PERSONALIZED MEDICINE. HISTORY, CURRENT STATE AND FUTURE DIRECTIONS

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ABSTRACT

The review assesses history of personalized approach in medicine, terminology and definitions and current situation in personalized medicine in the world. Major fields of implementation, classification, advantages and practical barriers are also discussed as well as future perspectives.

Key words: personalized medicine, precision medicine, pragmacogenetics, OMICs-technologies.

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INTRODUCTION

Personalized medicine (PM), although it is in its infancy today, is already an important evolutionary step towards the creation of drugs, the development of diagnostic and prevention methods. Over time, due to the use of the concept of personalized medicine in everyday clinical practice, a significant improvement in the prognosis, accuracy of diagnosis and results of therapy is expected. At the same time, this can be achieved in real time, making it possible to stratify patients with pathophysiological diseases such as cancer and atherosclerosis, and determine the most a quick and effective way to provide assistance.

The modern development of molecular and information technologies in medicine has led to the fact that the concept of personalized medicine is experiencing an era of rapid development. Over two decades, this area has expanded from a narrow field of application in oncology of personalized drugs, such as gerceptin, to a huge list of nosologies, possibilities for accurate prediction of most diseases based on broad-gene screening, the creation of gene therapeutic drugs, technologies for modifying gene expression and the most powerful information-analytical system supporting the search for individual predictors of response to drugs.

The concept of personalized medicine dictates the need for a significant change in the infrastructure of biomedical science, emphasizes the importance of an interdisciplinary approach aimed at more effective use of knowledge obtained in the field of genomics, innovative bioinformatics and advanced nanotechnological achievements in clinical practice, i.e. for a fast translation of fundamental achievements in practical health care. To promote the concept, it is necessary to expand the resource base of scientific institutions, develop a network of biobanks and collective use centers, information banks and libraries and a broad international integration. It is even more important to change the essence and structure of training for the subsequent implementation of PM technologies.

Most innovations in medicine have already been built on the concept of personalized medicine today — the creation of new diagnostic technologies based on biomakers, the development of the industry of targeted drugs, formation of pharmacogenetics and pharmacogenomics as new disciplines of sciences, development of genome editing technologies, microbiota modification, nutritive genomics, functional nutrition, etc. In recent years, most biotechnological and pharmaceutical companies have declared personalized medicine one of the main development strategies for the future, many countries and major scientific centers are creating consortia for personalized medicine, launching large expensive projects of the national scale, services and a media environment are being developed, making it possible to involve more and more participants and replicate technologies [1—3].

The Strategy for Scientific and Technological Development of the Russian Federation has declared the transition to personalized health care one of the priorities of the strategic development of the Russian Federation for the period up to 2030 [4]. In this regard, as part of the implementation of the national project "Science", the Ministry of Science and Higher Education held competitions for the creation of genomic centers in 2019 and world level scientific centers (WLSC) in 2020, as a result of which at least 6 winners focused their research and development on the technologies of personalized medicine. The Almazov National Medical Research Centre in a consortium with the Institute of Experimental Medicine became one of the winners of the competition. WLSC Center for personalized medicine (headed by Academician of the Russian Academy of Science, Prof. E. V. Shlyakhto) became the founder of the first specialized scientific medical journal in Russia in this area — the Russian Journal for Personalized Medicine, and this review of the state of the problem is opening the first issue in 2021.

DEFINITION OF TERMS

The ideology of personalized medicine was laid long before the term had become customary in the health care practice, and genetic exposure to diseases and genetic predictors of response to therapy were regarded as of paramount importance. Rooted in ancient philosophy and medicine, historically an individual approach to the treatment of a patient was a key element of the Russian medical school of the 19th century (Table 1). The endeavor to treat "not a disease, but a patient", proclaimed by M. Y. Mudry, the extension of this ideology by S. P. Botkin and other best representatives of the domestic school of therapy, sounds more relevant than ever in the modern world, when the concept of an individual approach begins to defeat the ideology of the blown-up dogma of evidence-based medicine, relying only on the "dictatorship" of clinical research and statistics. At the same time, the modern concept of PM has long gone beyond the scope of geonomy and molecular biology and provides wide opportunities for the implementation of targeted prevention, diagnosis and treatment of diseases and prolonging the life of each person.

