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MODERN ASPECTS OF PHARMACOGENETICS: FROM THEORY TO PRACTICE IN PERINATOLOGY AND PEDIATRICS

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Summary

Pharmacogenetic testing (PT) is a modern tool in the doctor's practice, which allows to make the right clinical decision in difficult cases, when the expected result of medical measures is not achieved. It is clear that certain metabolic processes in the human body, as well as a number of diseases, are genetically programmed. Therefore, despite the large number of unexplained mechanisms of individual response to drugs, genetic testing occupies one of the leading positions among methods of selecting drug therapy in complex clinical cases.

However, the successful implementation of this promising method must overcome a number of obstacles, including limited evidence of effectiveness, ethical, legal, and social factors. The purpose of this review is to highlight modern concepts and practical aspects of the use of PT. The article addresses the problem of expanding the indications for PT when it is not limited to preventive use only. PT allows to identify drugs associated with an increased risk of causing side effects, with a narrow therapeutic index, to reduce the number of drugs in treatment, to choose the dosage of the drug. A variety of PT platforms can be used in a physician's office, which can be broadly divided into two categories – genotyping-based tests and sequencing-based tests. Depending on the gene being tested, different algorithms can be used to generate results. Some gene variants can be described in terms of metabolic activity or general function, while others can only be described as present or absent. Results for gene variants can also be reported as normal, intermediate or low function for the corresponding gene. Pharmacogenetic clinical decision support systems (CDSS) are computer-based systems that assist healthcare providers in prescribing medications at the point of care. These systems provide physicians and other healthcare providers with appropriately filtered pharmacogenetic information, such as drug-gene interaction alerts or patient-specific treatment recommendations. A pharmacogenetic CDSS can either be integrated into a local hospital information system or used as a stand-alone application such as a web service or mobile application. Pharmacogenetics can increase the quantity and quality of information available to pregnant women and their physicians about medication use during pregnancy. Implementation of PT recommendations into routine pediatric practice requires carefully coordinated strategies at the national, regional, and health system levels. To date, pharmacogenetics provides mosaic information on the association between response to drug therapy and genetic background. It is expected that the next step will be a study in a larger group of participants to investigate the contribution of epigenetic factors and to provide clinical recommendations for adjusting or selecting therapy based on the personal characteristics of the patient.

Key words: *Pharmacogenetic Testing; Genotyping; Sequencing; Clinical Decision-Making Systems; Pregnant Women and Children.*

Introduction

Pharmacogenetics is a branch of medicine that studies the genetically determined responses of the body to the administration of drugs. The term «pharmacogenetics» was first proposed in 1959 by the German scientist Friedrich Vogel, who drew attention to the involvement of genetic factors in the body's response to external substances, especially drugs [1].

Today, it is generally known that the response of the human body to treatment with pharmaceutical drugs is often controlled by genes encoding proteins that participate in the metabolism of these drugs, their transformation, and determine the peculiarities of their pharmacokinetics and pharmacodynamics [2]. The disadvantage of a significant part of research in the field of pharmacogenetics is the incorrect interpretation of results due to biased experimental design, insufficient observation period, small sample size, disregard of population differences, etc. Therefore, the challenge of today is the need to develop and conduct valid research in this field.

In clinical practice, the physician adheres to national standards and protocols of specialized medical care based on the principles of evidence-based medicine [3]. However, the physician, guided by alternative drugs that are not prohibited by the instructions for use, may significantly change the therapy, taking into account the individual needs of each patient, his financial capabilities, preferences and lifestyle. Another reason for changing the therapy is side effects and lack of effectiveness of drugs. Despite the fact that the causes of resistance to the action of drugs are still not studied, there is an assumption about the genetic determinism of this phenomenon, which has already been proven by the example of several genetically determined types of nitrate metabolism in the body and explains the different duration of

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tolerance to drugs of the nitrate group during the treatment of cardio-vascular diseases. [4]. It is clear that certain metabolic processes of the human body, as well as a number of diseases, are genetically programmed. Therefore, despite the large number of unexplained mechanisms of individual response to drugs, genetic testing occupies one of the leading positions among the methods of drug therapy selection in complex clinical cases.

