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CLINICAL METABOLOMICS: CURRENT STATE AND PROSPECTS IN RUSSIA

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Using analytical technologies it is possible now to measure the entire diversity of molecules even in a small amount of biological samples. Metabolomic technologies simultaneously analyze thousands of low-molecular substances in a single drop of blood. Such analytical performance opens new possibilities for clinical laboratory diagnostics, still relying on the measurement of only a limited number of clinically significant substances. However, there are objective difficulties hampering introduction of metabolomics into clinical practice. The Institute of Biomedical Chemistry (IBMC), consolidating the efforts of leading scientific and medical organizations, has achieved success in this area by developing a clinical blood metabogram (CBM). CBM opens opportunities to obtain overview on the state of the body with the detailed individual metabolic characteristics of the patient. A number of scientific studies have shown that the CBM is an effective tool for monitoring the state of the body, and based on the CBM patterns (signatures), it is possible to diagnose and monitor the treatment of many diseases. Today, the CBM creation determines the current state and prospects of clinical metabolomics in Russia. This article, dedicated to the 80th anniversary of IBMC, is a review of these achievements focused on a discussion of their implementation in clinical practice.

Key words: clinical metabolomics; clinical blood metabogram; disease diagnostics; mass spectrometry

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INTRODUCTION

Problems of Clinical Laboratory Diagnostics

Clinical laboratory diagnostics plays a key role in modern medicine. Physical examination of the patient, is immediately accompanied by laboratory tests, which provide important information to a physician needed for correct diagnosis. Therefore, the use of a wide range of clinical laboratory tests is mandatory in modern medicine, and constant replenishment with new ones is a permanent task.

The central role of clinical laboratory diagnostics is also visible at the level of the entire healthcare system. Laboratory diagnostics helps to optimize medical care for the population, to reduce research costs, and improve the outcome of patient treatment. Therefore, the main goal of the development of clinical diagnostic laboratories is to expand the range of available laboratory tests. New tests are expected to identify an increasing number of nosologies, provide long-term monitoring of patients' condition and the ability to track treatment results.

Imperfect clinical laboratory services are a source of errors in the diagnostics of diseases that lead to serious consequences, including cardiovascular, oncological and infectious diseases (74% of diagnostic errors) [1]. In 85% of cases, the cause of the error is the failure to prescribe a diagnostic test or its untimely prescription, a very narrow focus of the diagnostic test and incorrect interpretation of its results [1].

It is believed that medical diagnostic errors make a hidden but huge contribution to morbidity and mortality [2]. According to the US National Academy of Medicine, diagnostic errors are a serious public health problem that will likely affect absolutely every person during their lifetime [3]. It has been found that diagnostic errors are the cause of approximately 10% of deaths and from 6% to 17% of adverse events in hospitals, as well as the main cause of lawsuits in medicine [3]. According to statistics, about 795 thousand Americans become disabled or die in medical institutions every year due to incorrect diagnostics of diseases [4]. The lack of such data for other countries does not allow us to hope for a better situation in them, given the high level of medicine in the United States. Thus, new diagnostic capabilities are really necessary, and this primarily concerns laboratory diagnostics.

Clinical Metabolomics — a Response to Today's Challenges

"There are over 10,000 diseases, each of which can manifest with a variety of symptoms, so it can be daunting to think about how to even

begin tackling diagnostic problems." These words said by David Newman-Toker, Director of the Armstrong Institute Center for Diagnostic Excellence, give an idea of the scale of the problem, the solution to which is unlikely to lie in the plane of developing diagnostics for individual nosologies. The nature and size of the problem forces scientists to seek new solutions for the development of diagnostics.

A promising option for the development of clinical laboratory diagnostics is the use of metabolomics. Metabolomics is a large-scale study of small molecules, known as metabolites, inside cells, biofluids, tissues or organisms. The set of these small molecules inside a biological system is known as a metabolome. The applied uniqueness of metabolomics comes from the organization of living systems, which are based on a static genome, represented by macromolecules, nucleic acids, potentially determining characteristics of a living system (Fig. 1). Through transcription and then translation, information from the genome is transmitted to proteins (enzymes), which are the "engines" of biochemical reactions; the sum of these biochemical reactions reflects manifestations of life at the molecular level. All anabolic and catabolic processes (the processes of synthesis and decomposition of substances in the body) are realized in biochemical reactions. The flow of signals (regulation) and energy (the formation of energy molecules and their use) is also carried out with the participation of biochemical reactions. Substrates and products of biochemical reactions, metabolites, are measurable characteristics; they form a dynamically changing metabolome. Measuring the metabolome with modern mass spectrometers, it is possible to comprehensively assess the functional state of the body at the molecular level, which is confirmed by the results of medical research in metabolomics [5–12].

With some limitations, the blood metabolome can be considered representative for the entire organism. Nutrients are transported through the blood, cells excrete waste products into the blood, and signaling molecules involved in regulation come from the blood and secreted into the blood; cells disintegrate and release their contents into the blood. All this, combined with easy sampling makes blood the main biomaterial for both clinical laboratory tests and medical metabolomics. Metabolic data accumulated in databases over the past decades confirm that it is the blood metabolome that is a collector of measurable low-molecular signs of a huge variety of diseases and abnormal conditions of the body [13]. The data accumulated in the Human Metabolome Database are very demonstrative: the number of metabolites associated with diseases is 22,600; the number of diseases with described metabolite changes is 657.

