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Personalized medicine in a multidisciplinary specialized hospital. Implementation in clinical practice

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ABSTRACT. ***Introduction.*** The strategy of personalized medicine is currently expanding in various fields, transforming medical practice on a new level. This review aims to examine the impact of personalized medicine on clinical practice by discussing key areas of interest, presenting current findings, and exploring future prospects. ***This review aims*** to summarize the existing data on the implementation of personalized medicine approaches in healthcare practice. ***Materials and methods.*** A literature search was conducted using PubMed, Web of Science, UpToDate, and relevant genetic databases with the specified keywords "personalized medicine", "molecular genetic testing", "DNA". Additionally, expert opinions from a multidisciplinary team of healthcare professionals were consulted. The data from 39 relevant articles was analyzed. ***Results.*** The article discusses the practical applications of personalized approach and provides examples of laboratory methods and the potential for pharmacogenetic research. It emphasizes the significance of adopting an individualized approach to diagnosis, treatment, and monitoring, including the utilization of modern technologies and traditional methods, drawing on experience gained through work with patients in a specialized multidisciplinary hospital. ***Conclusion.*** Personification allows the improvement of medical care by preventing and early diagnosis of diseases, and it also increases the effectiveness of medicine therapy and significantly reduces the material costs of treatment. It is essential to emphasize the significance and necessity of a mutual understanding and constructive dialogue between doctors and patients, as the focus of this approach should be on the patient rather than the disease. The personalized approach to patient care is now a promising trend in medicine that requires not only scientific resources but also organizational efforts, as it represents a new paradigm in modern healthcare.

KEYWORDS: personalized medicine, molecular genetic testing, DNA

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Молекулярно-генетическая диагностика как инструмент персонализированной медицины. Возможности применения в многопрофильном стационаре

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РЕЗЮМЕ. ***Введение.*** В настоящее время стратегия персонализированной медицины (ПМ) расширяется во многих областях, выводя тем самым медицинскую практику на новый уровень. В обзоре представлено влияние данного подхода на клиническую практику, обсуждаются основные области, представляющие интерес, имеющиеся результаты и будущие перспективы. ***Цель настоящего обзора*** — обобщить имеющиеся данные о реализации технологий персонализированной медицины в практическом здравоохранении. ***Методы.*** Проведен поиск литературы в базах данных PubMed, Web of Science, UpToDate, генетических базах данных с использованием ключевых слов «персонализированная медицина», «молекулярно-генетическое тестирование», «ДНК». Использовались данные 39 статей и экспертное мнение специалистов многопрофильного стационара. ***Результаты.*** В статье рассмотрены области практического применения персонализированного подхода, приведены примеры основных лабораторных методов, возможности фармакогенетических исследований. Продемонстрирована значимость применения индивидуального подхода в диагностике, лечении, наблюдении, в том числе с использованием современных технологий, традиционного опыта, основанные на опыте работы с пациентами в рамках многопрофильного специализированного стационара. ***Выводы.*** Персонификация позволяет не только улучшить качество оказания медицинской помощи путем профилактики и ранней диагностики заболеваний, но и повысить эффективность медикаментозной терапии и существенно сократить материальные затраты на лечение. Необходимо подчеркнуть важность и необходимость взаимопонимания и конструктивного диалога между врачом и пациентом, ведь объект применения данного подхода не заболевание, а пациент. Персонализированный подход к лечению пациентов в настоящее время является одной из самых перспективных тенденций медицины и требует не только привлечения научных ресурсов, но и организационных усилий, поскольку является новой доктриной современного здравоохранения.