This article discusses the achievements of pharmacogenomics in the field of health care and personalized medicine. Also, this review summarizes information about pharmacogenomics and modern directions of pharmacogenetic testing, its clinical application, practical approaches, and aims to outline the problems and drawbacks of this method.

Technical features of pharmacogenetic testing

Pharmacogenetic testing (PT) consists in determining the genetic characteristics of patients in order to select an effective drug, its effective dose and determine the treatment regimen. It should be noted that PT has been available for clinical use for about 20 years. A variety of PT platforms can be used in a physician's office and can be broadly divided into two categories – genotyping-based tests and sequencing-based tests.

Genotyping-based tests identify specific gene variants that are associated with a particular drug response and predict the phenotype of the patient/subject based on the identified genotype of the patient/subject. The use of such tests is particularly effective for well-studied and common gene variants. The disadvantage is that the rate of such gene variants usually varies between populations. Therefore, the safety and efficacy of drug use may vary greatly depending on the ethno-geographic origin of the patient [5]. In addition, tests based on genotyping cannot detect gene variants that were not included in the original design of the test, which significantly reduces the ability to predict the efficacy of a specific drug. Another disadvantage is that the determination of the phenotype may be incorrect. For example, a patient/subject is tested for the CYP2C9 gene only for the rs1799853 variant (also known as the CYP2C9*2 variant). The result of this test can determine the genotype *1/*1. However, this patient/subject is a carrier of the *3/*3 genotype for the rs1057910 variant of the CYP2C9 gene (also known as the CYP2C9*3 variant), which is not included in the design of this PT. Therefore, this patient/subject will be erroneously identified as a «wild-type» carrier (or a carrier of the *1/*1 genotype) and, accordingly, will be predicted to be a «normal metabolizer,» i.e., to have an enzyme with normal activity [6].

Sequencing-based tests, on the other hand, can detect all variants anywhere in a sequenced region of a gene, including new ones not previously identified. The use of this type of test is particularly effective for highly variable genes. However, this type of test is characterized by a difficult interpretation of the results because the identified gene variants often have an unknown/conflicting effect on drug metabolism or are generally newly detected with uncertain effects. There may also be technical difficulties related to pseudogenes, gene conversion, etc. [7]. Another major disadvantage of sequencing-based PT is its high cost. Nevertheless, the use of both types of tests in modern clinical practice for diagnostic and preventive purposes (in phenotypically healthy individuals with risk factors) is increasing.

It is clear that there are differences in the results of PT laboratories using different methods. However, you should be aware that results from laboratories using the same methods may differ. For example, laboratories using genotyping-based tests may identify different variants of the same gene. And laboratories using sequencing-based tests may sequence different regions of the same gene. Such a difference in laboratory results is not a false result of PT, but is related to the development of new modern testing methods and their lack of proper standardization [7].

Time and the contingent for pharmacogenetic testing

In the past, testing was done only when a specific treatment was to be prescribed (in which case the test could become the basis for drug selection and dosing) or when the patient reported a specific adverse reaction to the drug in their medical history. Since such a PT is performed when a specific patient is referred and there is a need to prescribe certain medications, it is called a «point-of-care test» [8]. In this case, the timing of the test is very important. In most cases, the time required to perform PT in the laboratory is several days to several weeks. In some cases, such time frames are unacceptable for effective implementation in daily clinical practice. An example is the scheduling of the antiplatelet drug clopidogrel, which is based on the determination of variants of the CYP2C19 gene, where the patient's genotype must be known before starting therapy [9]. To solve this problem, biotech companies are developing special genotyping platforms that allow rapid analysis of samples directly at the point-of-care [10]. Despite the success of the use of such types of PT, certain problems remain, particularly regulatory and legal, due to their translation from scientific research to everyday clinical practice [9].

