of NCDs and its relevance to the Russian Federation. The seminar, hosted by the Almazov National Medical Research Centre and with support from the Ministry of Health of the Russian Federation, took place on 14 May 2018 in Saint Petersburg. The 30 participants in this "meeting of the minds" included experts from the Russian Federation and from elsewhere in the European Region and North America and WHO advisers.

Opening remarks

On behalf of the WHO European Office for the Prevention and Control of Noncommunicable Diseases, Dr Luigi Migliorini welcomed all participants. He thanked the Almazov National Medical Research Centre for hosting the meeting and the Ministry of Health of the Russian Federation for its support.

Dr Melita Vujnovich added her welcome on behalf of the WHO Country Office in the Russian Federation and formally opened the meeting. The meeting provides an excellent example of collaboration between the WHO Office for the Prevention and Control of NCDs, the WHO Country Office and the Russian Federation. The Russian Federation is working with WHO and sharing its experience and expertise to capitalize on new developments and innovation to help achieve the goals of universal health coverage and reducing the burden of NCDs.

Dr Eduard Salakhov, Deputy Director, Department of International Cooperation and Public Affairs, Ministry of Health of the Russian Federation, set the scene by reminding participants of the complex challenge facing Member States in their efforts to tackle NCDs. This collaboration between WHO and the Russian Federation in relation of diabetes, cancer and other NCDs seeks to find innovative approaches, while continuing to respect some basic principles, such as the need for intersectoral solutions and the importance of applying a combination of population-level and individual-level approaches.

Dr Jill Farrington, Division of Noncommunicable Diseases and Promoting Health through the Life-course, WHO Regional Office for Europe, explained the background to the meeting and outlined the programme, which was designed to stimulate healthy discussion and facilitate learning from experience in the Russian Federation and elsewhere. The intention is that the outcome of this discussion will, in turn, feed into the process of finalizing a situation analysis paper on this topic; such a paper will be influential in future considerations of PM in the Russian Federation.

It is important that discussions of this topic consider what can realistically be expected of PM and identify some of the challenges for NCD prevention and control. Such analyses should take place through the lens of

[2] Definition according to the "Council conclusions on personalised medicine for patients", Council of the European Union, 2015 (2015/C 421/03).

Health 2020, the European health policy framework and, in particular, its two strategic objectives of improving health for all and reducing health inequalities and improving leadership and participatory governance for health. This work will build on the policy approaches for strengthening health systems' response to NCDs discussed at the high-level meeting on that issue in Sitges, Spain, in April 2018. The meeting presents an opportunity to examine whether PM can contribute to the possibility of "leapfrogging", whereby countries make rapid advances in tackling NCDs by learning from other countries' earlier experiences.

SESSION I

Overview of PM in the context of NCD prevention and management

The first session set the context with an overview of the PM approach, both internationally and as it is used in the Russian Federation.

PM: a new paradigm and challenge in clinical practice

Professor Dragan Primorac, St Catherine Specialty Hospital, Croatia, and Penn State University, USA, gave an overview of PM approaches in use in current clinical practice; he highlighted some of the most exciting prospects for the future, as well as some of the challenges.

The Horizon 2020 Advisory Group has defined PM as "a medical model using characterisation of individuals' phenotypes and genotypes (e.g. molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention". The goals of personalized or individualized medicine include prevention of disease, application of therapy appropriate to the patient, and screening family members for risk.

One important area for application of PM is potential reduction of adverse drug reactions and unnecessary drug use by moving away from trial and error and a one-dose-fits-all approach towards identification of people for whom a particular drug is beneficial and non-toxic. In around 40% of patients with, for example, asthma, cardiac arrhythmias and diabetes, the usual drug treatments are ineffective in practice, and this proportion rises to 75% in recipients of some cancer drugs.

PM can be seen as a two-level risk reduction model, which uses molecular diagnostics to test genetic predisposition to disease and pharmacogenetic testing to test predisposition to adverse drug reactions. In relation to blood clotting disorders, for example, the first level would include testing for inherited blood clotting disorders (such as factor V Leiden and prothrombin gene mutation); the second level would involve gene testing to minimize the risks associated with anticoagulant therapy, where there can be marked differences in patient dose-response. With PM, the aim is to find the right drug for the right person at the right dose.

Another important area where a PM approach is in current clinical use relates to the use of biomarkers. Glycans, for example, have anti-inflammatory properties and have been implicated in the pathophysiology of many major diseases. It is claimed that they are an important marker of true biological age, and this may have implications for conditions such as rheumatoid arthritis.

Other areas of activity include exploration of stem cell therapy for use in cartilage repair for joints affected by osteoarthritis; treatment of osteogenesis imperfecta; and regeneration of human tissue.

The future scope of PM should be seen as much broader than diagnostics (genomic sequencing, new biomarkers, epigenomics, etc.); it should also encompass pharmacogenomics (cellular therapy, regenerative medicine, gene therapy and tailored treatment) and rehabilitation. The key challenges facing PM, as identified by the International Consortium of Personalised Medicine (ICPerMed), include:

- developing awareness and empowerment;
- integrating big data and information and communications technology (ICT) solutions;
- translating basic science to clinical research and beyond;

- bringing innovation to market; and
- shaping sustainable health care.

