PERSONALIZED MEDICINE — STAGES OF CONCEPT FORMATION AND WAYS OF ITS PRACTICAL IMPLEMENTATION

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ABSTRACT

Personalized medicine is a new paradigm in healthcare, based on understanding of the importance of an individual treatment approach and based on knowledge about genomic predictors and post-genomic markers of various diseases. Complementing the concept of evidence-based medicine, personalized medicine opens up new opportunities for doctors and researchers to treat patients more effectivel. At the same time it raises many medical, ethical and legal issues.

This article describes the current state of the problem with specific examples of the implementation of this approach by the leading institutions of the Russian Federation (including the Endocrinology Research Center).

Key words: endocrinology, evidence-based medicine, pharmacogenetics, precision medicine, rare diseases, translational medical research.

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INTRODUCTION

Personalized medicine is a new paradigm in healthcare — preventive medicine built on genomic predictors and postgenomic markers. Endocrinologists were among the first in our country who started to develop the concept of personalized medicine, and as far back as in 2011 I. I. Dedov already presented his keynote paper on this subject at the Presidium of the Russian Academy of Medical Sciences. A year later, plenary lecture by Academician I. I. Dedov at the Congress of Endocrinologists was focused on speaking about the importance and, most importantly, the potential practical benefits of the implementation of this concept, quite achievable in the near future. In the same year, the most authoritative Russian scientists I. I. Dedov, V. P. Chekhonin, A. Archakov and others presented a keynote article on the need for the development of personalized medicine in the journal "Ve — stnik RAMN" [1].

Of course, the very idea of personalization in medicine is not new, and the concept of "treating not a disease, but a person", coming from Hippocrates, is a classic of the Russian therapeutic school.

But now this idea is taking on a new meaning, and its development is supported at the state level. The development and implementation of personalized medicine technologies are regulated in the Strategy for the Development of Medical Science in Russia until 2025 and the Strategy for Scientific and Technological Development of Russia until 2035 approved by decree of the President of the Russian Federation in December 2016. In this publication, the authors propose to consider the stages of forming the concept of personalized medicine and the experience of its practical implementation.

MAIN CONTENT

Specific personalization tools vary in different periods of technology development.

Endocrinology has always emphasized the personalization of the treatment choice, even in those distant years, when the choice was in fact small. Suffice it to recall the extremely important for the training of doctors "Algorithms for the treatment of patients with diabetes", published from 2002 to 2020, where the principles were thoroughly based on individualized approach — from body weight and diabetes experience to taking into account complications [2, 3].

Already at the beginning of the development of the concept of personalized medicine, there were attempts to oppose it to the ideas of evidence-based medicine, while the latter was indulgently defined as "statistical data medicine", "cookbook", an old anecdote from the XVIII century (a hint of encyclopedists' requirements for evidence in science), while personalization was rather associated with the so called translational medicine, or medicine based on the early implementation of the latest scientific achievements into practice, and was considered through the prism of powerful machine learning technologies and artificial intelligence.

Indeed, the philosophical basis of evidence-based medicine (hereinafter abbreviated EBM), although formulated in the 80s of the last century, dates back to the XVIII century, since the concept requires proper research to answer a correctly formulated question. EBM still remains a topic of heated debate between clinicians, health care organizers and the public today.

EBM, as determined by Sackett [4], is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients, based on common sense. The practice of EBM combines the experience of a particular clinician with the best proven data obtained from systematic, correctly constructed trials, and for a good clinician these two components are important parts in making a treatment decision. The concept of evidence itself is multifaceted and does not always flawlessly reveal cause-and-effect relationships, the ones that are so important for the clinician from the standpoint of preventive work.

But if it takes a lot of evidence and they are not always obviously unidirectional, then why is the evidence-based medicine still interesting today, in the XXI century? Although we support the principles of EBM, can we fully solve all problems with it? EBM is supposed to be aimed at bridging the gap between good quality clinical trials and clinical practice, but is it always possible? Population studies solve many problems that are important for an optimal approach to the health of population groups, but are unlikely to solve individual problems. Alas, not all studies are of the same quality, and the data may well be contradictory. Nevertheless, evidence-based medicine gives us the support in making clinically important decisions, combines our personal knowledge, the knowledge of other experts, allowing us to take into account the preferences of patients, improves medical practice and reduces the likelihood of errors. But no matter how good our current ideas about optimal treatment are, it lacks

individualization, and the assumption that all EBM-based treatments always resemble a perfectly lubricated machine, are naive.