Preventive PT is therefore becoming more and more common. When it is performed, data on the presence of certain pharmacogenetic markers in the patient/subject are collected prospectively and stored for possible future use. Among the advantages of this type of PT are the following: the vast majority of patients are carriers of at least one effective genotype; a significant reduction in the burden on laboratories performing PT compared to the reactive strategy; savings in money and resources; PT results are immediately available at the point-of-care; there is less uncertainty in the indications for PT, which in turn will lead to the disappearance of barriers to the application of pharmagenomics in clinical practice [9, 11]. Ideally, PT data will be included in the patient's electronic profile and will be available to physicians and pharmacists when prescribing a certain group of drugs. On the other hand, there is the question of the best time to perform PT. In particular, there is currently a lack of guidelines and protocols to help clinicians determine the indications for testing. Insurance coverage of preventive and reactive PT is also problematic, so this fact plays a significant role in medicine in developed countries

and may negatively influence a physician's decision to perform PT [6].

The survey conducted showed a high interest of patients in pharmacogenetic testing [12]. According to the results of this survey, patients are particularly interested in receiving recommendations based on PT results to reduce side effects of drugs and choose the right therapy. However, the cost of testing, insurance coverage, and availability of test results are significant limitations [12]. Given the uncertainty of some issues related to PT, patients should be properly informed about all testing options.

In summary, PT allows: 1) identify drugs with an increased risk of causing side effects; 2) identify drugs with a narrow therapeutic index; 3) reduce the number of drugs during treatment; 4) select the dosage of the drug [13]. At the same time, FT will be ineffective for predicting: 1) the occurrence of all possible side effects of the drug; 2) the risk of a specific side effect for all drugs, 3) the risk of complications [13]. That is, PT provides an opportunity to make a decision regarding the choice of a drug and the selection of a treatment strategy.

Online sources

Due to the rapid emergence of innovative technologies in genetic medicine, it is important to obtain timely information regarding changes in testing recommendations or interpretation of PT results. This task can be facilitated by a number of modern Internet resources (Table 1).

Table 1

The most popular internet sources in the pharmacogenetic sector

Name of the source, page URL	Description
The Clinical Pharmacogenetics Implementation Consortium (CPIC), https://cpicpgx.org/	An international consortium specializing in the publication of genotyping-based drug use guidelines to help clinicians understand the potential of using available genetic test results for optimization of drug therapy
The Genetic Testing Registry (GTR), https://www.ncbi.nlm.nih.gov/gtr/	A free resource that provides a comprehensive repository of comprehensive genetic testing information provided and maintained by laboratory providers
The Pharmacogenomics Knowledge Base (PharmGKB), https://www.pharmgkb.org/	An online knowledge base responsible for aggregating, curating, integrating, and disseminating data on the impact of gene variants on human drug response.
The Implementing GeNomics In pracTicE (IGNITE), https://gmkb.org/ignite-gdp/	A network designed to improve the use of genomic medicine by supporting the incorporation of genomic information into clinical practice and exploring methods for effective implementation, dissemination and sustainability in a variety of clinical settings
The Pharmacogenomics Clinical Annotation Tool (PharmCAT), https://pharmcat.org/	A software tool for extracting variant recommendations from a genetic dataset (represented as vcf), interpreting variant alleles, and generating a report with genotype-based prescribing recommendations that can be used to inform patient treatment decisions.
The Drug-Gene Interaction Database (DGIdb), https://www.dgidb.org/	A web resource that provides drug-gene interaction information from publications, databases, and other web sources. Drug, gene, and interaction data are normalized and clustered into conceptual groups. The information contained in this resource is accessible to users through a simple search interface.
The Pharmacogene Variation Consortium (PharmVar), https://www.pharmvar.org/	An international group of experts that supports a standardized system of nomenclature of genes included in PT.