Discussion

This overview clearly shows the potential breadth of a PM approach and the many ways in which this type of medicine is already being used clinically today.

The discussion confirmed that one of the key challenges is how best to translate science into clinical practice and to enhance understanding of practitioners on the ground and transfer knowledge in a sensitive manner at various levels (government ministers, policy-makers, physicians). There are signs that doctors are already using some tests in situations where there is no clear evidence that they are appropriate.

There was discussion of how financial reimbursements are organized for use in PM. In Croatia, although the cost of some of the most common tests can be reimbursed, most patients are currently paying out-of-pocket expenses for the treatments described. Discussions relating to reimbursement mechanisms are part of the process of integrating a PM approach into clinical practice.

There is a need for advocacy, therefore, both *for* integration of effective and cost–effective applications of PM into health systems and *against* integration of ineffective, costly applications.

A situation analysis of PM in the Russian Federation

Dr Evgeny Shlyakhto, Director-General, Almazov National Medical Research Centre, presented a summary of the current use of PM in the Russian Federation.

PM can be applied in a variety of areas to improve the Russian health system:

- rapid detection of therapy targets
- focus on prevention and early interventions
- dose adjustment and adverse risk reduction
- faster access of patients to information and better treatment.

PM is a priority for the Russian Federation and has been included in a number of strategic documents, including the Scientific and Technological Development Strategy and the Strategy for Medical Science Development in the Russian Federation up to 2025. In April 2018, President Vladimir Putin instructed the Russian government to develop a programme of advanced genome studies and genetic technologies as part of the implementation of the Scientific and Technological Development Strategy.

The main areas of PM in the Russian Federation include:

- personalized approaches to diagnosis and treatment in everyday clinical practice (pharmacogenetics, genetic risks, prenatal diagnosis, genetic prevention);
- genomic research projects (new pathologic mutations, new molecular mechanisms of diseases and therapy targets, research in the area of small regulating molecules and microvesicles, mitochondrial DNA);
- innovations in PM (diagnostic panels, algorithms and decision-making support systems for oncogenomics, software for pharmacogenetics (drug dose adjustment), testing systems for prenatal diagnosis, etc.).

The Almazov Centre is working with the Ministry of Health on steps to introduce PM into clinical practice. This is achieved, first, by development of basic research and clinical trials, then by clinical testing, and then by inclusion in clinical guidelines/health care protocols/standards and incorporation into the medical insurance system. Changes in drug information for patients are also required. The process of introducing a PM approach involves research organizations, professional associations, medical organizations, pharmaceutical and biotechnology companies, and private medical organizations. The medical areas where

the PM approach is most active include oncology/oncohaematology, cardiology, endocrinology, rheumatology, paediatrics, antibiotic therapy and psychiatry.

In relation to cancer, the main research areas include finding new genetic cancer biomarkers; new techniques for tumour cell genome sequencing and detection of genetic variations; development of new diagnostic tests (including liquid biopsy); detection of predictors for therapy response or tumour progression; and development of new targeted drugs. More specifically, the following tests to identify cancer therapies are recommended:

- breast and ovarian cancer (BRCA1, BRCA2)
- colorectal cancer (KRAS, NRAS, BRAF)
- lung cancer (EGFR, ALK, ROS, BRAF)
- melanoma (BRAF, KIT).

In many regions, genomic testing is included in the medical care package reimbursed by the Russian state. The strategy to introduce oncogenomics within the scope of government-funded health care includes organizing a network of reference laboratories for molecular typing of tumours and devising algorithms for drug administration that take individual response into account.

For cardiology, there have been some fundamental breakthroughs, including in identification of new diagnostic and prognostic biomarkers, which are now being translated into a PM approach. This approach offers the prospect of improving prevention programmes in this complex area where there continue to be unknown risk factors and unknown protective mechanisms. It can also be used to improve decision-making in patients with life-threatening conditions such as aortic aneurysm. There is a move towards personalized therapy for thrombosis based on definition of molecular-genetic factors (genotypes that show resistance to antithrombotic drugs) and tailoring of drug treatment in response to those genetically determined characteristics.

More generally, pharmacogenetics can be used to identify individual variability in response to medical treatments for asthma, hypertension, depression, diabetes and osteoarthrosis – all areas where usual drug treatments are ineffective in a considerable proportion (20–75%) of cases. Future technologies offer some prospect of gene editing to treat (for example) arrhythmic cardiomyopathies.

It is clear that PM will be meaningless without implementation of information technologies, including establishment of various bio-information databases and registries, as well as techniques to use big data to support decision-making.

The private sector is involved in the expansion of the PM approach in the Russian Federation: pharmaceutical companies are involved in treatment development, laboratories conduct pharmacokinetic tests, and private centres perform genetic testing for disease risk and prenatal diagnostics. It will be important to establish criteria for the involvement of independent providers in this area.