At present, we are at the beginning of a new industrial revolution and the formation of not just a post-industrial society, but a society based on deep scientific knowledge. Bioinformatics, biology, medicine and, in general, "life sciences" have become the strongest

drivers of changing the life of society today. The combination of unlimited data storage and processing capabilities, rapid development of analytical methods, as well as the ability to translate analysis processes into real time, not only change production processes and social life, but also open up new possibility of a radical change in all processes in health care, from public health to personalized medical care. At the same time, such a rapid development of technologies carries certain threats, including the risks of introducing technologies that do not prove their safety and efficiency, as well as risks of discriminating certain groups of the population by providing all kinds of users with access to their personal data and, vice versa, by reducing their access to new technologies. In this regard, the use of personalized technologies, as well as any other innovation in medicine, requires serious scientific evidence and practical testing.

The term "personalized medicine" (or individualized, personified medicine) became popular in the late 20th — early 21st centuries [5]. It involves a choice of treatment based on the individual characteristics of the patient, primarily genetic, as well as age and gender, anthropometric, ethnic, environmental characteristics, etc. This principle fundamentally distinguishes PM from the concept of "standardized treatment", based on the results of clinical trials and large cohort studies [6]. In a narrow sense, PM initially focused on the potential of genomic markers (variants of the nucleotide sequence) to form ideas for risk stratification, prevention, dose selection for drugs, drug selection, prediction of therapeutic response and outcome [7—8]. This involved the development of two main directions — the study of rare cases with obvious genetic nature and frequent diseases with a genetic predisposition. Then the range of biomarkers began to expand, new areas appeared, such as personalized cell products, genome editing technologies, antisense therapy, which led to creating a complex modern PM architecture and highlighting a large number of different directions in it.

The evolution and expansion of the concept of personnel medicine has led to the emergence of a new term

Table 1. Historical milestones in the emergence and formation of the concept of personalized medicine (adapted and supplemented from [12])

Epochs and dates	Authors and country	The concept
4000 BC	Medicine in ancient India	System for individual selection of herbs and meditation regimes
510 BC	Pythagoras, Greece	Description of favism — he noticed that only some people react when eating fava beans (now this disease is known as glucose-6-fasfat dehydrogenase deficiency)
Middle Ages	Europe	Treatment is individual due to lack of knowledge and standard schemes
1789	Samuel Hahnemann, Germany	The principle of homeopathy. Similia similibus curantur
1908	Germany	The appearance of words: gene, genotype and phenotype
1931	Garrod [14]	Publication of a book that identified the individual effect of drugs DEPENDING ON THE GENETIC CONSTITUTION
1953	Watson & Creek	Double-stranded DNA
1956, 1957	Kalow; Motulsky [15, 16]	Pharmacogenetics concept
1962	Kalow [17]	The first monograph on pharmacogenetics
1986	Mullis, et al. [18]	Discovery of polymerase chain reaction
2000		Completion of human genome sequencing
2000–2020		Post-genomic era. Changing the strategy for creating drugs. PM as the basis of medicine of the future

"precision medicine", which implies the identification of a group of people (down to individuals) who have some common ways of the characteristics of disease development and response to therapy [5]. This term was officially recognized by the National Scientific Council of the United States in 2011 [5] as officially more correct and partially replacing personalized medicine. Precision medicine is a field of medicine that takes into account individual differences in genes, microbiomes, environment, family history and lifestyle to define a strategy for diagnosis, treatment and prevention, precisely aimed at a specific patient [5, 9]. And yet these concepts are close, but not identical. Precision medicine relies on search for probabilistic risks or the likelihood of an intervention to bring more or less benefit in relation to the outcome in a group of patients with common characteristics (for example, genes), whereas true personalization of medical care is observed only when the role of biomarkers and risk factors overlap with the preferences and needs of a particular patient, including his family, temper, expectations and features of interpersonal interaction with the attending physician [10].

Pharmacogenomics, pharmacogenetics and pharmacoproteomics remain the leading sections of PM, based on molecular diagnostics as a vital tool for PM [11]. As it is known, most modern drugs are developed and approved on the basis of their effectiveness in large groups of patients. The initial concept of creating drugs was the idea that, with an understandable mechanism, a response to treatment would be observed in all patients. Classical data from clinical trials of a new drug simply assessed the response of the study group (average decrease in blood pressure, cholesterol, decrease in the size of tumor, remission, pain reduction, etc.). Although the individualization of some treatment methods was proposed already in the pregenomic era, the concept of personalized medicine, which is developing in modern society, is founded on achievements in molecular diagnostics and drug development based on genomics, proteomics, metabolomics and biomarkers. The goal of personalized pharmacotherapy is not only to find the right drug for the right patient, but to select it without resorting to trial treatment, basing on knowledge about the genotype and biomarker levels. This increases the efficiency and safety of treatment and as naturally reduces its cost.