In addition, there are lesser known, local resources. For example, the African-American Cardiovascular Pharmacogenomics Consortium (ACCOuNT), which aims to study the feasibility of implementing preventive PT in African Americans [14]. Maintaining and developing this type of resource can be a valuable tool for studying future or lesser-known pharmacogenetic interactions.

How to choose the test?

Once the clinician has decided to order a PT, the next important step is to determine the type of test and select the appropriate clinical laboratory to perform the test [15]. Depending on the circumstances, internal testing may be available at the hospital, or PT may be performed at an external laboratory. Although medical geneticists are well aware of the genetic testing options available, for many physicians PT may be one of the first genetic tests they order. Therefore, one of the barriers to choosing the appropriate test may be finding information about testing options. Therefore, it is extremely important to create specific catalogs that include information about laboratories performing PT, their panels, methods, and testing timelines.

When testing for a specific indication, a patient may only need to be tested for one or a few genes. However, due to

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cost reductions, it is possible to obtain a panel that provides information on many genes and may influence future therapy for about the same cost as testing a single gene. In this case, the physician must consider whether the panel includes the gene(s) needed, whether the patient's insurance covers both options equally, whether the two tests are equivalent (i.e., whether the panel includes the same options as the single-gene test), and the patient's personal preference. It should also be noted that the PT gene panel may be more expensive than the single-gene test, but it ensures that concomitant medications are taken into account.

The gene panels used in PT are very diverse and are usually grouped into a specific category. Most panels include a few of the best-studied and «most powerful» genes. The panel may contain combinations of single nucleotide variants of genes selected as a result of some prospective study review. It is worth noting that a panel containing many genes may not necessarily be relevant to the patient, as not all variants have the same clinical significance. Some gene variants included in the panel may be extremely rare outside of certain populations, but may be quite common in others. For example, the HLA-B*15: 02 variant, which is associated with an increased risk of serious adverse events in patients prescribed carbamazepine, has an allele frequency of 0.04 % in Europeans and 6.88 % in patients of East Asian origin [16]. Therefore, the panel will be more useful to the patient if it analyzes gene variants that more closely match the patient's ethnicity.

In addition to the content of the panel, the type of biomaterial tested (buccal swabs, saliva, blood, etc.) should be considered, as the method of collection may pose a problem for the patient. Access to the results and the methods used to obtain them are also factors to consider, as some panels only provide raw genetic data. Finally, the potential cost of testing should be considered.

Interpretation of the results of pharmacogenetic testing

As mentioned above, another potential source of difficulty is the lack of standardization in the expression of results. Some laboratories may report only the identified genotypes and phenotypes, while others may also provide a list of drugs affected by the specific identified genotypes (with or without dosage recommendations). However, such pharmacogenomic reports may contain more than 300 drugs, which are categorized according to the risk of adverse effects or lack of efficacy for the patient: «red» (high risk), «yellow» (moderate risk), or «green» (low risk) [6]. And based on how the drug is metabolized, a patient's phenotype may indicate a higher risk of toxicity or potential lack of efficacy. At first glance, this drug grouping system seems very simple, but it may not provide all the information a clinician needs to make clinical decisions. It is also important for the clinician to be aware that PT is prognostic only on the basis of genetic findings and that other variables such as concomitant medications, diet, liver and kidney function, etc. may also be important or even override the influence of the genetic component in predicting drug response. Therefore, if the «best» drug is determined by PT, this does not necessarily mean that it should be used in therapy, since the patient's history may show serious adverse reactions to the drug. Conversely, the identification of an increased risk of adverse reactions by PT should not lead to discontinuation of therapy if the current therapy is effective.