The unique prospects for the clinical application of metabolomics prompted the Metabolomics Society to state that "the narrow range of chemical assays used by the medical community today will be replaced in the future by assays that detect much more comprehensive metabolic characteristics (signatures). These signatures are expected to describe global biochemical abnormalities that reflect patterns of changes in health status, more accurately describe specific diseases and their progression, and greatly assist in differential diagnostics" [14]. The prospects of this area have also been noted by the Russian

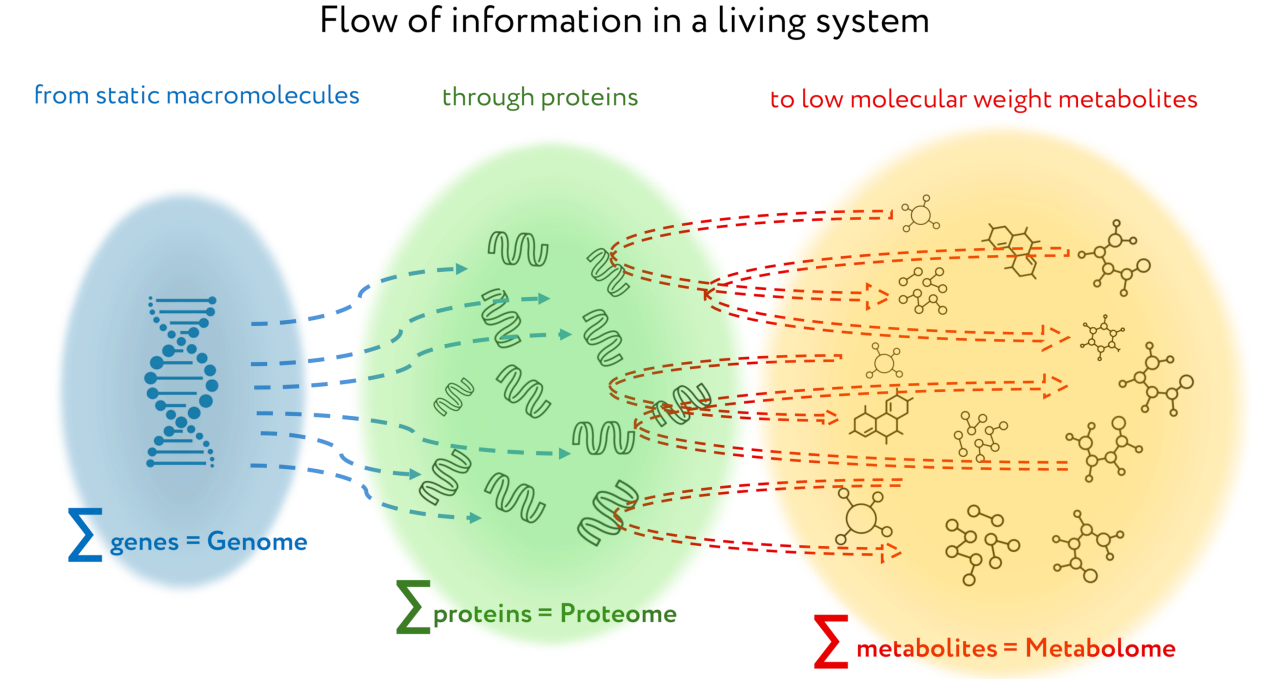

Figure 1. Information flow in a living system. Information flow goes from static macromolecules of the genome to a dynamically changing metabolome consisting of small molecules. Being a molecular phenotype of a living system, the metabolome reflects all significant molecular events in the organism.

Academy of Sciences. The Bureau of the Section of Medical and Biological Sciences of the Department of Medical Sciences, confirmed by its resolution of November 29, 2016 (Protocol No. 11), the importance of medical metabolomics in the diagnostics of diseases and supported scientific research in this area.

1. PROBLEMS OF IMPLEMENTING METABOLOMICS INTO PRACTICAL MEDICINE

Despite evident importance of implementing metabolomics in medicine [7–12], the number of successful examples of such implementation is insignificant. The ability to measure large sets of molecules not only underlies the existence of metabolomics, but is also the reason for its limited application in the clinics. Measurements of thousands of substances arise the problem of their reliable identification. Difficulties arise both from the number of substances measured and their various properties (different concentrations in the sample, different physicochemical properties leading to different ionization and fragmentation abilities used in their identification). As a result, metabolomic analysis of one biological sample results in a full-fledged scientific study that requires long-term work by a group of highly qualified specialists. Such study does not correspond to clinical laboratory tests either in time or cost. Thus, before being implemented in medicine, metabolomic research should be brought closer to the format of routine laboratory analysis. Giving such characteristics to metabolomic analysis is a non-trivial task, which has led to the existence of only a small number of clinical metabolomics analyses worldwide.

2. CLINICAL METABOLOMICS IN RUSSIA

In order to assess the state of clinical metabolomics in Russia, it is necessary to understand what metabolomic analysis is. The suffix “om” means belonging to “omics” technologies, that is, to measuring substances of an entire level of organization of living systems or a significant part of it. In this case, the metabolomic level is analyzed, which is the essence of metabolomic analysis. Measuring individual metabolites or targeted measurement of small groups of metabolites do not belong to metabolomic measurements, since they do not extract information at the “omics” level.

It should also be noted that it is difficult to classify metabolomic analysis used in science as clinical metabolomics, even if it is used directly to analyze a sample of a particular person. Scientific laboratories can conduct such studies, but they are far from clinical laboratory analysis in terms of complexity, labor costs, execution time, and reproducibility [13, 15]. Taking this into account and using a review of published information, including scientific publications, it can be confidently stated that clinical metabolomics in Russia today is concentrated at the Institute of Biomedical Chemistry (IBMC).

Consolidating the efforts of leading scientific and medical organizations in Russia, IBMC has achieved the first successes in this area, having developed and presented a clinical blood metabogram (CBM) in 2023 [16]. Being a method for measuring low-molecular substances (metabolome) of blood adapted for clinical laboratory practice, the CBM today determines the current status and prospects of clinical metabolomics in Russia.