КЛЮЧЕВЫЕ СЛОВА: персонализированная медицина, молекулярно-генетическое тестирование, ДНК

INTRODUCTION

Personalized medicine (PM) is a special evidence-based approach in medical practice aimed at treating patients individually, taking into account their unique clinical and genetic characteristics, thereby achieving optimal treatment outcomes and preventing the development of diseases and their complications [1]. Various descriptions of PM can be found in the literature. For example, the European Parliamentary Research Service defines PM as the use of genetic and molecular bases of physiological and pathological conditions for prognosis, prevention, diagnosis of diseases and determination of the correct therapeutic tactics [2]. The US National Cancer Institute emphasized three main goals of personalized medicine — to prevent, diagnose, and treat diseases using specific information about each patient's genes, proteins, and environment [3]. The Concept of 4P Medicine is often referred to in the context of PM. The concept is based on four ideas, each beginning with the Latin letter "P" (Fig. 1). These four concepts include prediction, prevention, personalization and participation [4]. In other words, the 4P-medicine concept predicts and prevents diseases, while a patient is an equal partner of a physician and should be involved in the treatment and decision-making process. Current capabilities of PM facilitate the transition of a health care system based on disease treatment to a system of "preventive health care". Based on numerous works and scientific data, the Russian Federation has issued regulatory documents that provide new opportunities for implementing diagnostic and treatment methods: the Order of the Ministry of Health of the Russian Federation dated April 24, 2018, No. 186 "On Approval of the Concept of Predictive, Preventive and Personalized Medicine" [5], as well as the Decree of the President of the Russian Federation dated June 6, 2019, No. 254 "On the Strategy for the Development of Healthcare in the Russian Federation for the period until 2025" [6]. Undoubtedly, PM requires effective implementation of advanced achievements in genomics, innovative bioinformatics, modern diagnostics and interdisciplinary approach to a patient to achieve an optimal effect of therapy and disease prevention [7].

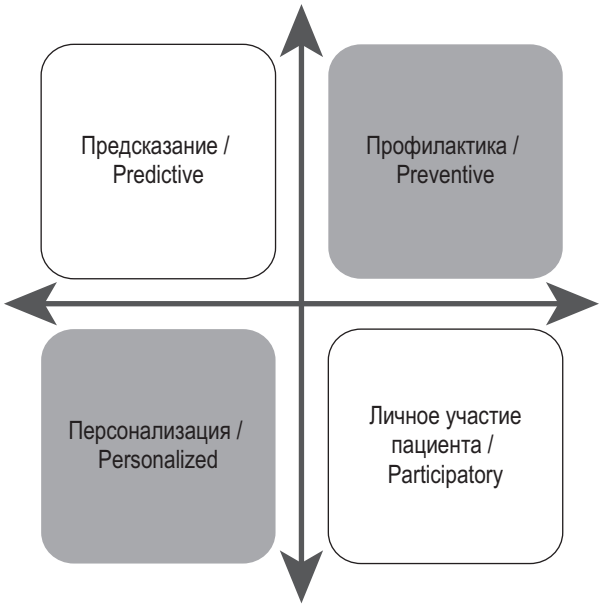

Fig. 1. 4P-medicine concept

Рис. 1. Концепция 4P-медицины

BASIC LABORATORY METHODS IN PERSONALIZED MEDICINE

Rapid development of technologies and innovations in molecular diagnostics and genomic analysis have expanded understanding of molecular pathogenesis of diseases and interpretation of findings in genome sequencing. Applying new technologies in the field of molecular medicine underpins an individualized approach at all stages of medical care. The ability to identify individual predisposition to certain diseases and potential response to therapy is a necessary step for proper implementation of optimal strategies for disease prevention and treatment [8, 9]. The main laboratory tool of PM is molecular genetic testing. DNA diagnostic methods can include both examination of common point mutations for a particular gene and whole genome sequencing. Polymerase chain reaction (PCR)-based test systems have been developed for most molecular disorders. However, comprehensive genomic profiling methods have also been developed to assess abnormalities in hundreds of target genes. Such tests are of limited use in clinical practice due to the high cost and complexity of the analysis methodology, but they have a high potential for identifying nonspecific targets and prescribing "off-label" therapy [10]. When searching for gene copy number changes or translocations, *in situ* hybridization methods, methyl-specific PCR to assess gene methylation, etc. are used [11]. A promising area of PM is studying epigenetic modifications, which makes it possible to identify potentially modifiable factors affecting the risk of disease development [12].