Depending on the gene being tested, different algorithms can be used to generate results [17]. Some gene variants can be described in terms of metabolic activity, some in terms of general function, and others only as present or absent. Results for gene variants can also be reported as normal, intermediate, or low function for the corresponding gene. For example, «normal gene function» indicates that a change in the patient's dosage regimen is not necessary. In other cases (reduced or intermediate function), the physician's recommendations are based on information about reduced functional activity (or complete inactivity) of the genes analyzed.

The way results are presented can vary widely from one report to another. Results may be presented either as raw genetic data or as a definitive therapeutic recommendation. As we can see, different ways of presenting information are used in the report, so special awareness should be present to correctly interpret the results obtained.

Clinical decision support systems

The major result of the development of genomic and post-genomic technologies has been a significant expansion in the ability to study the genetic nature of the entire spectrum of human disease. Genome-wide association studies (GWAS) of clinical samples have collected data on the genetic composition characteristic of specific groups (families or populations), which has contributed to the development of a personalized approach to treatment. In this context, the study of the mechanisms of genetic susceptibility to multifactorial diseases and the identification of specific genetic markers are of particular importance today.

Next-generation sequencing (NGS) is used to read genetic material in depth, as required for re-sequencing and assembly of de novo genomes, transcriptomes, and epigenomic studies. This method allows the detection of rare variants and a better understanding of genetic function. However, the avalanche of new data will also challenge researchers and clinicians, providing many «variants of unknown significance» in the absence of clear guidance.

Pharmacogenetic clinical decision support systems (CDSS) are computer-based systems that assist healthcare providers in prescribing medications at the point of care. These systems provide physicians and other healthcare providers with appropriately filtered pharmacogenetic information, such as drug-gene interaction alerts or patient-specific treatment recommendations. A pharmacogenetic CDSS can either be integrated into a local hospital information system or used as a stand-alone application such as a web service or mobile application [18]. In addition, pharmacogenetic CDSSs can provide passive or active clinical decision support. Active CDSSs include rules and alerts. For example, an alert may occur because a patient is prescribed a high-risk drug and there is an indication for PT before the drug is administered. Passive CDSSs require the user to actively search for information, such as pressing

a button or opening a report on a particular clinical case [19]. Changes to the CDSS are needed to support the storage and use of the new data architecture and new data access applications.

Several health systems are using CDSS tools to integrate data from pharmacogenetic studies into medical decision making and to provide information to end users [20]. CDSS systems can be used to introduce high-risk medications and provide automated recommendations on why certain changes should be made to a selected medication or dose. Similar information systems are already being actively used in allergology [21].

Raising awareness among physicians and patients can stimulate the use of PT. Laboratories, in turn, will adjust the number and type of tests available based on clinical needs. As a result of significant achievements in oncology, microbiology and other fields, the level of development of multigene panel tests is expected to increase. however, appropriate clinical use of PT results is more complex and will require the support and involvement of multiple stakeholders.

The main problems of the pharmacogenetic testing implementation

Training of specialists.

The scope of PT is primarily determined by the willingness and ability of healthcare professionals to use it. It should be noted that most clinicians are still not confident in PT and the subsequent interpretation of data, which can be explained by insufficient knowledge in this area. Insufficient awareness of the potential of PT among practicing physicians and poor or inadequate explanation of test results hinder the development of a personalized approach to the patient. In addition to the development of programs of thematic training courses at medical universities, it is necessary to include educational events in the systems of continuing professional education, free publication of information for practicing physicians. A clinical pharmacologist plays a crucial role in the implementation of pharmacogenetic testing due to his multidisciplinary training [22]. The competence of a clinical pharmacologist in the field of pharmacogenetics is crucial: this specialist organizes the use of PT in clinical practice, interprets test results, informs doctors about the possibilities of using PT for patients with certain nosological forms [23].

Quality of evidence and clinical relevance.

Many pharmacogenetic biomarkers have weak or conflicting associations with treatment outcomes [24]. For example, a study by Porcelli et al. found a statistically significant effect of the 5-HTTLPR gene variant on the efficacy of antidepressant use, but the strength of this effect (estimated by the OR value) was not significant [25].

