PHARMACOGENETIC TESTING: ETHICAL CHALLENGES AND SOLUTIONS

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The article reviews ethical and legal hurdles of integrating pharmacogenetic testing into personalized medicine. The aim of this publication was to systematize key ethical problems in clinical pharmacogenetics and find possible solutions in Russian legislation. It was an analytical review study that used a systematic analysis of scientific literature combined with comparative legal analysis of national/foreign regulations. The risks of confidentiality violations and unauthorized reuse of genetic data, difficulties in obtaining informed consent and interpreting incidental findings, and a threat of genetic discrimination from employers and insurance companies are reviewed. It has been shown that a high cost of genetic tests increases the inequality of access to medical technologies and highlights major social injustice issues. It is concluded that clarifying the legal status of genetic data, developing special mechanisms to protect patients from stigmatization and discrimination, and introducing educational programs on pharmacogenetics and genetic counseling for medical professionals are essential.

Keywords: pharmacogenetics, genetic passport, personal data protection, genetic discrimination

Contribution of authors: Demarina SM — selection and analysis of literature, writing the text of the manuscript; Sirotkina AM — literature analysis, editing the manuscript text; Usolkin AA — selection and analysis of literature, writing the text of the manuscript; Dombrovskaya ED — literature analysis, editing of the manuscript text.

Compliance with ethical standards: This work is a review and does not involve human or animal subjects. The approval of the ethics committee was not required.

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Received: 11.12.2025 **Accepted:** 18.12.2025 **Published online:** 27.12.2025

DOI: 10.24075/medet.2025.027

ФАРМАКОГЕНЕТИЧЕСКОЕ ТЕСТИРОВАНИЕ: ЭТИЧЕСКИЕ ВЫЗОВЫ И ПУТИ ИХ РЕШЕНИЯ

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Статья посвящена этическим и правовым аспектам внедрения фармакогенетического тестирования в клиническую практику персонализированной медицины. Цель работы — систематизировать ключевые этические проблемы клинической фармакогенетики и обозначить возможные пути их урегулирования в российском здравоохранении. Исследование выполнено в формате аналитического обзора с использованием методов системного анализа научной литературы и сравнительно-правового анализа национальных и зарубежных нормативных актов. Рассмотрены риски нарушения конфиденциальности и несанкционированного вторичного использования генетических данных, сложности получения информированного согласия и интерпретации «случайных находок», а также угроза генетической дискриминации со стороны работодателей и страховых компаний. Показано, что высокая стоимость генетических тестов усиливает неравенство доступа к медицинским технологиям и порождает вопросы социальной несправедливости. Сделан вывод о необходимости уточнения правового статуса генетической информации, разработки специальных механизмов защиты пациентов от стигматизации и дискриминации, а также внедрения образовательных программ по фармакогенетике и генетическому консультированию для медицинских работников.

Ключевые слова: фармакогенетика, генетический паспорт, защита персональных данных, генетическая дискриминация

Вклад авторов: С. М. Демарина — подбор и анализ литературы, написание текста рукописи; А. М. Сироткина — анализ литературы, редактирование текста рукописи; А. А. Усолкин — подбор и анализ литературы, написание текста рукописи; Е. Д. Домбровская — анализ литературы, редактирование текста рукописи.

Соблюдение этических стандартов: данная работа является обзорной и не предполагает проведения исследований с участием людей или животных. Одобрение этического комитета не требовалось.

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Статья поступила: 11.12.2025 **Статья принята к печати:** 18.12.2025 **Опубликована онлайн:** 27.12.2025

DOI: 10.24075/medet.2025.027

Modern medicine is undergoing a paradigm shift: from a standardized empirical approach of “one drug for all patients” to personalized therapy based on the individual characteristics of each patient. Pharmacogenetics ensures this transition. According to the research, genetic polymorphism accounts for 20 to 95% of patient variability in individual response to drugs. It means that two patients receiving the same dose of medication may experience different effects: one can have a complete recovery, whereas the other one can develop a serious adverse reaction. Pharmacogenetic testing for carriage of allelic variants of cytochrome P450 genes (CYP2C9, CYP2D6, etc.) has already been included in clinical guidelines and protocols of leading medical organizations.