Another separate area of applying personalized medicine in modern medical practice is cell technologies, which are already being actively used in the field of regenerative medicine and therapy of hematological diseases [13].

PERSONALIZED APPROACH IN ONCOLOGY TREATMENT

Over the past 30 years, the methods of diagnosis and treatment of malignant neoplasms (MNs) have advanced significantly. However, achieving a complete cure for a cancer patient is a very difficult challenge. As we know, MNs are clinically and genetically heterogeneous diseases that are able to adapt to internal and external conditions [14]. For this reason, the search and implementation of new approaches to diagnose and treat this group of diseases is an urgent task [15].

Diagnostic markers have auxiliary value for clinical diagnosis (e.g., the presence of chimeric *BCR/ABL* gene as a marker of chronic myelogenous leukemia); predictive markers indicate effectiveness of response to specific drug treatment, including targeting or immunotherapy; prognostic markers determine the outcome for a patient in case of no treatment [16]. In particular, when a patient is diagnosed with breast cancer (BC) and has other relatives of 1st and 2nd degree with BC or ovarian cancer, the patient should first search for the most frequent pathogenic variants of *BRCA1* and *BRCA2* genes, rather than starting a search for genetic causes by means of high-cost analysis genome sequencing [17].

The choice of DNA testing and biomaterial is usually based on a clinical objective. Up to 10% of all MNs are hereditary and develop as a result of germline mutations in oncogenes and tumor growth suppressor genes. In such cases, they are referred to as hereditary tumor syndromes (HTS). Other MNs occur sporadically due to accumulation of molecular abnormalities in somatic cell genetic code during an individual's life [18]. Thus, molecular diagnostic techniques focus on the study of germinal and somatic aberrations. DNA-diagnostics of germinal mutations allows to identify a group of patients of high hereditary risk for developing MNS within HTS [19]. Currently, more than 150 HTSs with different risks for MN development have been described. The spectrum of tumors and their localization are also extremely diverse. Patients with established HTS require individualized tactics of dynamic examination using additional methods of examination to detect malignant tumors. In some syndromes, such as adenomatous polyposis syndrome, surgery is the only way to avoid cancer development [20]. In addition, taking into account patient's genotype, surgical and drug treatment tactics may also differ significantly.

Currently, the main trend in the treatment of MN is aimed at transition from tumor-associated therapy, which takes into account the histological type of cancer, to tumor agnostic therapy, which is prescribed by molecular characteristics of the tumor.

A PERSONALISED APPROACH IN MANAGING PATIENTS WITH CARDIOVASCULAR DISEASE

Many studies have reported that variability in clinical cardiovascular disease (CVD) is influenced by hereditary factors and risk factors [21].

Examples are familial predisposition to myocardial infarction, atrial fibrillation and heart failure. The American Heart Association reviewed genetic aspects of three categories of cardiovascular conditions: atherosclerosis and myocardial infarction, elevated cholesterol and other lipid metabolism disorders, and blood pressure and hypertension. Many polymorphisms in various genes were found to correlate with an increased likelihood of coronary heart disease. From 2012 to date, genetic studies are presented in the European Society of Cardiology guidelines for the treatment and diagnosis of CVDs [22].

Hereditary cardiomyopathies (HCM) constitute a phenotypically and genetically heterogeneous group of diseases leading to heart failure, with a high probability of sudden cardiac death. Genetic panels have been developed for these diseases. However, half of the identified genetic markers associated with HCM lacks enough evidence to consider them as strongly associated with underlying disease aetiology [23].

Currently, an evidence base has been developed for the following clinical tasks: making or confirming a definitive diagnosis of inherited HCMs. An increasing number of pharmacogenetic tests are being introduced to predict

patients' responses to commonly used drugs and to select drug dosing regimens [22].