3. CLINICAL BLOOD METABOGRAM (CBM)

CBM is a clinical mass spectrometric analysis of the low-molecular fraction of blood, presented in the form of several values (metabologram components) reflecting the state of the main groups of blood plasma metabolites (Fig. 2) [16]. During CBM development, the composition of these groups and their clinical significance were elucidated. The main idea of the CBM is based on the assumption that metabolites, whose concentrations in the body

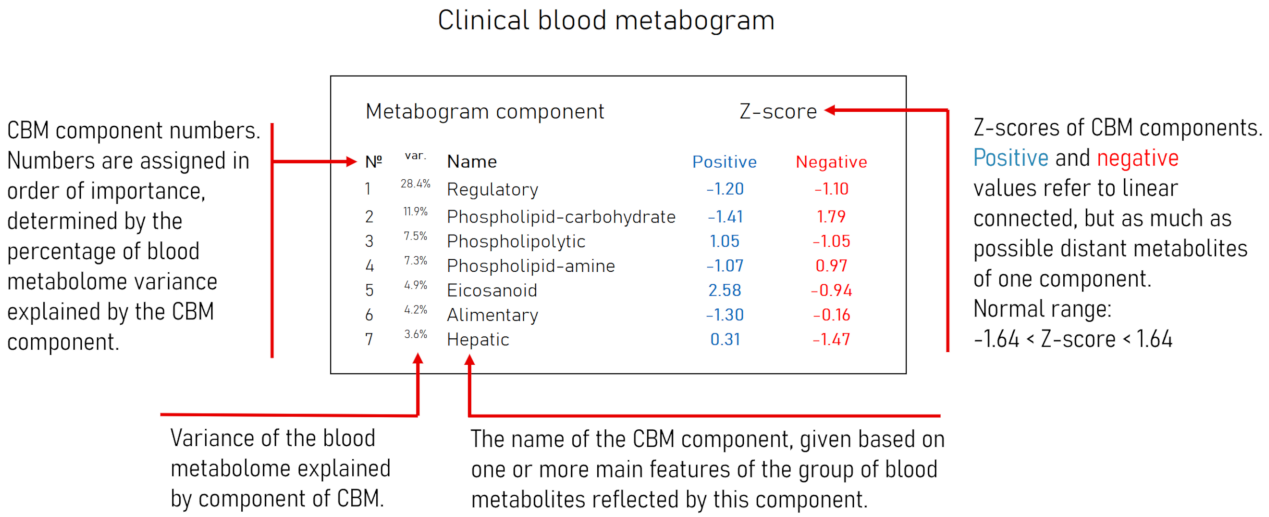

Figure 2. Fields in a clinical blood metabogram.

change simultaneously, are involved to a certain extent in identical processes occurring in the body and therefore they can be analyzed together. During CBM development special attention was paid to the quality of the set of volunteers, whose metabolomic data formed the basis for the detection of these groups of metabolites. All volunteers underwent a careful examination at the Institute of Medical and Biological Problems of the Russian Academy of Sciences under the program for studying the health of cosmonaut candidates. Blood metabolomes of volunteers recognized as healthy served to develop CBM and calculate its normative (reference) values.

Thus, the analysis of thousands of individual metabolites was replaced by the analysis of the main groups of metabolites describing 70% of all information presented in the human blood metabolome. Group analysis of substances radically reduced the time of metabolome analysis, significantly increased the reproducibility of results and resistance to errors. It has been found that these groups of blood metabolites are associated with humoral regulation of the body, lipid-carbohydrate and lipid-amine metabolism, eicosanoids, reflect the intake of substances into the body and characterize hepatic function. The composition and functional significance determined the name of these components (Fig. 3).

The directed flow of information from the genome through the proteome to the metabolome, as the final collector of manifestations of all molecular events in the body, allows us to classify the metabolome as a molecular phenotype. The concept of a molecular phenotype is closely related to the concept of molecular health and a molecularly healthy person, whose molecular phenotype corresponds to normative values. Deviations at the genomic and protein levels that are not reflected in the metabolome can be considered insignificant for health. With a normative molecular phenotype, only physiological processes corresponding to gender, age, ethnic characteristics and healthy aging of the body occur in the body. It can also be argued that the body is not susceptible to harmful external influences, or they are insignificant and the body is adapted to them, it does not have genetic anomalies that currently affect health, and a person's nutrition is adequate and fully correlates with its microbiome, which is also normal. Thus, the CBM is the first clinical laboratory test that allows objectively measuring and confirming a person's healthy state.

Among the limitations of such health assessment are genetic diseases that manifest themselves with age, but are not currently reflected in the metabolome; in other words genetic health can only be discussed in relation to the current moment, without prediction for the future. The same is applicable to the early stages of disease development, the manifestations of which in the metabolome are beyond the sensitivity of mass spectrometric detection.

4. RELATIONSHIP OF CBM WITH CLINICAL LABORATORY TESTS

The daily practice of physicians includes prescription of clinical blood tests and interpretation of results of these tests. Clinical tests are, in fact,