Perhaps our first priority is to accelerate the development of the so-called "translational medicine" — a new direction in biomedicine that provides the fastest possible transferring data from well-planned basic trials to clinical practice?

An important role in the development of this direction in our country was played by Academician of

the Russian Academy of Sciences V. Shlyakhto, whose works emphased that the huge achievements of medical and biological science currently do not find proper application in the practice of a doctor, and this is a problem of world medicine [5]. Scientific thought is developing more rapidly than its real results have time to be adapted in the practical medical field. Bridging the gap between fundamental sciences and the clinic will be helped by a direction called "translational medicine", whose goal is to accelerate the introduction of the latest technologies into real practice. What is very important is that translational medicine is "sharpened" to solve specific practical problems, this is a "technological assault" carried out by order from the clinic. Even today there is some confusion in understanding that translational medicine is not telemedicine, not distance learning in advanced clinics [6].

Translational medicine is a clearly formulated clinical task that is solved in close contact between specialists in the field of fundamental biology, physics, chemistry and clinicians, while the result should be obtained as quickly as possible and at the lowest cost. Academician of the Russian Academy of Sciences E. V. Shlyakhto proposed a form of cluster association of fundamental medicine specialists and clinicians with the incorporation of business, and the Almazov Center launched the publication of the Translational Medicine journal in 2017.

Of course, both clinical, evidence-based, and translational medicine are different aspects of the same medicine, where strict adherence to the optimal scientific principles of building clinical trials with the evaluation of "responders" and "nonresponders" allows to identify target groups for finding optimal treatment methods, finding fundamentally new methods of care and prevention as quickly as possible, and in the future, by comparing with individual data, including genomic predictors, to fulfill the dream of all generations of doctors by finding a way to provide each person with the right treatment at the right time, avoiding side effects and treatment failures. The main branches of medicine where new principles are applied are oncology, pharmacy and pharmacogenomics. The latter studies the body's reactions to medications, depending on individual hereditary factors.

However, the development of personalized medicine is also taking place in other areas, and it is not surprising that pharmacogenomics immediately became the leader in the development of personalized medicine. It is no coincidence that back in 2017, when the National Medical Research Center of Endocrinology of the Ministry of Health of Russia began publishing the online journal World of Personalized Medicine, editor-in-chief Academician I. I. Dedov proposed to open the journal with an editorial by associate member of the Russian Academy of Sciences D. A. Sychev, the foremost scholar in the field of pharmacogenomics. This article, entitled

"Stages of development and implementation of personalized medicine technologies in clinical practice: the role of the Ministry of Health of Russia and the Russian Academy of Sciences" [7], contained current postulates about ways of evolution of developing real personalization of the treatment process, the development and implementation of technologies for personalized medicine. According to D. A. Sychev, "personalized medicine is a new doctrine of modern health care, which is based on the use of new methods of molecular analysis (genomics, transcriptomics, proteomics , metabolomics, microbiomics) to improve the assessment of predisposition (prediction) to diseases and their management." In other words, an extremely interesting idea was already voiced in the first publications — the concept of personalized medicine requires not only the involvement of scientific resources, but also organizational efforts, since it is a "health doctrine".

"The essence of implementing the methodology of personalized medicine in clinical practice," writes D. A. Sychev, "is an approach to providing medical care based on the individual characteristics of patients, for which they should be divided into subgroups depending on the predisposition to disease and the response to an intervention that should be applied to those who will really benefit from it, for whom it will be safe and will lead to cost saving". The leading article emphasized the need for a step-by-step development of the concept of personalization in medicine, the need to accumulate data, also by using biobanks, and the development of personalization algorithms/models based on bioinformation technologies with their clinical validation, the use of personalized approaches in real clinical practice when applying preventive and curative measures by creating and maintaining an electronic register of patients who underwent personalization, with a periodic assessment of changes in the clinical status (including outcomes), as well as preservation of the biomaterial of these patients.