Randomized controlled trials (RCTs) are considered the highest quality studies, but they are not always necessary for pharmacogenetic studies. For example, it is known that the presence of a variant of the CYP2D6 gene is dangerous for the life of infants whose mothers used codeine [26]. It is clear that in this type of research (when the effect of the gene variant studied on the development of toxic reactions is known), an observational «case-control» study is a more ethical design.

Many companies or clinical laboratories offer PT. They routinely test for hundreds of gene variants and provide information on gene-drug associations. However, the level of evidence used to report gene-drug associations is often inadequate. Companies limit the value of the tests by reporting only the number of studies that found an association between a gene variant and drugs, omitting important study details (number of patients, their age composition, the strength of the association found, etc.). In addition, reporting conflicting results without assessing the quality of each study also reduces the relative value of PT.

Life-threatening adverse drug reactions.

The low incidence of serious and life-threatening side effects poses another problem for the implementation of PT. Finally, it may be difficult to enroll a sufficient number of cases in the clinical trial to determine clinically relevant biomarkers.

Differences in gene variant frequencies between populations mean that PT must also account for this potential variability. In different countries, a different variant within the same gene may be significant for a particular drug. This, in turn, may affect regulatory actions in the healthcare systems of different countries around the world. For example, in Thailand, HLA-B*15:02 testing is publicly funded prior to the prescription of carbamazepine [27]. In most European countries, the cost of this type of genotyping is not covered by government programs due to the low frequency of this variant in patients.

Economic aspects of pharmacogenetic testing.

Until recently, PT was expensive, often ranging from hundreds of dollars to over $ 1,000 for single gene tests and up to thousands of dollars for gene panels. As a result, widespread drug prescription based on PT results was not possible due to cost. However, rapid advances in technology have greatly reduced the cost of testing, and today gene panels are becoming increasingly accessible to patients. The transition from reactive to preventive testing has begun. Developments and improvements in technology, as noted above, have also helped to reduce the time required to perform PT, so that test results can be obtained before therapy is prescribed.

A Food and Drug Administration (FDA) review of the economic evaluation of PT showed that 57 % of the tests were cost-effective: 30 % at acceptable incremental cost and 27 % at low cost [28]. Of course, the cost-effectiveness of using PT also depends on the specific country, such as the health care economy of the country in which this testing is performed, as well as the prevalence of specific pharmacogenetic biomarkers in the country's population.

For successful implementation of PT, it is important to assess the economics in each country to find the optimal strategy. Yes, PT with reliable evidence can be reimbursed by health insurance companies. Economic evaluations usually consider cost-effectiveness based on the possible number of patients with the relevant pharmacogenetic variant. However, in the case of serious effects that can be caused by the use of drugs, the knowledge that the patient is not at increased risk for such a reaction also provides a particularly high value and should be taken into account.

At the same time, despite the positive results of pharmacoeconomic studies, where the use of PT allowed

to reduce the cost of treatment by decreasing the amount of money spent on correcting the consequences of therapy ineffectiveness or unwanted side effects, not all insurance companies and health care systems are ready to include genotyping in their programs.

Storage and use of results.

With the widespread use of preventive PT comes the problem of long-term storage and use of the results. The primary goal of preventive testing is to obtain results that can be used to prescribe medications in the future. For this approach to be effective, the clinician who will use the results must know that the patient has already been tested and have access to the results. This problem can often be overcome by entering the results into an appropriate electronic database, but the process can be complicated when results from multiple testing laboratories are used and entered due to differences in testing and reporting formats [6]. Therefore, future use of the results will depend on their manual entry into the electronic medical record, and then the physician will have to find the entered data by hand among all the other patient notes and test results. Another problem is that patients can change their place of residence and therefore their health care system during their lifetime, making it impossible for electronic health records from different countries to interact. Other mechanisms for data transfer are also being explored – QR codes, PT «cards,» portals, etc. [29], but they require direct patient involvement and responsibility.