To select the dose of Indirect-acting anticoagulants, data on the polymorphism of the CYP2C9 and VKORC1

genes are required. Thus, it is possible to select the optimal dose of warfarin, reducing the risk of bleeding by 30–40%. Without the test, a long period of dose titration is required, the cost of INR control increases, and the likelihood of thromboembolic complications is higher. In oncology, determining the status of the DPYD, TPMT, and NUDT15 genes is critically important for preventing fatal toxic reactions to chemotherapy [1,2]. Rapid genetic advancements often outpace legal and ethical frameworks. The genetic passport of a patient creates unprecedented bioethical challenges related to the storage and protection of "sensitive" genetic information, interpretation of results, accessibility of technologies and fairness of their distribution. The results of the genetic test are unchanged throughout life. They relate not only to patients, but also to their blood relatives and may have a prognostic value that goes beyond the current disease or the reason for the test.

The review purpose is to systematize the key ethical and legal hurdles of clinical pharmacogenetics and identify possible ways to resolve them.

CONFIDENTIALITY AND PROTECTION OF GENETIC DATA

The risk of unauthorized access to genetic information and its leakage belongs to major, acute ethical and practical challenges in pharmacogenetics. Genomic data are exceptional as they are unique for every person and allow to identify a personality even following formal anonymization. Unlike other types of medical information, genetic data disclose information not only about the patient, but also about his biological relatives, which creates additional ethical obligations to third parties [3, 4]. In the Russian Federation, genetic information is subject to Federal Law on Personal Data (No. 152-FZ) and is classified as a special category of personal data requiring the highest protection. There are gaps in legislation regarding the secondary use of genetic data for scientific purposes and their transfer [4, 5].

Biobanks and centralized databases of pharmacogenetic research create a dilemma between the need for an open exchange of scientific data under Open Science and the fundamental right of a patient to privacy and confidentiality of genetic information. Disclosure of information about a genetic predisposition to socially significant diseases (mental, oncological, neurodegenerative ones) can cause irreparable damage to a person's reputation and social status, and lead to refusal of employment or training. Ownership of genomic data is a complex issue. Who is the owner and manager of the genomic data — the patient, the medical organization that conducted the testing, or the laboratory? Ethical expertise requires a clear distinction between the rights of access and use of information for different purposes (personal use, scientific research, commercial purposes, government regulation), especially when using cloud technologies for storing data and transferring test results to third parties. Russia needs to develop specific laws for genetic info similar to the EU's GDPR (General Data Protection Regulation), which clearly defines the rights of patients, obligations of data warehouses and penalties for violations [6].

THE PROBLEM OF INFORMED CONSENT AND INCIDENTAL FINDINGS

The classic model of informed consent is not adapted for genetic testing. Patients struggle to understand probabilistic pharmacogenetic results, especially when they are more related to predispositions rather than diagnoses. Clinical practitioners struggle with complex genotypes especially in the presence of rare or previously undescribed allelic variants. How can I explain to a patient that he is a carrier of a CYP2D6 intermediate metabolizer and what it means for his treatment? Specialized genetic counseling and advanced genetic testing are often limited in Russia's public healthcare.