This important road map, of course with the amendments made by time, is being implemented now. The first issue of the journal included reviews of the literature on pharmacogenetic studies of the efficacy and safety of antipsychotic drugs, which made it possible to identify several of the most significant polymorphisms that have a pronounced effect on the occurrence of adverse drug reactions when receiving antipsychotic drugs, and on the individualization of the use of tamoxifen in the treatment of breast cancer [8, 9], while a comparison of these reviews performed at a high methodological level gives a clear idea that not

only genomic studies determine a personalized approach to treatment, but it is also necessary to use other "omics" technologies for flawless individualization of treatment. Clinical examples that were regularly published in the journal, mainly from the Institute of Pediatric Endocrinology of the National Medical Research Center of Endocrinology of the Ministry of Health of Russia, told about unique clinical observations. Not long ago, treatment with sulfonylureas of infants with diabetes mellitus seemed fantastic. As it turned out, a special form — neonatal diabetes mellitus — does not require insulin treatment, and most patients with mutations in the genes of ATP-dependent K-channels can be successfully compensated against the background of treatment with sulfonylureas. Thus, out of 70 patients with neonatal diabetes mellitus, compensation of carbohydrate metabolism during monotherapy with glibenclamide was achieved in 22/35 (65.7%) cases. At the same time, the authors confirmed information previously known in foreign literature on the diagnostic value of detecting mutations in the KCNJ11 gene, and found an important association between the localization of the mutation in the KCNJ1 gene, the severity of clinical manifestations of the disease and the sensitivity of patients to sulfonylureas. It was also confirmed that the need for glibenclamide increased in patients with long-term neonatal diabetes. In recent years, the Institute of Clinical Endocrinology of the National Medical Research Center of Endocrinology of the Ministry of Health of Russia and the Institute of Pediatric Endocrinology have been working extensively and successfully in the field of studying bone tissue both as an acceptor and as a producer of hormones, and pathological conditions due to a mutation in the FGF23 gene, as well as the study of tumors producing phosphaturic fibroblast growth factor 23 and hypophosphatemic conditions associated with this pathology. The unique, first case of autosomal dominant hypophosphatemic rickets in Russia was presented by K. Kulikova et al. from the

National Medical Research Center of Endocrinology of the Ministry of Health of Russia [10], the diagnosis was confirmed by the detection of a heterozygous mutation of c.536g>A:P.r179Q in the FGF23 gene. The life of the journal (its published issues are available at https://www.wjpm-endojournals.ru/jour/ index) was not easy, and we welcome the initiative of the Almazov Center to organize the new Russian Journal for Personalized Medicine, available both electronically and on paper, bringing together scientists and doctors of various specialties, and to involve all grantees working in the field of personalized medicine, while maintaining a balance between fundamental works, descriptions of unique clinical cases and discussion of bioethics of personalization and digitalization.

It is in patients with orphan diseases that the benefits of personalized treatment are most clearly manifested today, and these patients propel the study of genomic pathology and make it possible to identify less aggressive forms of the disease in relatives. Therefore, in our opinion, another important function of the new journal should be a library of clinical observations allowing to "build a bridge" between molecular genetics laboratories and the patient's bed.

Genomic predictors make it possible to foretell the risk of diseases, and post-genomic markers, which form the basis of diagnostic search, allow individual monitoring of human health, to find and level out pathological processes at the earliest stage and/or prescribe a purely individual treatment.

Currently, four medical centers have received grant funding for the development of a model of personalized medicine. Although the beginning of work on grants took place during hard years, when the efforts of doctors and funds were diverted to the fight against the pandemic of the new coronavirus infection, undoubted progress is the development of new laboratory structures and digitalization of medicine of the National Medical Research Center of Endocrinology of the Ministry of Health of Russia, a multidisciplinary research medical center that has no analogues in the world, consisting of five clinical institutes specialized in: diabetes, clinical endocrinology, pediatric endocrinology, reproductive endocrinology, oncoendocrinology, as well as the Institute of Higher and Additional Professional education and the Institute for Personalized Medicine. The unique clinical experience of the National Medical Research Center of Endocrinology of the Ministry of Health of Russia has formed a reproducible system of training doctors in technologies for diagnosing individual endocrinopathies, from socially significant (diabetes in its various forms with various complications and any history of the disease) to the rarest (orphan) diseases, but now, when new directions and new laboratories are to be created , training programs will have to be updated. In accordance with the Decree of the President of the Russian Federation dated May 7, 2018 No. 204, the National Medical Research Center of Endocrinology of the Ministry of Health of Russia as an institution combining medical, medicinal and scientific activities with the most important pedagogical function of training qualified personnel for health care, received the right to implement a program for the creation of the National Center for Personalized medicine of endocrine diseases (NCPMED). The Center proposed a unique integrative solution to the problem of personalization of diagnosis and treatment by comparing genomic data with metabolic and hormonal data in the groups of "natural models" of primary and secondary disorders in one of the