Prescribing medicines to pregnant women.

A large number of women take medication during pregnancy, and their use increases over time: according to recent data, 93.9 % of pregnant women took at least one medication (excluding vitamins) during pregnancy [30]. Concerns about the use of drugs during pregnancy became widespread after the identification of unexpected side effects of thalidomide and diethylstilbestrol [31]. When the teratogenic effects of these drugs became apparent, the FDA developed guidelines to protect women of reproductive age from adverse effects during clinical trials. However, the participation of pregnant women in research is still inadequate. For example, Scaffidi et al. conducted a global analysis of clinical trials and found that only 0.32 % of all active clinical trials were trials of drugs for pregnancy [32], with less than 6 % of these trials focusing on maternal or fetal health as a specific primary outcome.

Since there are often no recommendations for the dosage of medications for pregnant women, physicians are often forced to prescribe medications by trial and error. The risk-benefit ratio of drugs in pregnant women is often incorrectly assessed, since only the effect of drugs is evaluated, whereas the consequences of untreated disease for the health of the woman and the fetus must also be taken into account. When discussing the participation of pregnant women in pharmaceutical research, it should be kept in mind that the real trade-off is between the risk of the research and the decision of pregnant women's physicians to treat them based on limited or no information. A number of research opportunities can help to bridge this gap by increasing the quantity and quality of information available to pregnant women and their physicians about the use of medications during pregnancy. In addition, post-marketing surveillance and pregnancy registries can provide real-world data on the use of certain medications during pregnancy.

In vitro models provide a convenient system to study the possibility of pregnancy-specific metabolic effects and to understand the mechanisms underlying pharmacokinetic changes during pregnancy. Recently, mathematical physiological pharmacokinetic modeling has been increasingly used in the context of pregnancy [33]. Despite significant shortcomings, it is hoped that the availability of in vitro data and clinical trials will improve the quality of these prognostic models and ultimately play a role in improving drug therapy for pregnant women.

Approaches to the implementation of pharmacogenetic testing in pediatrics.

Implementation of PT recommendations into routine practice requires carefully coordinated strategies at the national, regional, and institutional levels. Guidelines on the needs for pediatric PT and strategies for its implementation should not necessarily be separated from the work of consortia engaged in developing approaches for adult patients [34]. There are clear advantages to integrating pediatric PT into national approaches, rather than postponing it to future years, to avoid unnecessary delays in realizing the true benefits of pharmacogenomics for children.

It is necessary that the implementation of pediatric PT in each country should be based on evidence, experience and scientific validation of the results obtained. The national program of PT should be continuously monitored for the achievement of clinically significant outcomes with an evaluation of established success and cost-effectiveness indicators. Rapid exchange of information through peer-reviewed publications and pediatric PT databases will enable collaborative development of adaptive implementation models applicable to different health care systems. The approach to the use of PT should take into account the specifics of prescribing in pediatrics in each country. It is important to continue to share experiences between countries to ensure that the benefits of PT in pediatrics are available worldwide. The importance of promoting implementation among medical students should be considered and included in planned educational strategies.

Conclusions

The introduction of PT will inevitably stimulate the development of data storage and analysis methods necessary for the integration of modern information technologies into routine clinical practice. However, improving digital information processing systems and increasing the volume and availability of databases is not the only issue in integrating genetic testing into health care. This, in turn, requires changes in the interaction between the patient and the health care system, since the ultimate goal is the patient's recovery or disease control, regardless of the laboratory methods and data analysis technologies used. In other words, treatment should take into account both the patient's needs and the results of the tests obtained. Today, pharmacogenetics is still in its infancy. A considerable amount of experimental, but mainly pilot, research has already been conducted in this field. However, the generalization of these data is still lacking, making it difficult to explain the observed

correlations between the presence of a single gene variant and epigenetic factors, disease severity, and resistance to therapy. To date, pharmacogenetics provides mosaic information on the association between drug response and genetic background. It is expected that the next step will be a study in a larger group of participants to investigate the contribution of epigenetic factors and to provide clinical recommendations for adjusting or selecting therapy based on the personal characteristics of the patient. Nevertheless, the field of pharmacogenetics is actively developed and discussed.