There are many terms and definitions that have a close relationship with PM. Actually, the term was established after the publication of the monograph of the same title in 1998 [12], at the same time it appears among the keywords indexed in MEDLINE system since 1999, but for a long time was associated only with areas of pharomacogenomics.

Very close concepts, but in fact at the present stage, PM fields, are such terms as:

- Genomic medicine.
- Genotype-based therapy.
- Individualized medicine, or individual-based therapy.
- Information-based medicine.
- Omics-based medicine.
- pharmacogenomics/pharmacogenetics/ pharmacoproteomics/pharmacometabolomics.
- Precision medicine.
- Rational drug selection
- Stratified medicine.
- Systems medicine.

MAIN ADVANTAGES OF PM AND BARRIERS TO IMPLEMENTATION

The possibility of more balanced medical decisions based on a deeper comprehension of the mechanisms of a disease and the effect of drugs.

- Increasing the probability of a good prognosis due to a more targeted impact.
- Reducing the probability of drug side effects and other iatrogenic complications.
- Concentration on prevention, including the individually justified one.
- Earlier treatment of diseases based on more sensitive markers, including the possibility of treatment before the onset of symptoms.
- Prenatal diagnosis of genetic defects and prevention of childhood disability.

Significant problems in healthcare are the low accuracy of diagnostic procedures and the periodic absence of the effect of treatment, including expensive ones. Both lead to unjustified costs in health care — research that does not provide the required information and useless prescription of drugs. This is especially evident in those areas of medicine where treatment is very expensive and involves large risks — oncology, rheumatology, psychiatry. In the treatment of some tumors or diseases such as rheumatoid arthritis, the number of "non-responders" to treatment can reach 50% or more [12]. This leads to unnecessary costs and a decrease in aid effectiveness. In this regard, from the point of view of cost planning and their rationality, the presence of specific biomarkers that reliably determine the medical tactics in relation to the patient is necessarily accompanied by a direct and indirect financial benefit.

However, making a truthful prognosis about how much the introduction of PM will lead to a decrease in costs in healthcare today is quite hard. In order to introduce approaches into real clinical practice, a lot of investments are needed in changing the structure of medical care: in laboratory and information equipment, in increasing qualifications of medical workers, to the sys-

tem for assessing the quality of care and even in clinical guidelines and protocols for the treatment of diseases. Today, no country can say yet, how long it will take and how widely it is possible in the near future. Unfortunately, the experience of the last ten years shows that the cost of medical care around the world is only increasing, so the momentary widespread introduction of PM should be considered without blind enthusiasm and even with a proper degree of skepticism. The real economic efficiency of precision treatment approaches will be visible after a considerable period of time and requires constant evaluation and reinterpretation. Unfortunately, there are risks that the widespread introduction of additional survey methods, including the identification of new genetic markers, at the initial stage will only increase the cost of health care. Targeted drugs have a very high cost in the treatment of tumors and a number of other pathologies, while their advantages in terms of long-term prognosis often still require clarification. Even such a revolutionary approach to the treatment of hyperlipidemia as PCSK9 inhibitors is already considered by some experts to be a controversial achievement in terms of the ratio of efficacy and cost [18]. In this regard, the introduction of PM methods and technologies around the world is gradually spreading from areas with a high grade of evidence of the result onto more controversial fields.

THE STRUCTURE OF PERSONALIZED MEDICINE

Today, personalized medicine includes several strategic areas of innovation in medicine, such as:

Personalized diagnostics, including information on biomarkers.

- Personalized prevention.
- Nanotechnologies and nanodevices.
- Personalized information technologies in medicine. Computational tools and translational bioinformatics. Artificial intelligence.
- Personalized pharmacology, including personalized biological therapy.
- Personalized cellular products and gene drugs.

Particular issues of PM in the diagnosis and treatment of diseases led to independent sciences, which are actively developing in the relevant fields. Among them, the maximum achievements are in the following areas:

- PM in oncology.
- PM in psychiatry and treatment of neurological disorders.
- PM in the treatment of cardiovascular diseases.
- PM and metabolic diseases.
- PM and autoimmune and autoinflammatory diseases.
- PM, perinatal medicine and hereditary diseases. Reproduction.
- PM and lifestyle.
- PM and treatment of infections.