Human resources will be critical to the implementation of PM. To enhance professional education in this field, the majority of medical universities now have short courses on PM, pharmacogenetics and digital medicine. Such courses are short, however, and there is still insufficient education about the new technologies in postgraduate training. New training centres are required and a medical specialty in PM should be developed. The Almazov Centre, for example, is working on a project to facilitate a swift introduction of PM into clinical practice and training of young people.

These various activities and initiatives culminate in a vision, to be realized by 2020, of precision medicine all in one day, from the patient's visit through to targeted medical therapy. Such a development could transform future practice and bring social and economic benefits.

Discussion

This overview of the current situation clearly shows how PM is being applied in the Russian Federation today; it highlights, in particular, the importance of multisectoral engagement in policy implementation in this field.

SESSION II

Person-centred care for NCDs: how can PM contribute?

The second session explored the benefits and challenges of PM specifically for the control of NCDs, globally and in the Russian Federation.

Benefits and challenges of PM for the control of NCDs

Dr Kiu Tay-Teo, Essential Medicines and Health Products, WHO headquarters, gave an overview of the benefits and challenges currently presented by PM in its application to NCD prevention and control.

It is clear that there has been much encouraging progress in recent years in the science behind PM. The science has come a very long way since the discovery of DNA in 1953 and the mapping of the human genome in 2001. Important technological developments include next-generation sequencing, out-of-the-laboratory sequencing, and the emerging capability for analyses using big data and genome engineering. There has been considerable investment in this field, both through the involvement of private companies and through government-funded genome projects (the latter include, for example, projects in the United States, the United Kingdom, the Kingdom of Saudi Arabia, China, the Netherlands, Qatar, Turkey and Japan. In addition, the science is moving on with many academic institutions producing evidence through, for example, studies on genome-wide associations, linkage mapping, diagnostics and drug discovery.

Given the extent of this progress, some fundamental questions are important. In particular, does genetic and genomic profiling allow more accurate prediction of disease risk and better treatment selection compared to traditional assessment of risk factors or clinical practice? With our current state of knowledge, there is some evidence of areas where this is the case, but many unknowns remain.

There is some evidence of benefits when identifying higher disease risk for cancers (BRCA, HER2, EGFR, BRAF, KRAS, ALK), familial hypercholesterolaemia and cystic fibrosis (F508del-CFTR). There is also some evidence in relation to preventive and/or targeted interventions – specifically, in relation to over 100 approved targeted cancer therapies, prophylactic mastectomy or oophorectomy, and warfarin dosing.

There is no evidence of additional benefits, however, in relation to the specific areas of diabetes (TCF7L2), prostate cancer (PCA3), cardiovascular disease (CVD) (9p21) and drug metabolism (SNP on CYP450). There is also evidence to suggest that, even when people know about their genetic risk, it does not necessarily lead to risk-reducing behaviours. In addition, there are many “known unknowns”. Only about 5% of cancer genes, for example, are targeted by drugs. Disease progress is affected by many nongenetic factors. There are also some risks to consider, such as the possibility of treatment resistance and – particularly if the levels of practitioner understanding are low – the possibility of overtreatment and overdiagnosis.

In assessing the benefits and risks, it is necessary to balance population and individual needs. It is clear that there are a number of challenges facing operationalization of a PM approach. These include:

- a lack of legislative clarity, whereby there are many unresolved issues – such as questions of what can be patented in relation to genetics – that have led to many legal challenges;
- the need for a clear regulatory framework to protect individuals, with clear regulatory power and enforcement in areas such as direct-to-consumer testing;
- responsiveness to needs to ensure the availability of targeted therapies and companion diagnostics;
- ensuring fair and inclusive access, so that people have fair and equitable access to these targeted diagnostics/therapies; and
- effective and efficient use of resources and – given the financial costs – a need to work out how these technologies can be implemented in a way that is sustainable for health systems.

Governments can take a number of steps in order to respond to these challenges; they can:

- prepare for technological change by establishing a regulatory and governance system; and seeking alignments between laws and policies, health care and industry development, health care needs and resource capacity;
- take a highly selective and cautious approach, by (among other things) bearing in mind that not all technological developments will be valuable; and planning implementation in order to facilitate a smooth transition for proven techniques, ensuring that access is safe, affordable and equitable and that systems are in place to manage any risks that may arise;
- focusing on value for money and ensuring that this new approach does not grow at the expense of existing better-value-for-money interventions for NCDs.

In summary, progress has been made in PM and there are some well-established practices. There is, however, uncertain evidence on the benefits and harms compared with the traditional model of NCD prevention and control. In particular, there are issues with operationalization of PM into health services and the approach can be expensive when delivered at large scale, especially when dealing with the extent and complexity of the NCD challenge.

Discussion

There was some discussion of the role of biobanks in the future of PM. This is a tremendously important area, where there are some major challenges in relation to the law, ethics, investment, information technology and science. It is particularly important to have clear systems and to properly plan the implementation of biobanks, with pilot testing before larger-scale rollout.

Experience from the Russian Federation

Dr Oksana Drapkina, Director, National Medical Research Centre for Preventive Medicine (NMRC PM), outlined the Russian experience of using PM to implement patient-oriented medical help for NCDs.