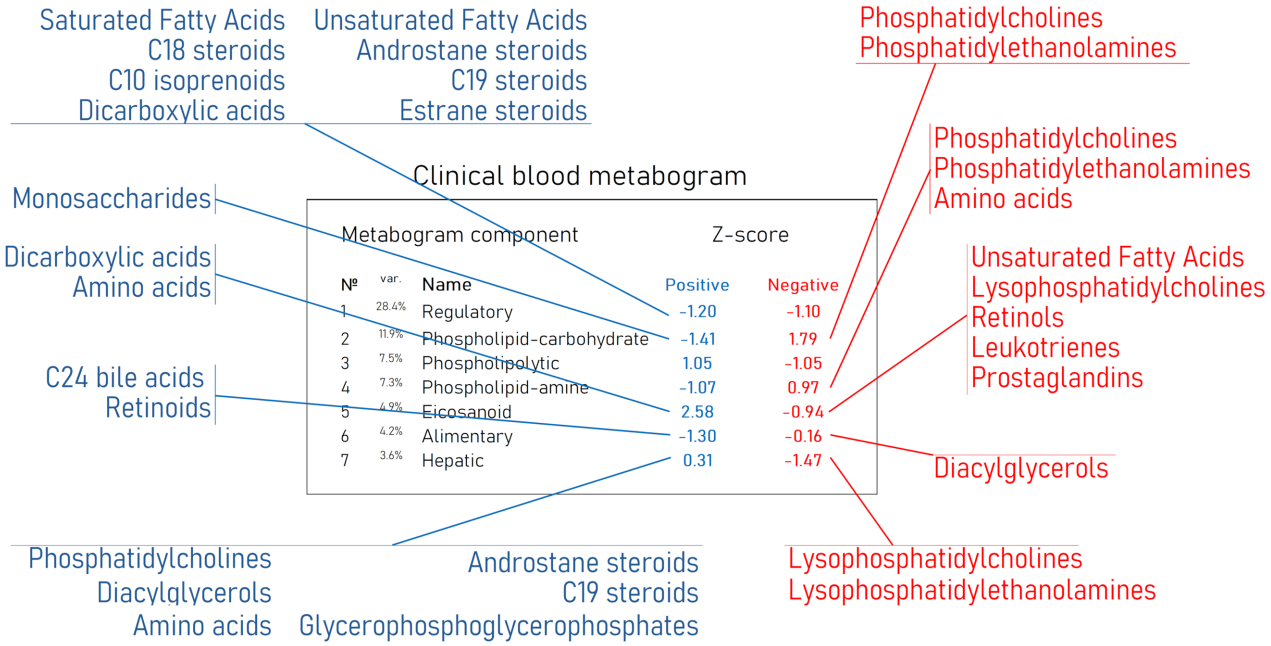

Figure 3. Blood metabolite groups reflected in the components of the clinical blood metabogram (CBM). Z-value is a measure of the metabogram component (a value from -1.64 to +1.64 corresponds to the norm; increased and decreased concentrations of metabolites reflected by the component correspond to a higher and lower Z-value, respectively). “var.” is the percentageof variability (dispersion) of the blood metabolome explained by the metabogram component. Adapted from [16].

narrowly focused monitors of the body's state. Many substances measured in the clinical practice are directly included in the blood metabolome, for example, glucose, cholesterol, steroids, amino acids, vitamins, etc., while others are involved in processes that are reflected in the blood metabolome. Thus, CBM, acting as a unified (panoramic) monitor, has direct and indirect links with clinical tests. The easiest way for physicians to get acquainted with CBM for subsequent use in their practice is to use information about these links. Figure 4 shows the correlation of the CBM components with some widely used blood tests in the clinical practice, which may be used to associate deviations in the CBM components with the clinical experience of physicians and methodological recommendations for the diagnostics and treatment of diseases.

5. RELATIONSHIP OF CBM WITH HUMAN GUT MICROBIOTA

The human body is in a symbiotic relationship with the microorganisms that inhabit it, mainly the intestine. Healthy microbiota neutralizes toxins and harmful metabolites, thereby protecting the body from carcinogens and other damaging factors. Microflora is an integral part of the digestive system, cleaving, for example, complex carbohydrates for their further absorption. Microflora synthesizes micro- and macroelements, such as vitamins C, B, K, PP. Thus, human health is closely related to the presence of a healthy microbiota.

It is known that the gut microbiota has a significant impact on the blood metabolome [17], while components of the blood metabolome can affect the composition of the gut microbiota [18–21]. Therefore, as a part of the CBM preparation for clinical use, a relationship was established between the components of the metabogram and the parameters of the gut microbiota. For this purpose, CBMs were obtained from the same individuals and the gut microbiota was analyzed using the method of seeding on selective media and real time polymerase chain reaction (PCR) [22]. Correlation analysis determined, which components of the metabogram were associated with which gut microorganisms,