PM is very limited in this field since there are many studies conducted, but the literature evidence is contradictory and inconclusive. This may be attributed to inappropriate quality of researches, different drug response phenotypes or patient populations, subtlety of functional effects of polymorphisms, etc. [24]. Applying genomic technologies, as well as other advanced complex methods of identifying the molecular basis of disease pathogenesis, will eventually make it possible to gain a closer understanding of HCM development.

PERSONALISED APPROACH IN DIAGNOSING GASTROENTEROLOGICAL DISEASES

Molecular genetic diagnostics is being actively introduced into gastroenterologist's practice [25]. In order to more precisely determine prognosis and course of autoimmune diseases of the gastrointestinal tract (GIT), such as autoimmune gastritis (AIg), hepatitis, achalasia cardia, specialists actively explore genetic variations in the major histocompatibility complex (HLA). Establishing markers of autoimmune diseases (AIDs) will help to develop new therapeutic approaches.

Autoimmune gastritis (AIG) is an immune-mediated disease. The etiology of AIG is still unclear, thus the use of extended genetic tests to understand the pathogenesis is relevant. To date, no genetic markers associated exclusively with AIG have been described, making diagnosis by molecular genetic methods difficult. Genetic studies such as analyses of polymorphisms in *IL-1, IL-10, IFNγ, TNFα* or *HLA* genes, as well as extended full-exome or full-genome sequencing, have identified some genetic markers of susceptibility to AIG in different populations worldwide. For instance, the study "Genetic determinants of autoimmune gastritis" [26] determined that *HLA* DRB1 *04 and *HLA* DQB1 *03 alleles may be risk factors for AIG in Finns. Patients with AIG are at high risk of developing MNs and neuroendocrine tumors [27]. The risk of developing MNs in this cohort of patients is 7 times higher (28). The use of genetic testing makes it possible to determine these risks not only for patients but also for their relatives, which may serve as a basis for preventing complications of AIG and gastric MNs.

Loss of immunological tolerance to commensal intestinal microflora caused by environmental factors plays a key role in chronic inflammation in genetically predisposed individuals [29]. Major genetic factors associated with the risk of inflammatory bowel disease (IBD) include *IL23R, NOD2, PTPN22* and *HLA*. IBDs which include ulcerative colitis (UC) and Crohn's disease (CD) are characterized by unknown aetiology, unpredictable course and lack of improved treatments. A promising approach to diagnosing and assessing the prognosis of IBD is the comparison of genetic markers associated with different manifestations of the disease course [30]. According to the literature, it is known that the *rs10761659* polymorphism may be a protective factor for both UC and CD in Caucasians, while the *rs10995271* variant may be a risk factor for UC but not CD in Caucasians. Meanwhile, some polymorphisms in the *NOD2* and *PTPN22* genes are risk factors for CD, however, at the same time, they have protective effects for UC. These variants have low or medium penetrance, which emphasizes the complexity and polygenic nature of these diseases [31].

There is some evidence for regulation of microRNA expression by epigenetic mechanisms such as DNA methylation, histone modifications and microRNA modifications [32].

Epigenetic modifications of DNA have been reported to influence the pathogenesis of IBD. DNA methylation is the most studied epigenetic modification. DNA methylation-based technologies will help identify unique markers in patients with inflammatory bowel disease, which may be useful as part of identifying predictors of therapeutic response. Several studies have shown a difference in microRNA expression in tissue and blood samples in patients with IBD compared to healthy individuals, suggesting that microRNAs may be considered as new biomarkers of these diseases [33].

In addition to the above forms of polygenic GI diseases, it is important to determine a precise molecular cause of monogenic pathologies within the framework of PM. Genetic analyses are actively used in clinical practice to establish the diagnosis of hereditary hemochromatosis, Wilson–Konovalov disease, chronic pancreatitis, etc. [34, 35]. Timely genetic diagnosis of these diseases allows us to determine the prognosis, select effective treatment and take pre-

ventive measures against the risk of complications in such patients.