The “4P” model of modern medicine in the Russian Federation can be portrayed as a tree bearing four principal leaves: predictive, preventive, personalized, participatory.

Recent clinical guidelines at the European level recommend use of genetic testing for monogenic diseases, but not for assessing risk of developing CVD and other complex conditions. Research shows, however, that genetic examination can be important in predicting outcomes for patients with cardiomyopathy or stratifying risk of ischaemic heart disease.

A laboratory of molecular genetics was established at NMRC PM in 2012; the main directions of its work are:

- Developing and optimizing statistical methods to search for rare genetic variants associated with the development of complex diseases (in partnership with Lomonosov Moscow State University and Skoltech). For example, published papers include the prediction of polygenic hypercholesterolaemia and nucleotide sequence options associated with integrated diseases.
- Identifying molecular genetic risk markers of NCDs in the framework of population research. For example, a pilot study identified rare variants associated with the presence of ischaemic heart disease or atherosclerosis.
- Researching monogenic diseases with a high risk of sudden cardiac death (familial hypercholesterolaemia, cardiomyopathy, channelopathies). For example, the above-mentioned pilot study has identified a high frequency of hereditary family hypercholesterolaemia in the population in two regions.
- Exploring the genetics of noncompaction cardiomyopathy. For example, probable pathogenic mutations for further exploration have been identified in families of patients with a familial form of left ventricular noncompaction myocardium.

In the field of epigenetics, a special microchip has been developed to show the level of gene methylation - (which can influence gene expression) and will now provide a basis for further research, such as exploring the effects of smoking and diet on gene methylation.

An important development is the launch of a biobank in 2016. The NMRC PM biobank is responsible for the collection and storage of biological material for 18 clinical research projects; by April 2018 it was storing more than 170 000 samples of serum/plasma/whole blood. The biobank has joined the International Society for Biological and Environmental Repositories (ISBER) and conducts sample preparation, transportation and storage according to international standards and ISBER best practices.

With the support of the Ministry of Health, the Centre for Genetic Prediction has been established; its role is to produce individual genetic passports by creating biological samples, developing diagnostic panels and developing programmes for the prevention of disease. The diagnostic panels could, for example, identify frequent monogenic hereditary diseases, identify risk of hereditary cancer, assess the efficacy and tolerance of drugs, and genetically identify risks of important NCDs. The four major blocks of the Centre's work are molecular-genetic, analytical, scientific and clinical, and biobank.

PM will be part of the future of medical practice and should not be seen as something completely separate from it. The NMRC PM is now working to try and translate the many new developments outlined above into routine practice.

SESSION III

Managing diabetes, cancer and CVD: the role of PM

The third session explored the specific role of PM in the prevention and control of diabetes, cancer and CVD.

Can PM help improve prevention and care of diabetes, cancer and CVD?

Professor Thomas Pieber, CBmed and Medical University of Graz, Austria, presented an overview of how PM is used in Austria.

There are clearly unmet needs in relation to tackling the NCD challenge. Inadequate early risk detection and unpredictable treatment responses for CVD highlight the need to identify people at risk for personalized interventions. In relation to cancer, there is an urgent need for early diagnosis and for identification of the most effective and least invasive therapy.

CBmed is a national research centre, established in 2014, which is focused on translational biomarker discovery and validation. Its vision is to become the world's most recognized centre for biomarker research in PM by 2030.

CBmed has a consortium structure which brings together the main scientific partners (academic institutions), led by the Medical University of Graz, and other scientific consortium members, including private sector actors. The consortium takes the form of a public–private partnership, through which for-profit industry stakeholders can submit project requests to CBmed, which then provides access to data and biospecimens from biobanks. The European Biobank Consortium, with its headquarters in Graz, links 515 biobanks across Europe, which contain more than 60 million biospecimens. Access to biobank data from an early stage is important because the likelihood of approval of a new cancer drug is almost three times higher with selection of biomarkers from phase 1 of the development. The fusion of biobank data with clinical data can be seen as an important breakthrough.

CBmed is a company in legal terms, but it is owned by the universities involved. Its work is facilitated by its in-house IT infrastructure, which requires substantial investment, in a model that could be replicated elsewhere.

PM and diabetes: experience from the Russian Federation

Dr Alina Babenko, Almazov National Medical Research Centre, gave an overview of how PM has been applied to type 2 diabetes and the Almazov Centre's work in this area.

Prevalence of type 2 diabetes in the Russian Federation is estimated at 5.4%, with a further 19.3% considered to have pre-diabetes. Of those with type 2 diabetes, it is estimated that over 50% of cases remain undiagnosed.

There is a role for personalized (precision) medicine in the prevention of diabetes mellitus, treatment of the condition and prevention of complications. Diabetes is an extremely polygenic condition; more than 150 genes have been identified as having a potential influence over type 2 diabetes. This makes it challenging to consider a personalized approach to the condition. A number of different phenotypes for diabetes have been identified and – despite the strong influence of environmental factors – there are some possibilities for use of PM.