Major divers of PM development

- Political and socio-economic factors
- Growing demand and public pressure on the government to introduce safer and more effective treatments.
- A demand towards pharmaceutical and medical industry regarding reduction of drug side effects and reduction of iatrogenic complications.
- The aspiration of businesses to make genetic screening more available.
- Increasing requirements for the quality of medical care, encouraging medical workers to seek safety guarantees.
- A demand for decrease of the cost of medical care by reducing losses from non-effective drug therapy and treatment of the consequences of iatrogenic complications.
- Reducing the cost of genetic tests, including genome sequencing

Factors related to the development of science and technology

- The availability of genomic knowledge obtained as a result of sequencing the human genome.
- The availability of new technologies that make it possible to widely and universally apply personalized medicine, such as biochips and high-performance sequencing.
- Changing generations of medical workers to the younger generation, increasing awareness of pharmacogenomics, pharmacogenetics and molecular medicine.
- Introduction of personalized medicine in scientific medical centers.

Industrial drivers

- The spread of biotechnological companies interested in personalized medicine.
- An increase in the number of companies that combine diagnostics with therapy (theranostics).

- The aspiration of companies to increase the reliability and safety of their products, reduce repetition losses due to the development of inefficiency or side effects. Development of value medicine and the concept of risk sharing.

BIOMARKER DEVELOPMENT

One of the most important conditions for the development of PM is the validation and introduction of new

biomarkers. The process of creating a new biomaker includes the following areas that are actively developing at present and will be improved in the future:

- Detection and validation of the marker.
- Assessment of predictive potential and comparison with other markers.
- Preclinical and clinical trials.
- Animal models.
- Bioinformatic processing of genetic data.
- Approaches based on the principles of systems biology.

THE FUTURE OF PERSONALIZED MEDICINE

The rapid evolution of biomedicine will lead to major changes in healthcare in the nearest future. In particular, the real molecular mechanisms of most diseases that we previously considered idiopathic and unclear will be deciphered and detailed. Based on omics data, a large number of medical services, including commercial ones, will be created, which will be widely developed and offered to the population not only by medical institutions. Genomic data and risk calculation systems will be gradually integrated into clinical medicine. Over time, ethical and regulatory problems of introducing advanced genetic technologies will be solved, and they will quickly become a part of practical activity. The rapid development of nanomedicine and the so-called "connected health" is expected, which involves the use of a huge variety of remote communication services that ensure the concentration of wireless, mobile, electronic and other services created for the needs of the patient and providing the patient with the opportunity to share this data in order to receive the most effective medical care [19].

Preventive medicine will make a huge leap forward, which should be crowned with success in the treatment of diseases in the preclinical stage and the creation of other technologies of treatment "before the disease".

Automation, robotization, decision-making support systems and predictive analytics will become firmly established in clinical practice and will lead to a serious transformation of the function of a doctor and other medical employees. The combination of information and artificial intelligence technologies with progress in molecular biology will lead not only to the creation of "smart" health care, but also to a truly individualized approach, including nutrition, physical activity, the use of drugs and other methods of treatment.

First of all, this transformation of medicine should be expected in the field of oncology, neuroscience and the treatment of viral infections, where the advances in molecular biology are already most noticeable. It is believed that PM technologies in these areas will already be widely used by 2025 [20]. Not only will new targeted drugs be created taking into account personalization, but also the use of many known molecules and technologies will be refined based on genomics and proteomics data. There is an opinion that genotyping will become the "X-ray of the XXI century", which is based on the idea of the role of genetic factors in the prediction of diseases, accurate diagnosis, choice of treatment and prognosis [21—23].

Of course, not all diseases will quickly require personalized treatment, this field will develop gradually and cover new areas more and more. But what is extremely important to realize is that we should not wait another couple of decades to enter the era of personalized medicine, we must already actively introduce its principles into clinical guidelines and protocols of treatment, into practical life, which is already taking place actively in progressive health care systems. Great progress is expected in the biopharmaceutical sector in this field, which will ensure the generation of innovations and new scientific knowledge. For many countries, such as the United States, Japan, and China, the strategy of personalized medicine has become the mainstream of public health policy. It is extremely important that within the framework of the national project "Science", so much attention is paid today to genomic research and personalized medicine. Without a doubt, the activity of the WLSC in this area will contribute to the progress and generation of technologies. And this new journal should become an information platform for scientists and the business community to publish new data and discuss the importance of the problem.

Conflict of interest

The authors stated that there is no potential conflict of interest.

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