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СУЧАСНІ АСПЕКТИ ФАРМАКОГЕНЕТИКИ: ВІД ТЕОРІЇ ДО ПРАКТИКИ В ПЕРИНАТОЛОГІЇ ТА ПЕДІАТРІЇ

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Резюме.

Фармакогенетичне тестування (ФТ) – сучасний інструмент у практиці лікаря, який робить можливим прийняття правильного клінічного рішення у складних випадках при відсутності очікуваного результату від вжитих лікувальних заходів. Зрозуміло, що так само, як цілий ряд захворювань, запрограмованими генетично є і певні метаболічні процеси людського організму. Тому, незважаючи на велику кількість нез'ясованих механізмів індивідуальної реакції на лікарські засоби, генетичне тестування займає одну з провідних позицій серед методів підбору медикаментозної терапії у складних клінічних випадках.

Проте для успішного впровадження цього перспективного методу необхідно подолати цілу низку перешкод, серед яких – лімітованість доказів ефективності, етичні, юридичні і соціальні фактори. Метою даного огляду є висвітлення сучасних концепцій та практичних аспектів використання ФТ. У статті розглянута проблематика розширення показань до ФТ, коли воно не обмежується лише превентивним застосуванням. ФТ дозволяє ідентифікувати препарати з підвищеним ризиком спричинення побічних ефектів, визначити ліки з вузьким терапевтичним індексом, зменшити кількість лікарських засобів при лікуванні, підібрати дозування препарату. У практиці лікаря можуть використовуватися різноманітні платформи ФТ, які, в основному, можна поділити на дві категорії – тести на основі генотипування та секвенування. В залежності від того, який ген тестується, можуть бути використані різні алгоритми побудови результатів. Деякі варіанти генів можна описати з точки зору метаболічної активності, деякі – за їхньою загальною функцією, а інші – лише як присутні або відсутні. Результати для варіантів генів також можна повідомити у вигляді нормальної, проміжної або низької функції відповідного гена. Фармакогенетичні клінічні системи підтримки прийняття рішень (Pharmacogenetic Clinical Decision Support Systems, CDSS) – це комп'ютерні системи, які допомагають постачальникам медичних послуг призначати ліки на місці надання медичної допомоги. Ці системи надають лікарям та іншим постачальникам медичних послуг належним чином відфільтровану фармакогенетичну інформацію, таку як попередження про взаємодію варіантів генів з ліками або рекомендації щодо лікування для конкретного пацієнта. Фармакогенетичну CDSS можна або інтегрувати в локальну лікарняну інформаційну систему, або використовувати як окрему програму, таку як вебсервіс або мобільний додаток. Фармакогенетика може збільшити кількість та якість інформації, доступної вагітним жінкам та їхнім лікарям про застосування лікарських засобів під час вагітності. Впровадження рекомендацій з ФТ в рутинну педіатричну практику вимагає ретельно скоординованих стратегій на національному, регіональному рівнях і в медичних установах. Поки що фармакогенетика надає мозаїчну інформацію, пов'язану з асоціацією між відповіддю на медикаментозну терапію залежно від генетичного фону. Очікується, що наступним етапом буде дослідження на більшій групі учасників, вивчення внеску епігенетичних факторів, і надання клінічних рекомендацій для коригування або вибору терапії на основі особистих характеристик пацієнта.

Ключові слова: фармакогенетичне тестування; генотипування; секвенування; клнічні системи прийняття рішень; вагітні жінки і діти.

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