Most promisingly, PM offers potential to improve the outcomes of diabetes treatment. This is important because people react differently to antidiabetic drugs and it may be possible to reduce the frequency and severity of side effects, thereby improving the individual's quality of life and improving treatment adherence. A study of reasons for compliance and noncompliance with therapy in real clinical practice found that nearly two thirds of people with diabetes had experience of stopping their antidiabetic treatment; the main reasons were side effects, ineffectiveness and high cost. Genetic prediction, therefore, could be useful for improving the effectiveness of treatment if it is possible to predict those treatments with low or no effectiveness. An ongoing area of work for the Almazov Centre is to identify a set of predictors for the effectiveness of treatment and to develop an understanding of the factors involved.

PM and cancer: experience from the Russian Federation

Dr Evgeny Imyanitov, N.N. Petrov Institute of Oncology, Saint Petersburg, described the Russian experience of using a personalized approach to oncology.

The use of molecular tests for hereditary cancer syndromes – including 10% of breast cancers, 20% of ovarian cancers and 3% of colorectal cancer incidence – is one area where there has been much progress in the last 20 years. Tests in the Russian population revealed that the BRCA1 5382insC mutation is particularly common in breast cancer and ovarian cancer patients. In addition, a new gene (BLM), which was previously associated with Bloom syndrome, has been validated as being associated with a higher risk of hereditary breast cancer and is now included in cancer diagnostic panels.

The use of molecular markers for choice of therapy is an emerging field. This will help to determine the origin of tumours where the primary site is unknown. It is important because of the low, or even very low, response rates of many cancer drugs, which are still exceptionally effective in a small subset of patients. In addition, adverse effects – often serious – are particularly common for cancer drugs. Better drug-to-patient matching, therefore, could improve efficacy, avoid adverse events and decrease costs.

The predictive mutations that research has identified have an exceptionally high predictive significance in many instances. They provide positive or negative answers, without any ambivalent results. There are now 10 years of clinical experience with such predictive mutations and, in general, there is excellent interlaboratory reproducibility. They offer a low probability of false positive results, but do have a higher probability of producing false negatives. The effects can be organ-specific and may not apply to other types of tumour, meaning that PM requires a tissue diagnosis. It has now been found that archived cytological slides can be used for molecular analysis.

One area of work that is ongoing, and where the picture is complex and confirmatory studies are needed, relates to use of neoadjuvant chemotherapy (NACT) for BRCA1-driven ovarian cancer.

Discussion

This session highlighted the importance of biomarkers for improving treatment outcome and selection of the most appropriate treatment. There is a clear need to reduce the cost of these technologies to allow rollout beyond research facilities. Another key challenge is to increase awareness and improve the understanding of medical professionals. Translation of scientific findings to clinical practice is one of the major challenges, and professional education is therefore essential.

There was clarification that some of the genetic testing (for pregnant women and some areas of oncology) currently in use in the Russian Federation is publicly funded and reimbursed by the Ministry of Health.

There was discussion of the different models for biobanks that are in place. In the Russian Federation, public sector research bodies are driving the process, and this is appropriate to the context. There is, however, a need for start-ups and private sector bodies to take forward some of the knowledge generated in the public sector. In Austria, a public–private partnership, mediated through the interface of a nonprofit body, is in place with shared funding from the public and private sectors. This system is intended to protect data and be economically viable, while allowing academic partners to join with industry partners for scientific progress. In the United Kingdom, a third party provides information for industry or academic users, giving access only to the data required and not to all the underlying data. In Finland, the national health institute controls access to publicly collected data for a fee, and there are discussions about creating an independent entity (a company) for this function. The interface between private and public entities is an important issue to consider.

There are important issues to do with data protection, data ownership, and the right to conduct research on such data. Privacy and data protection are very important issues that need to be handled extremely carefully. Medical confidentiality is paramount, and recent research suggests that – while it is not currently possible to identify individuals from the depersonalized data that are currently held – it may be possible to do so in the near future.

Another important issue is to recognize that appropriate regulatory structures should be developed alongside scientific and technological developments. It is often difficult to find the appropriate place for new PM techniques within the structure of existing regulatory regimes. New regulatory fields are needed for the emerging techniques.

SESSION IV

PM: role in the prevention of NCDs and future steps

The final session drew on experience with PM from Finland, the United States and Italy to feed into discussions on the potential future role of this approach in the Russian Federation.

Motivation, current status and strategies for PM in Finland

Professor Markus Perola, National Institute for Health and Welfare, Finland, described the Finnish experience.

Genomic medicine is already in use within clinical practice in Finland, with tests being ordered for genetic variants relating to lactose intolerance, familial hypercholesterolaemia, venous thrombosis and pharmacogenetics (particularly in relation to cancer).

A large ongoing study in Finland is the FinnGen project, which brings together academic researchers, publicly funded biobanks and private sector companies. In Finland there is good access to digital health data linked to a social security number. The FinnGen project builds on the findings of the Sequencing Initiative Suomi (SISu) project, which has already collected 200 000 samples. FinnGen will create a reference database of 500 000 samples and will combine genome and health data.