main integrative systems of the body — the endocrine system. Fundamental research conducted on the basis of the National Medical Research Center of Endocrinology will be expanded through de novo laboratories, in particular laboratories of general, molecular and population genetics, cellular technologies, bioinformatics, metabolomic and proteomic studies with a microbiota laboratory, genome editing laboratories, immunology and autoimmune diseases, non-invasive technologies for the diagnosis of endocrinopathy, clamp technologies and pharmacokinetics, pharmacogenomics, intelligent mathematical technologies and personalization of diagnostics and forecasting, embryology and comparative endocrinology, molecular oncoendocrinology.

Despite all the difficulties of work in 2020-2021, when the center was partially repurposed as a clinic for the treatment of patients with COVID-19, work began on the implementation of the projects laid down in the basis of the center, and most of them work on the basis of a pre-created database of patients, primarily with pituitary tumors, multiple endocrine tumors, parathyroid tumors and skeletal diseases. During the year of work, we can confidently talk about significant progress in the study of the molecular foundations of the pathology of the parathyroid glands and the publications of National Medical Research Center of Endocrinology of the Ministry of Health of Russia issued in 2020—2021, in which preliminary results have already been summed up, revealed the importance of early detection of hypercalcemia and the importance of assessing hyperparathyroidism not only as an isolated syndrome, but as a possible debut of a genetically determined disease [11—13], while an important basis was the creation of a database of patients with hyperparathyroidism [14]. We are already considering the possibility of creating new cellular products for the treatment of a hormone-deficient condition, including growing an authentic parathyroid gland from the patient's own cells in a Petri dish. In our opinion, the data obtained over these two years on the role of the post-transcriptomic DNA-miRNA silencing system in the differential diagnosis of various forms of hypercortiolism are also very important [15]. These studies on the role of non-coding miRNAs in endocrinopathies have been conducted at the Center for a long time, but we believe that in the new conditions we will be able to systematize the previously obtained information and translate it into practice [16-18], the center also continued to develop predictor models for assessing remission/ recovery after removal of corticotropinomas [19].

If the trajectory of organizational and scientific perspectives of personalization in healthcare is clear, despite all the complexity, then bioethical and economic issues are not much discussed.

Today we are not yet thinking much about the ethical issues of expanding our knowledge about disease predictors, about the burden that a person and his family receive based on the results of genome-wide screening of newborns, when the risks of diseases that will manifest in the fourth or fifth decade will be formulated, about the psychological consequences of information regarding the "fatal inevitability of the disease". This raises the question of the risk of spreading personal information obtained on the basis of knowledge of the genotype. How will the balance of scientific interest, interests of society the individual be maintained?

Of course, the very idea of replacing "one size for all" as a disadvantage of EBM [20] with the idea of "the right medicine for the right patient at the right time" as the slogan for personalized treatment would be unthinkable without the achievements of genetics and the completion of the Human Genome Project. Although no one denies the variability of post-genomic changes and lifestyle, the fastest possible acquisition of genomic information is necessary for solving pharmacogenomics issues, in the first place, according to FDA [21]. This, in fact, obliges us in the future to confirm the specificity of the disease and choose the optimal treatment at the molecular level, to translate genomic information into the practice of medicine and public health.

At first glance, the advantages are obvious — knowledge of risks provides a strategy for preventing/ overcoming them, speeding up diagnosis facilitates the search of treatment, increasing its effectiveness and reducing the risk of adverse events.