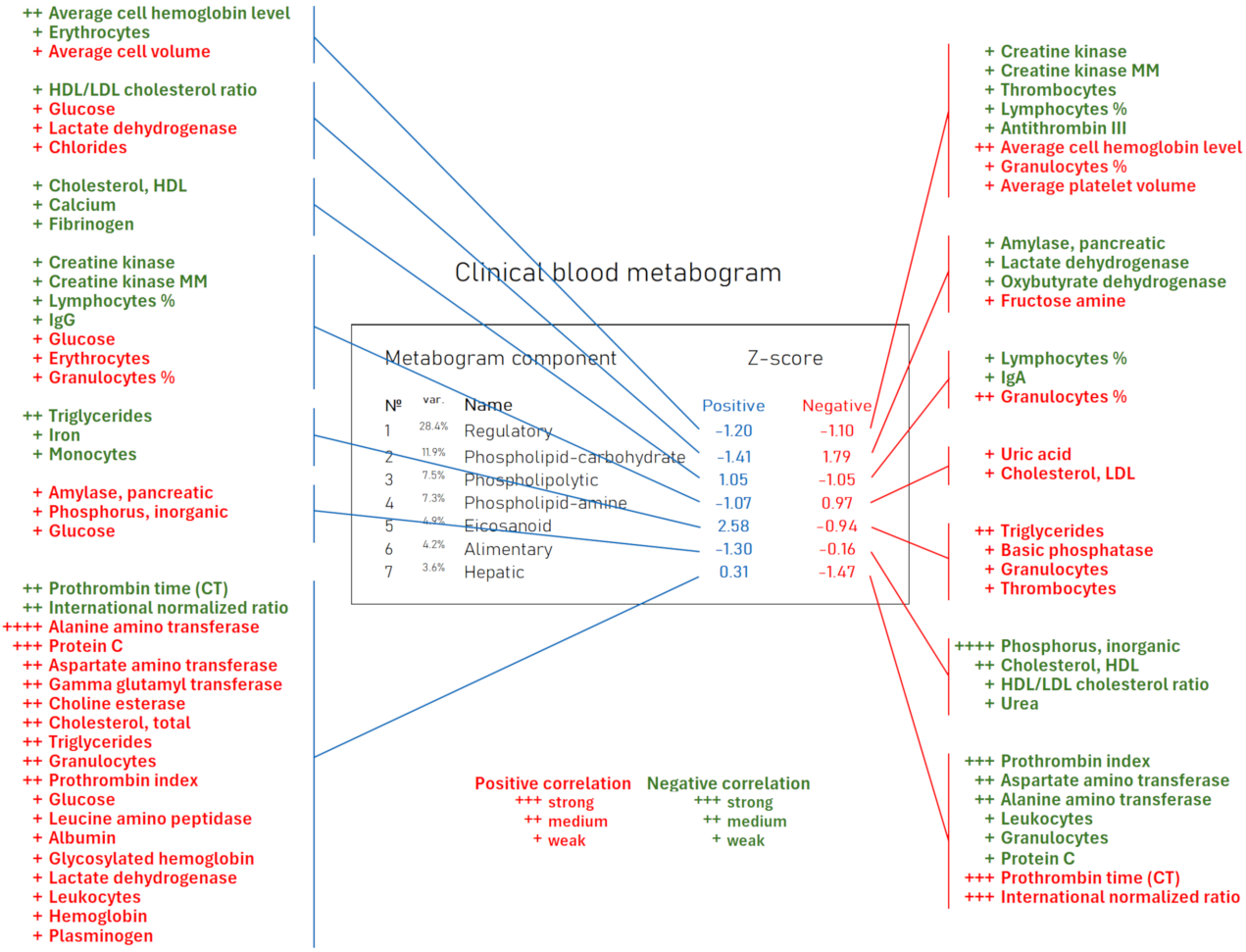

Figure 4. Correlation between the components of the clinical blood metabogram (CBM) and clinical laboratory tests. Red and green colors indicate clinical tests that positively and negatively correlate with the metabogram components, respectively. The strength of the connection between the clinical analysis results and the values of the metabogram components is expressed as the absolute value of the correlation coefficient ('+' is the correlation coefficient from 0.3 to 0.4; '++' – from 0.4 to 0.5; '+++' – from 0.5 to 0.6; '++++' – above 0.6). Adapted from [16].

as well as the strength of this relationship. Figure 5 shows the results for the culture seeding data. Full data, including data for PCR analysis, are presented in a previously published article [22]. The results of the study confirmed both the possibility of CBM use taking into account the impact of the gut microbiota on it, and diagnosing deviations in the gut microbiota based on the CBM data.

6. CBM SIGNATURES FOR DISEASES

In contrast to conventional monomarker clinical tests, CBM, as a method of panoramic assessment of the molecular composition of blood and consisting of a set of components reflecting groups of blood metabolites that differ in the composition and function, is capable of forming signatures specific