Another important study, designed to bring the renowned North Karelia Project into the 21st century, is the P6 – Genomics to Healthcare study. This study aims to bring genomics to health care and to prevent common chronic diseases with the help of modern medicine. Its specific objectives are:

- to produce genomic and metabolomic data for use in precision medicine;
- to adopt precision medicine in day-to-day practice by training and informing health care professionals, decision-makers, other experts in the field and the general population;
- to expand the focus from treatment of diseases to effective prevention;
- to encourage and enable members of the public to take responsibility for their health;
- to prepare the health care system for fulfilling the National Genome Strategy and the Health Sector Growth Strategy planned by the Finnish government.

The P6 study will involve at least 100 000 participants whose genomic and metabolomic results will be returned to them as risk scores for a disease. Polygenic risk scores can be generated by combining information on an individual's risk at the many different sites that each modify the risk for a particular disease. These scores will be used with, and are complementary to, traditional risk factors. The study will clarify how participants understand the information that is returned to them and how it affects their health. Importantly, a randomized controlled trial will then be conducted on the impact for 10 000 participants with the highest genomic/metabolomic risk. Participants will receive face-to-face counselling from a doctor and/or nurse. There may be inclusion of social media prompts to change behaviour.

The P6 project is being led by the National Institute for Health and Welfare and involves an extensive collaboration network including the Ministry of Social Affairs and Health, Business Finland, Sitra, Finnish biobanks, universities, medical specialists in various fields and health technology companies.

A pilot project for the P6 study was launched in February 2018, when 6500 individuals were invited to receive genomic and metabolomic feedback on the risk of three diseases (coronary heart disease, type 2 diabetes, venous thrombosis).

The study is intended to have a broad impact, influencing individual health, the health care professions, health care administration and society as a whole. It is hoped that it will make an important contribution to understanding whether there is enough evidence to integrate this approach into the publicly funded health sector, particularly in the face of rapid private sector development in the field.

Discussion

There was clarification that the P6 project will have data on around 10% of the Finnish population. Results of the pilot project will be available in 2019 and the bigger study will then be launched, with results available within five years.

All participants – not only those involved in the intervention – will receive feedback via the internet. In order to help health professionals to counsel the trial participants on risks, clinical teams will work on a so-called "doctor's note" for each endpoint. Doctors will then be able to personalize their feedback. The importance of very clear guidance for study participants was highlighted; it will be a challenge for the study to ensure that communication is clear and appropriate, particularly given the interaction between genetic and traditional risk factors.

The Finnish law on biobanks enables anyone to ask for access to data, so participants will be able to log in to a comprehensive information system. Participant involvement will be a key element of the study.

PM, innovation and access to medical technology

James Love, Knowledge Ecology International, United States, set out some of the issues regarding access and other challenges associated with innovation in this field.

One area of concern is the extent to which patents have been filed for tools such as the gene-editing tool CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats). There are concerns that patents will be used to establish a monopoly on particular therapies; governments should consider using compulsory licences to ensure that the tools are accessible to developers and that patents on the tools are not used to limit competition for the applications.

Another issue of concern is that public funding goes into research and development which is then patented and into products that are marketed with very aggressive pricing strategies.

Furthermore, patents are being filed for techniques that can be considered to be procedures rather than products. Patents on the first two techniques developed using chimeric antigen receptor therapy (CAR T), for example, have been used to extend the monopoly so that only the companies' approved doctors and medical facilities can carry out the procedure. The difference between a drug and a procedure is also important because health services often have different reimbursement rules for drugs and many countries have exceptions in patent laws for medical procedures. The number of patent applications for CAR technologies has been increasing.

Knowledge Ecology International has raised some questions about the WHO model list for essential medicines. The medical standard for a product to be considered for inclusion on the list is that it makes a significant advance in terms of outcomes. Is there a case, however, that WHO should also consider products that match or slightly improve median outcomes? The problem is often that prices are too high. It can be argued that a category should be created for products that are medically important but expensive, conditional on the fact that they are accessible at affordable prices.

Given that the prices of important medicines are often so high that they represent a barrier to access, some strategies to deal with high prices are required. Possible strategies include:

- imposing price controls or dictating reimbursement terms;
- using compulsory licences;
- introducing exceptions for medical procedures;
- making the supply of biologic drugs more competitive;
- creating patent pools for the collective management of intellectual property rights;
- delinking research and development incentives from product prices;
- exploring medical tourism, to countries with weak patent rights and more affordable competitive suppliers (particularly feasible for “curative” treatments).

Use of compulsory licences is one avenue available to governments, as long as they follow the rules set out in patent law. Under international trade agreements – including the World Trade Organization (WTO)’s TRIPS (Agreement on Trade-Related Aspects of Intellectual Property Rights) – governments can eliminate the exclusive rights of a granted patent when there is compensation or remuneration. The WTO Doha Declaration states that governments should use compulsory licences when necessary to provide “access to medicine for all”, but few compulsory licences have been granted in practice because of trade pressures. Governments should use compulsory licences to demonstrate that – when there are disputes over prices – it is the monopoly, not the patient, that will be put at risk.

Governments can also limit the patents granted for new uses of a drug. In addition, many governments do not grant and/or enforce patents on medical procedures – this could be relevant for CAR T and other gene- or cell-based therapies.