Incidental findings in research are ethically complex. Pharmacogenetic testing for the DPYD gene (to select a safe dose of chemotherapeutic drugs) can reveal genetic variants that, while not impacting drug metabolism, might signal predispositions to other serious hereditary conditions (familial hypercholesterolemia, early Alzheimer's disease). But do doctors have a legal and ethical duty to inform patients about significant, unexpected findings, even if not initially sought? And what should I do if there is no effective treatment or prevention for the identified predisposition? Can such information cause psychological harm to the patient, leading to unreasonable anxiety? International ethics committees (Nuffield Council on Bioethics, American Medical Association) tend to recognize the patient's right to "not know" about such findings, however, in clinical practice, this right often conflicts with the classic principle of medical ethics "do no harm" and the physician's duty to act in the patient's best interests [7, 8]. These issues are relevant in the field of reproductive medicine. When conducting preimplantation genetic testing to select an embryo without a hereditary disease (cystic fibrosis), the analysis may reveal that both partners are carriers for hemophilia B. Information about the carrier does not affect the IVF decision, but it is important for the future health of patients and their children. Should the doctor share this information? The answer is obvious — yes, but it takes time, a trained genetic counselor, and clear protocols of action [7, 8].

RISKS OF GENETIC DISCRIMINATION

The fear of genetic discrimination is a significant social and psychological hurdle to pharmacogenetics adoption in clinical practice. Genetic discrimination is defined as infringement of the rights of an individual based on information about his genome. In the context of pharmacogenetics, this can be manifested as refusal of insurance companies to conclude voluntary medical insurance or life insurance contracts, or in an increase in insurance premiums for people with an unfavorable metabolic profile, which implies high treatment costs [9].

The problem of labor discrimination is urgent. Employers may be interested in screening employees to identify predisposition to occupational diseases or predict frequent sick leaves. For example, carrying slow acetylator (NAT2) alleles significantly increases the risk of toxic effects from certain industrial chemicals. From an ethical point of view, it is unacceptable to use such data to refuse employment. In the United States, the GINA (Genetic Information Nondiscrimination Act) federal law has been in force since 2008, which explicitly prohibits the use of genetic information to make decisions about hiring, promotion, or dismissal. Similar laws exist in most developed countries of Europe and in Canada. The Russian Federation still lacks a specific law for genetic discrimination, although Article 19 of the Constitution of the Russian Federation guarantees equality of rights and freedoms regardless

of origin and other circumstances. It is necessary to develop legal mechanisms that clearly prohibit the use of pharmacogenetic data by third parties (insurers, banks, employers, educational institutions) and provide for real penalties for violations [9, 10].

SOCIAL JUSTICE AND ACCESSIBILITY OF TECHNOLOGY

Personalized medicine and pharmacogenetic testing create an ethical issue of inequality in healthcare based on access to genetic technologies. The cost in commercial laboratories varies from 5 to 50 thousand rubles, depending on the number of analyzed genes and technology. It is critical that most pharmacogenetic tests, even those with proven clinical significance (WHO classification levels of evidence A and B), are not covered by compulsory health insurance programs. It means that not all groups have an equal access to healthcare. Well-off patients receive access to safe and effective personalized therapy based on the results of pharmacogenetic testing and avoid dangerous adverse reactions, while socially vulnerable patients continue to be treated by empirical trial and error, at risk of adverse outcomes, including hospitalization, disability and mortality [11, 12]. The ethical principle of equity states that innovative and effective medical technologies should be available to all patients in need, regardless of their socio-economic status. This is especially true in oncology, cardiology, and psychiatry, where the cost of medical error or suboptimal selection of therapy is critically high.

CONCLUSIONS

Pharmacogenetics changes modern medicine by offering tools to personalized treatment. However, technological progress should not outpace ethical thinking. In our opinion, protection of genetic data confidentiality, prevention of discrimination, and ensuring equal access to innovations are still the key challenges.

To solve these problems, the following steps are necessary:

1) **Improvement of legislation:** consolidation of genetic information status and a direct ban on genetic discrimination.
2) **Medical education:** professional development for medical professionals in test interpretation and ethical counseling of patients.
3) **Infrastructure development:** creation of secure national biobanks and integration of validated tests into clinical guidelines and standards of care.

The balance between innovations and human rights protection is the main condition for ethically sound personalized medicine and pharmacogenetics in the Russian Federation.

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