Skeptics emphasize that personalized medicine will generate, like many other achievements of mankind, new ethical challenges — starting with genetic tests of obscure significance with no obvious purpose [22].

A sober assessment of the possibilities of real personalization at each new stage of development of society can ensure a long and effective life for the personalization paradigm. Excessive enthusiasm and "hype" (using today's glossary) can generate mistakes and ruin an important area, so understanding the ethics of personalization should also be a matter of discussion on the pages of our journals.

What obvious problems are already being discussed today?

Undoubtedly, major concerns are the high cost of genetic research, inequality in access to health resources, the opposition of personal and public rights to access information, discrimination and genetic stigmatization, invasion of totally personal space, accidental findings, a new status close to research, genetic counseling, a negative undeniable impact on the relationship between a doctor and a patient — is all this redeemed

by improving the quality of medical care for everyone and for everyone in society?

Undoubtedly, as we have already emphasized, the main expectation of society is safe pharmacogenetics, effective drugs without side effects (which, by the way, contradicts the old medical rule "there are no effective drugs without side effects"). Of course, these will be more expensive drugs, but drugs alone are not the most expensive part of the health budget. In addition, the emphasis on safety is an extremely rational approach, since it is genetic factors that are among the most important predictors of undesirable side effects, especially severe ones.

A serious objection for the world community in relation to the idea of developing genetic tests is their economic inaccessibility for many countries [23].

It is difficult to object to genetic testing in risk groups, but in the future tests will become cheaper and more accessible, which will allow changing also the design of clinical trials, with the selection of the most genetically favorable cohorts, reducing their volume, accelerating research time and reducing costs. Perhaps the need for phases 1-2 will disappear, and a new model of clinical research is on the way.

There are also serious concerns about the readiness of the pharmaceutical business to produce drugs that will be close in their intended use to drugs for orphan diseases. In fact, if we identify certain genetic subgroups among very common diseases that do not need banal and well-selling medicines, but need rare drugs — will such production be supported? How will society support the possible racial or social "coloring" of the disproportion in the need for such medicines for diseases of the same type?

We don't have to solve these problems yet, but one of the most important ethical organizational aspects concerns the so-called biobanks and their functions. Working in this direction for several years, we faced ethical problems of organizing biobanks, including the need to combine the availability of samples and the preservation of medical confidentiality when it is mandatory to have informed consent.

No less skepticism is caused by a change in the relationship between the doctor and the patient when genetic information appears. Today, attending doctors who are specifically examining the panel of genes in search of an answer to the question of an accurate diagnosis, resort to the help of geneticists to answer the questions of patients receiving genetic information. Erroneous interpretation of complex and ambiguous data can negate all the bonuses inherent in personalization.

It would seem to be an obviously wonderful idea — the selection of patients based on genetic data implies the availability of genetic databases of patients to pharmaceutical companies, as well as the availability of personal data from case histories.

The bioethics of genetic research will also require the fullest possible explanation of the limitations of our current (and maybe tomorrow and the day after tomorrow) knowledge about genetic information and its implementation at the level of the organism, a clear indication of the ways to use and store biological samples, coding and maintaining anonymity, ways to withdraw samples and recall research results, the possibility of using a wide / limited network of national / international databases. The risks of getting acquainted with these databases of insurance companies and employers are obvious. Thus, the protection of personal data is more relevant than ever in relation to personalized medicine, and personalized medicine can create a crisis of trust between various healthcare institutions, this concern has been expressed since the implementation of the Human Genome Project.

Today, the ideal doctor-patient relationship includes, as far as possible, cooperation and understanding of the treatment goals by the patient, and understanding the patient's wishes and priorities by the doctor... How achievable it will be in the digital age of personalized medicine!

And, finally, the last, but no less significant objections: already today the cost of unique drugs for the treatment of orphan diseases is off the scale. Will the financial capabilities of insurance campaigns provide all patients, for example, with oncological diseases, with the necessary medicines and tests?

CONCLUSION

Thus, the implementation of the concept of personalized medicine is associated not only with great hopes and successes of researchers and doctors, but also with certain difficulties. Probably, all these discussion issues, as well as scientific problems, will also become the subject of discussion on the pages of the new journal, to which the author of the article wishes success and a long life!

Conflict of interest

The authors declare no conflict of interest.

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