Another issue is that there is generally a low level of competition in the field of biologic drugs. Only 17% of novel biologic drugs approved by the US Food and Drug Administration (FDA) between 1995 and 2005 faced competition from another drug by 2017. This compares to 56% for small-molecule drugs. To address this issue, it could be possible to make it a condition of registration for biotherapeutic products and services that information about materials and methods, along with quantities of the approved material for testing, be made available to providers of generic or biosimilar products.

Given the highly complex patent landscape around new technologies such as CRISPR and CAR T, another potential strategy could be to create patent pools on fair, reasonable and nondiscriminatory terms. There is precedent for this as the US government forced patents on aircraft and radio into a patent pool.

Another option is to delink research and development incentives from prices. This means finding other ways to reward pharmaceutical companies that do not depend on creating monopolies through patents and high prices. This could be done by creating innovation funds to provide remuneration to patent owners and developers when technologies are used to treat patients and incentives to open-source research.

It is important that discussions of these issues are free from conflicts of interest and undue or improper influence of private sector actors. WHO’s Framework of Engagement with Non-State Actors (FENSA) should apply to all WHO discussions. WHO and United Nations agencies should, of course, listen to the voices of the pharmaceutical industry, but care must be taken that private companies are not seen as partners in the development of policies and the setting of norms and standards.

From public health genomics to precision health: towards the implementation of PM in health care systems

Dr Stefania Boccia, Catholic University of the Sacred Heart, Rome, Italy, outlined some of the specific challenges associated with using genomics as part of a public health approach and described how such issues are being addressed in Italy.

The issue of PM needs to be considered within the context of a growing demand for health care as the population ages (by 2050, 37% of the EU population will be over the age of 60) and the high burden of NCDs (which account for 87% of deaths in high-income countries). This implies that health spending needs to grow by at least 20% every year, yet the current situation is characterized by cuts in health expenditure in many countries. At the same time, the expectations of patients and citizens are growing – including in relation to techniques involved in PM.

A key question is how we can tackle these issues with scarce resources. Such issues are being explored by a Horizon 2020-funded initiative, TO-REACH, which has looked at how to incorporate biomedical innovations into health services in a challenging context. This coordination and support action (CSA) – which is *not* a research project – seeks to prepare a joint European research programme aimed at producing research evidence that will support health care services and systems in becoming more resilient, effective, equitable, accessible, sustainable and comprehensive. The initiative involves 28 partners from 20 countries.

The key elements of a sustainable health care system were set out in a 2016 report by the European Steering Group on Sustainable Healthcare, which emphasized the need to invest in prevention and early intervention. There is a need to shift from treatment of established disease to early diagnosis and disease prevention. Currently, however, only a small fraction of health spending goes on prevention activities, and a large proportion of that is allocated to healthy condition monitoring programmes. It is important to be honest, recognizing that not all preventive actions are truly cost-saving, but preventive care does tend to be cost–effective and improves quality of life at a very reasonable price.

The “hygienic revolution” from 1860 onward, which brought sewage systems and the first antibiotics and vaccines, and the “technological and evidence-based medicine revolution”, which has been underway since 1980, can be thought of as medicine’s first and second revolutions. Some are asking whether precision medicine is the third revolution.

In fact, to date there is little evidence that knowledge of one’s own genome has any impact on primary prevention of disease. The results of the P6 study in Finland should contribute to enhancing our knowledge in this area. Some have pointed to the global failure to ensure universal access to essential drugs – including inexpensive ones such as aspirin – as a sign of the potential difficulty in ensuring equitable access to gene-based therapies. Although there are some evidence-based preventive programmes based on genomics, very few health services are implementing them.

The concept of public health genomics is well established; it was defined at an international workshop held in Bellagio, Italy, in 2005 as “the responsible and effective translation of genome-based knowledge and technologies into public policy and health services for the benefit of population health”. The issues involved in public health genomics have been addressed by a number of projects and working groups, including the Public Health Genomics European Network (PHGEN), funded by DG SANCO in 2006, ICPerMed, funded under Horizon 2020, and the Public Health Genomics (PHG) Foundation.

There are many challenges associated with the implementation of PM for public health. The main prerequisites for achieving radical change in health care have been set out as follows:

- achieving better genetic literacy for professionals and the public;
- engaging citizens in the discourse;
- improved governance, consent and trust in health care;
- feeding and harnessing the data knowledge cycle for better health;
- adopting and adapting the Health Technology Assessment framework for evaluation of the new technologies; and
- retaining humanity and community in health and care.

One project that aims to address these topics is the Personalized PREvention of Chronic Diseases (PRECeDI) project, which sets out to provide high-quality, multidisciplinary knowledge through training and research in PM, with specific reference to prevention of chronic diseases. The project involves a consortium of 11 partners from nine EU Member States and two third countries, including seven academic partners and four nonacademic partners. The recommendations from this project were presented to public authorities and policy-makers in Brussels in November 2018.