Currently, pharmacogenetics in gastroenterology is being actively developed. Protocols of some clinical guidelines affirm that diagnosis and choice of treatment are based on genetic data. According to the updated Maastricht VI recommendations [36], it is advisable for all patients to determine sensitivity to antibiotics in order to rationalize their use. Molecular genetic testing of *H. pylori* resistance seems to be very promising. The method has high sensitivity and specificity, does not require large time expenditures and can be applied routinely. It makes it possible to assess the prevalence of antibiotic resistance in previously untreated patients and the impact of any resistance on the effectiveness of modern eradication methods. A substitution at codon 91 of the *gyrA* gene increases the risk of resistance to levofloxacin by 125,427-fold compared to the wild type, while a substitution at codon 87 of the *gyrA* gene increases the risk of resistance to levofloxacin by 70,156-fold [37].

The gut microbiome plays a key role in the pathogenesis of several diseases, as well as in regulation of the immune, endocrine and nervous system and defense against pathogens. There is increasing evidence of gut microbiota involvement in the pathogenesis of many other diseases, such as type 1 diabetes mellitus, IBDs, autoimmune pathologies. Human microbiome research as well as whole-genome studies are contributing to new advances in the diagnosis, treatment, and prevention of human diseases. The goal of microbiome analysis is to examine all bacteria in feces using next-generation sequencing by determining the bacterial *16S* RNA gene. By using sequencing data, the opportunity arises to categorize gut bacteria and draw conclusions regarding health. Frequently, these results can reveal a correlation between clinical findings and the microbiota. There is no doubt that more information will soon become available with regard to the intestinal microbiome in disease diagnosis and therapy selection.

PHARMACOGENETICS AS A TOOL FOR PERSONALIZED MEDICINE

Pharmacogenetics is a branch of PM. It is aimed at adapting selection of drugs and their dosage on the basis of genetic characteristics of a patient. Currently, a number of genetic markers are known — polymorphic variants of drug biotransformation genes, transporter protein genes, as well as genes of drug target molecules. Cytochromes CYP2C9 and CYP2C19 are involved in metabolism of many drugs [38]. There are several allelic variants of genes encoding these enzymes. Nonsteroidal anti-inflammatory drugs (NSAIDs) are a widely used group of drugs; however, undesirable drug reactions from the GI tract are a significant problem during their intake. Genetic factors, in particular *CYP2C9* gene polymorphism, may contribute to the risk of adverse drug reactions. Proton pump inhibitors (PPIs): omeprazole, lansoprazole, rabeprazole are widely used for preventing undesirable adverse reactions from the GI tract. The effectiveness of these PPIs depends on the polymorphism of the *CYP2C19* gene [39]. Currently, there are numerous coordinated international efforts aimed at overcoming the existing barriers to implement pharmacogenetics methods in clinical practice.

CONCLUSION

Personalized medicine is a modern approach to patient management based on individual approaches in treatment. It consists of combining modern technologies, traditional experience and study of individual characteristics of a patient. Personalization allows to improve the quality of medical care both through prevention and early diagnosis of diseases, as well as to increase the effectiveness of drug therapy and significantly reduce material costs of treatment.

Even now, some areas of medicine cannot be imagined without methods of a personalized approach: oncology, therapy, cardiology, family planning, especially in the concept of a multidisciplinary specialized hospital. At the same time, the results of numerous international scientific studies allow using these approaches in medical practice on a larger scale. It is necessary to emphasize the importance and necessity of mutual understanding and constructive dialogue between a doctor and a patient, since the object of this approach is not the disease, but the patient. Patient participation can be ensured by implementing the provisions of informed consent with careful explanation of the need to expand the conducted examination. A personalized approach to patient care is currently one of the

most promising trends in medicine and requires not only scientific resources but also organizational efforts, since it becomes a new doctrine of modern health care.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published was agreed to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

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