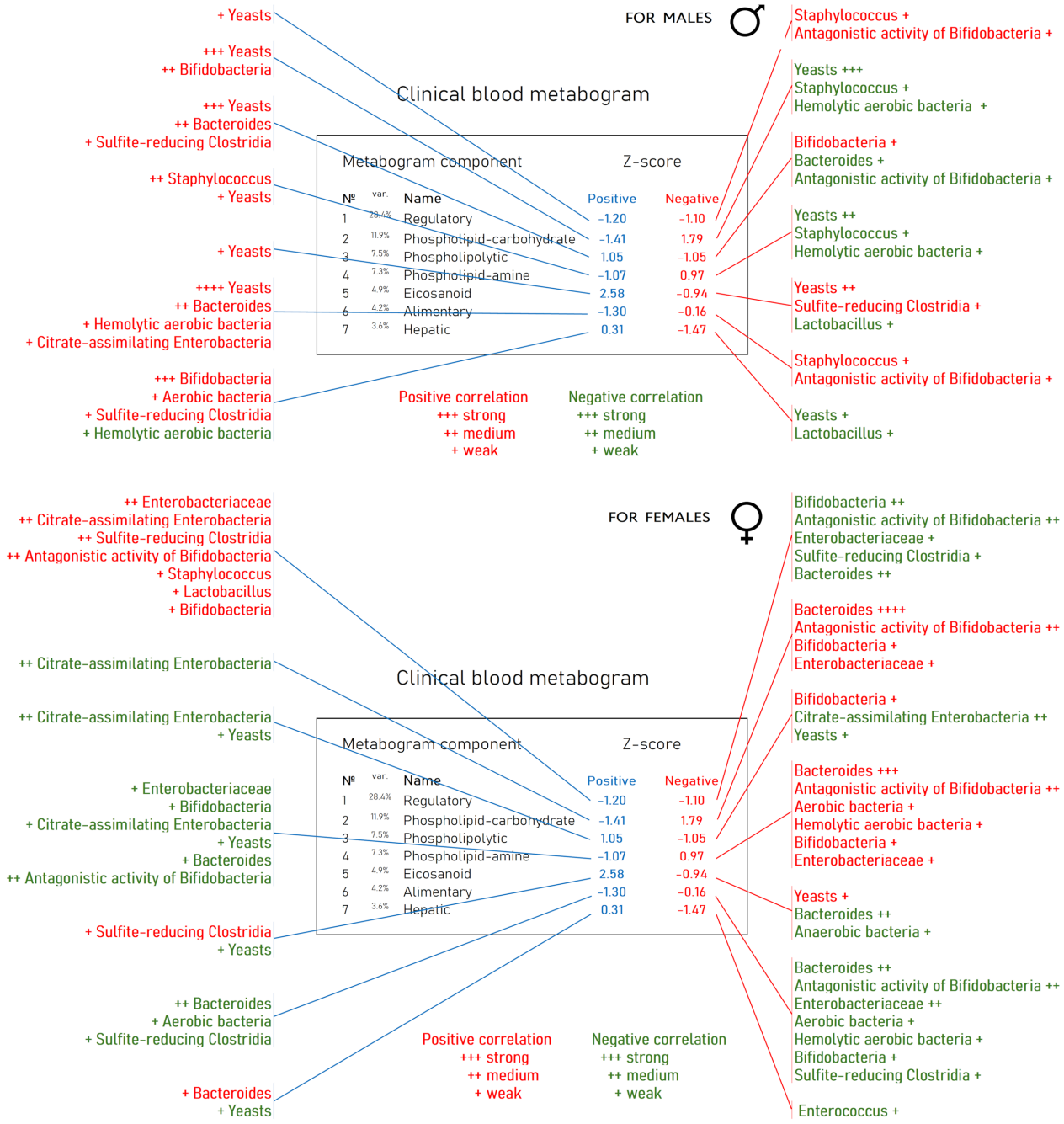

Figure 5. Correlation between the components of the clinical blood metabogram (CBM) and the gut microbiota of men and women. The gut microbiota was measured by the culture seeding method. Full data on the relationship between CBM and intestinal microorganisms, including data on the microbiota measured by PCR, can be found in the published materials [22]. Red and green color mark the culture tests that positively and negatively correlate with the metabogram components, respectively. The strength of the connection between the amount of microorganism and the values of the metabogram component is expressed as the absolute value of the correlation coefficient ('+' is the correlation coefficient from 0.3 to 0.4; '++' – from 0.4 to 0.5; '+++' – from 0.5 to 0.6; '++++' – above 0.6). Adapted from [22].

to particular diseases. The fundamental principles that formed the basis for the CBM development determined its sensitivity to various deviations in the body, including diseases, while the multiparametric nature of CBM determined the high specificity of detecting these deviations. To confirm this unique diagnostic ability of CBM, its signatures were described for diseases common in the population, such as obesity, diabetes mellitus, Parkinson's disease, and kidney cancer (Fig. 6). The list of signatures is constantly being updated, which makes the diagnostic capabilities of CBM constantly increasing.

6.1. The CBM Signature of Overweight and Obesity

The CBM study in overweight and obesity was conducted by IBMC in collaboration with the Federal Research Center for Nutrition, Biotechnology and Food Safety (Moscow). The study involved 20 healthy individuals, 20 overweight individuals and 60 individuals with grade 1, 2, or 3 obesity [23]. The results have shown that the CBM components have deviations that form a disease-specific pattern (disease signature) (Fig. 6A). These deviations are associated with changes in the blood levels of steroids, amino acids, fatty acids and phospholipids; this is consistent with the currently available scientific data. Thus, using the metabogram it is possible to study overweight or obese patients, providing both a general overview of their metabolic changes and detailing individual characteristics. It was concluded that the CBM represented an accurate and clinically applicable test for assessing the metabolic status of an individual in this disease.

6.2. The Metabolic Signature of Type 2 Diabetes Mellitus

The relevance of the use of the CBM in patients with type 2 diabetes mellitus (T2DM) was studied by IBMC in collaboration with the National Medical Research Center of Endocrinology (Moscow). For this purpose, metabolic signature was obtained for 18 healthy individuals, 12 individuals with prediabetes, and 64 patients with T2DM [24]. The CBM showed a metabolic signature of blood (Fig. 6B) associated with T2DM; it reflected changes in the level of carbohydrates, ketone bodies, eicosanoids, phospholipids, and amino acids consistent with the scientific data available to date. Based on the CBM data, T2DM patients were divided into different metabolic types (metabotypes). It was concluded that the CBM represented an accurate and clinically applicable test for assessing the metabolic status of T2DM patients for diagnostic and therapeutic purposes.

A) CBM signature for Obesity

Metabogram component		Z-score	
# var.	Name	Positive	Negative
1 28.4%	Regulatory	-3.20	-1.10
2 11.9%	Phospholipid-carbohydrate	-1.41	1.16
3 7.5%	Phospholipolytic	1.05	-1.05
4 7.3%	Phospholipid-amine	-1.07	0.97
5 4.9%	Eicosanoid	0.58	-2.94
6 4.2%	Alimentary	-1.30	-0.16
7 3.6%	Hepatic	3.49	-1.47

C) CBM signature for Parkinson's disease

Metabogram component		Z-score	
# var.	Name	Positive	Negative
1 28.4%	Regulatory	-1.23	1.04
2 11.9%	Phospholipid-carbohydrate	0.37	1.47
3 7.5%	Phospholipolytic	-1.27	-1.95
4 7.3%	Phospholipid-amine	-1.67	0.75
5 4.9%	Eicosanoid	0.44	-2.34
6 4.2%	Alimentary	1.23	-0.16
7 3.6%	Hepatic	0.31	1.55

B) CBM signature for type 2 diabetes mellitus

Metabogram component		Z-score	
# var.	Name	Positive	Negative
1 28.4%	Regulatory	-1.20	1.60
2 11.9%	Phospholipid-carbohydrate	1.86	1.58
3 7.5%	Phospholipolytic	0.25	0.95
4 7.3%	Phospholipid-amine	2.14	1.37
5 4.9%	Eicosanoid	-0.81	0.94
6 4.2%	Alimentary	-1.03	-0.94
7 3.6%	Hepatic	3.31	-0.36

D) CBM signature for renal cell carcinoma

Metabogram component		Z-score	
# var.	Name	Positive	Negative
1 28.4%	Regulatory	-1.03	0.76
2 11.9%	Phospholipid-carbohydrate	1.08	-1.28
3 7.5%	Phospholipolytic	1.98	1.16
4 7.3%	Phospholipid-amine	0.05	0.07
5 4.9%	Eicosanoid	2.84	3.45
6 4.2%	Alimentary	-1.87	1.76
7 3.6%	Hepatic	-0.12	-1.99

Figure 6. Signatures of the clinical blood metabogram (CBM) for obesity (**A**), type 2 diabetes mellitus (**B**), Parkinson's disease (**C**), and renal cell carcinoma (**D**). Z-value is a measure of the metabogram component (a value from -1.64 to +1.64 corresponds to the norm; increased and decreased concentrations of metabolites reflected by the component correspond to a higher and lower Z-value, respectively). The main components of the metabogram that form the disease signatures are highlighted in color. Additional components of the metabogram that are part of the disease signatures are shaded. Adapted from [23–25].