Few governments have produced broad policy documents on genomics in health care – within the EU, only Belgium, France, Italy and the United Kingdom had produced such a policy by September 2016. Taking the specific example of Italy, a seven-year process was undertaken to produce a guideline on genomics in public health. The policy document is based on three main pillars:

- systematic assessment of health technologies (Health Technology Assessment) of genomic tests currently in use and evaluations pre-marketing of those not yet available to the public;
- promotion of extensive training in genomics and capacity-building for potential stakeholders involved in the delivery and management of health care; and
- promotion of basic literacy of the population on health and genomics to sensitize citizens/patients on advantages, limitations and risks of "omics" technologies.

Health Technology Assessments – incorporating a systematic review, semi-structured interviews with experts and a cost–effectiveness analysis – have been conducted on the identification of BRCA-mutated women and Lynch syndrome (a hereditary form of colorectal cancer).

Training is being delivered through residential courses (funded by the Italian Ministry of Health) and distance learning courses. A new training course, primarily for general practitioners, has been set up in cooperation with the Italian National Institute of Health.

The third pillar, improving the basic literacy of the population on these issues, is still a work in progress.

In conclusion, coordinated strategies for educating clinicians and policy-makers, and addressing public concerns, are necessary to ensure that public health needs are satisfied through appropriate and sustainable health care services in the era of precision health.

Discussion

There was clarification that the BRCA1 test is the only test included in the Italian National Prevention Plan 2014–2018. This provides for women to be interviewed at the time of their mammography, and if they have a particular profile, they are invited to see a geneticist, who advises on whether or not to conduct the test. In such cases the test is free of charge to the woman. For Lynch syndrome, the economic evaluations have not yet been published, so it was not included in the 2014–2018 plan.

Italy published a new National Plan for Innovation in Medicine in 2018. One of the tasks under this plan will be to identify new priorities for Health Technology Assessments.

There was clarification that the second pillar of the Italian approach – i.e. training – also applies to policy-makers and that many of the physicians trained are public health doctors. The objective of this training is to encourage use of genetic tests in an appropriate way and to avoid inappropriate use of resources. Among the factors that prompted this process were the increasing consumer demand for tests and the need for doctors to have greater understanding of when such tests are appropriate or inappropriate.

Reflections on the day and implications for the Russian Federation

The final session sought to summarize the main messages from the presentations and discussions and to consider the implications for the Russian Federation.

On behalf of the Ministry of Health, Mr Igor Korobko thanked all participants for their contributions and emphasized the importance of these discussions for the Russian Federation. It is clear that a personalized approach can be applied to prevention as well as treatment. It is also clear that a participatory approach to

implementing this type of medicine is important. Personalized medicine needs to be seen alongside the other three Ps of the 4P model of modern medicine (predictive, preventive, participatory). This model will provide a framework for the development of health care for today and tomorrow in the Russian Federation.

On behalf of WHO headquarters, Dr Kiu Tay-Teo thanked the Russian Federation and the Regional Office for Europe for a most stimulating discussion. It is clear that there are a lot of exciting possibilities emerging in the field of PM. There are also many challenges, including privacy, cost and patent issues. The priority must be to bring knowledge to patients at an affordable cost. It should also be noted that not all solutions will apply to all country contexts – it is important to look closely at the country context in designing national approaches.

The key messages of advice for countries can be summarized as follows:

- Be prepared – the technology is already here, health systems need to prepare well.
- Be selective – not every intervention is relevant for establishing sustainable health systems in every context.
- Take care to remain conscious of value for money.

Dr Eduard Salakhov, Ministry of Health of the Russian Federation, commented that the discussion had confirmed that PM does have a place on the agenda for the future of the Russian health system, but that it does need to be treated very carefully. Universal access to the whole spectrum of effective medicines and interventions must remain paramount. In addition, particular care is needed on managing the financial costs associated with PM.

On behalf of the WHO Country Office, Dr Melita Vujnovich thanked the Ministry of Health and the Almazov Centre for hosting the event. This policy dialogue is extremely important for the shape of the future health system in the Russian Federation, and also for the collaboration between WHO and the Russian Federation. The goal remains to ensure access to the highest-quality services for all people, as part of achievement of the Sustainable Development Goals. The discussions of the science of PM have played an important role in highlighting key policy questions that need to be further discussed and addressed.

On behalf of the Almazov Centre, Dr Evgeny Shlyakhto summarized the main outcomes of the valuable discussion at this “meeting of the minds”. One key message is that further national and international collaboration is necessary, and further work is needed to explore many of the issues raised in more depth. Questions around access to big data, data security and privacy/confidentiality issues will need to be addressed. Another issue that requires further consideration is the shape and extent of private sector involvement in the development and implementation of PM. Furthermore, there are concerns about affordability and it is essential to focus on ensuring good access for all to important innovations. Finally, the vital role of education in translating innovations into medical practice and integrating them into health systems is clear.

ANNEX

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The WHO Regional Office for Europe

The World Health Organization (WHO) is a specialized agency of the United Nations created in 1948 with the primary responsibility for international health matters and public health. The WHO Regional Office for Europe is one of six regional offices throughout the world, each with its own programme geared to the particular health conditions of the countries it serves.

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