6.3. Parkinson's Disease CBM Signature

For further development of CBM, its ability to detect metabolic changes in the blood at an early stage of Parkinson's disease (PD) has been investigated. In a study conducted by IBMC in collaboration with the Koltsov Institute of Developmental Biology (Moscow), a CBM signature was identified for 1–2.5 clinical stages of PD according to the modified Hoehn and Yahr scale (Fig. 6C), which was formed due to changes in eicosanoids, phospholipids, and butadione metabolism [25]. The results of the study expanded the range of diseases, for which the CBM method could be applicable, and opened new opportunities for identifying PD-specific molecular changes that would be potentially used for diagnostic and therapeutic purposes.

6.4. Renal Cell Carcinoma CBM Signature

A study of CBM in renal cell carcinoma was conducted by IBMC in collaboration with the Blokhin National Medical Research Center of Oncology (Moscow). The study involved over 360 volunteers and patients with early-stage carcinoma. The study confirmed that the identified CBM signature (Fig. 6D) was fully consistent with the known biochemical picture of renal cell carcinoma, described by changes in the lipid and eicosanoid profile (research results at the publication stage). This result confirmed the diagnostic versatility of CBM and justified its further study in the diagnostics of oncological diseases.

7. THE FORMAT OF CBM IMPLEMENTATION IN CLINICAL PRACTICE

Traditionally, “omics” methods are introduced into clinical practice in the format of their own tests developed by a separate laboratory (and known as laboratory-developed tests, LDTs). LDTs are a type of an *in vitro* diagnostic device [26–29]. The US Food and Drug Administration (FDA) defines LDTs as “*in vitro* diagnostic tests that are produced and used in a single laboratory”. Performance of laboratory analysis by means of protocols and procedures developed by a single laboratory (the LDT format) helps to overcome problems associated with implementing methods, which are difficult to reproduce and standardize [30]. Several metabolomic LDTs, such as Meta UDx™, Meta IMD™, and Meta IMD™Plus, were created by Metabolon Inc. (USA) in 2018 to identify abnormalities in important metabolic pathways and genetic diseases. Nightingale Health (Finland) created LDT based on nuclear magnetic resonance (NMR) spectroscopy of a finger-prick blood sample to estimate the age a patient is likely to live to before developing any of 10 major diseases [31]. The “healthy life years” calculation used data from hundreds of thousands of people. Ajinomoto (Japan) has created a minimally invasive LDT for early cancer screening [32] based on the analysis of blood plasma by liquid chromatography combined with mass spectrometry. Thus, the introduction of metabolomics methods into medicine in the LDT format can be considered the most promising.

The implementation of the LDT format, i.e. in single laboratory, seems flawed and is not capable of significantly affecting healthcare. However, this is a false feeling. For mass spectrometric analysis of the blood metabolome, 10 microliters of blood are sufficient due to the sensitivity of modern mass spectrometers. Thus, to obtain the CBM, it is possible to use a drop of blood dried on paper, which the patient can obtain at home (the practice of obtaining a blood sample at home is well known to the population, for example, from the use of personal glucometers). A drop of blood dried on paper is stored at room temperature and can be sent by mail or using specialized delivery to the laboratory where the CBM in the LDT format is implemented. This makes CBM unlimited in terms of coverage of the territory of service provision to various segments of the population in various regions of the country (Fig. 7).

Compatibility with dried blood spot and panoramic analysis of the molecular phenotype, which is the basis of the CBM, allow predicting the significant impact of the CBM on the healthcare system and population health. The scheme of the proposed integration of the CBM into the healthcare system is presented in Figure 8.

8. SELF-CONTROL AND INFORMATIONAL AND EDUCATIONAL FUNCTION OF THE CBM

According to David Newman-Toker and his colleagues, in order to solve diagnostic problems, in addition to the emergence of new, more effective methods, it is important to increase people's awareness of diagnostic methods, receive feedback (physicians should receive information about adverse events after patient discharge), and teamwork in making a diagnosis with the participation of both the patient and specialists from various related fields of healthcare [1]. The CBM in the LDT format is an ideal tool that ensures both the full integration of the patient into the process of disease diagnostics and the involvement of various specialists. And the implemented sending of CBM data to the BioGPT artificial intelligence (Fig. 7) allows for the effective use of all relevant and displayed in PubMed human experience in medicine to maintain the patient's health.

The degree of integration patients into the process of maintaining their health is visible from the user interface of the CBM Viewer mobile application, designed for viewing metabograms (Fig. 9).

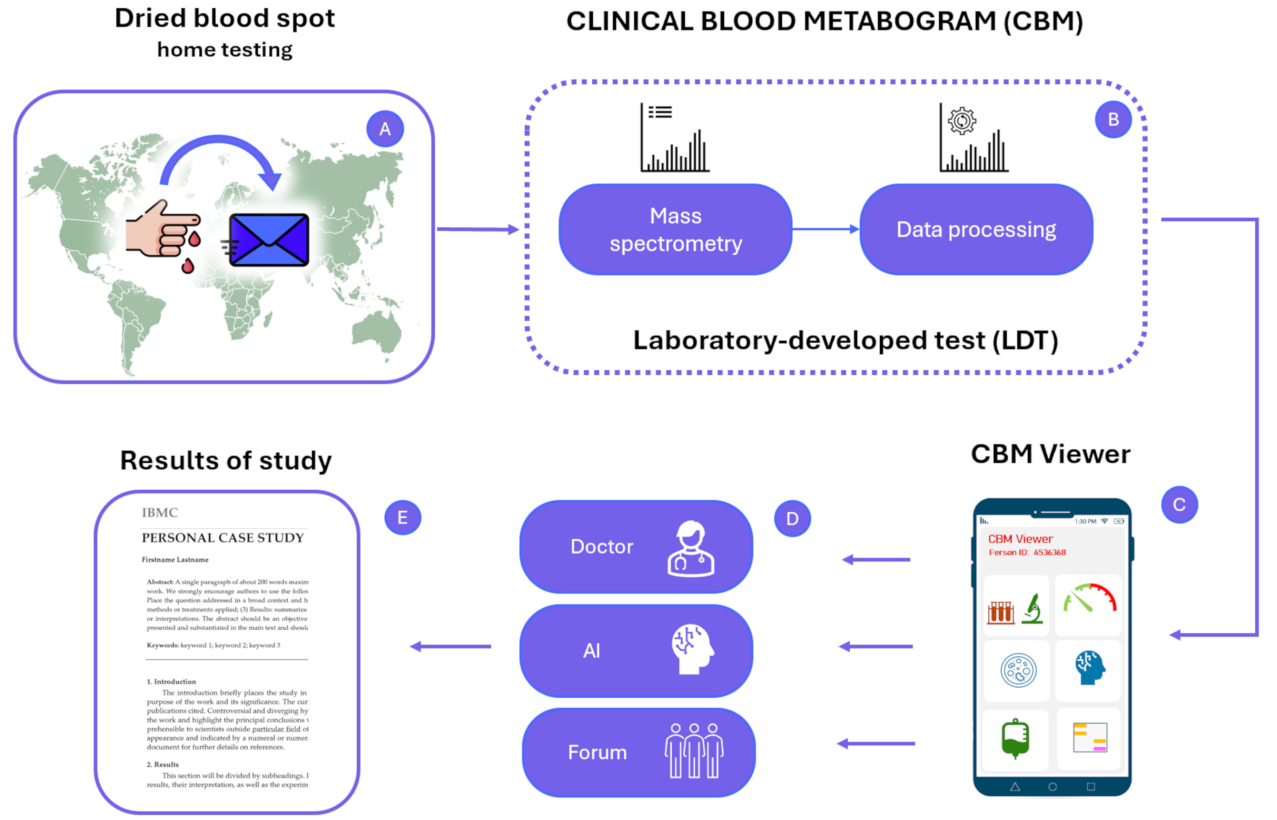

Figure 7. The concept of using a clinical blood metabogram (CBM) as a proprietary test developed by a single laboratory (LDT). The patient takes a blood sample at home and sends it to the laboratory by mail as a dried drop (**A**). In the laboratory, after sample preparation and direct high-resolution mass spectrometry, the clinical blood metabogram data are obtained (**B**). The patient views the metabogram data in a mobile application (**C**) and, if necessary, sends it for interpretation to a physician, artificial intelligence, or posts it for discussion on a specialized forum (**D**). As a result, the patient receives an interpretation of the metabogram in a form accessible to him (**E**).

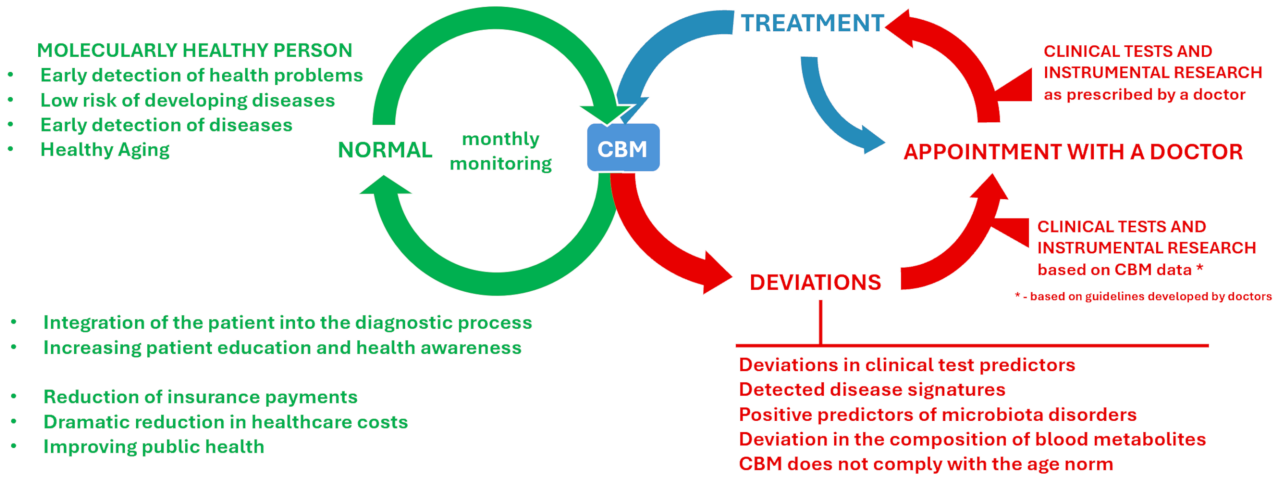

Figure 8. Scheme of integrating a clinical blood metabogram (CBM) into the healthcare system.

In the case of a normative blood metabolome (when the molecular phenotype corresponds to the age norm) the patient is informed about this on an ongoing basis with the frequency of blood sampling for analysis. Thus, self-monitoring of the patient's health state is maximally automated, simplified and accessible to people with different levels of knowledge.

Patient participation in interpreting deviations in the CBM is slightly more complicated than monitoring the norm. The patient is involved in the research process, which ensures complete self-monitoring of the health status and participation in diagnosis. In the process of working with the mobile application, feedback from the patient to the physician is provided, a collective opinion on the patient's

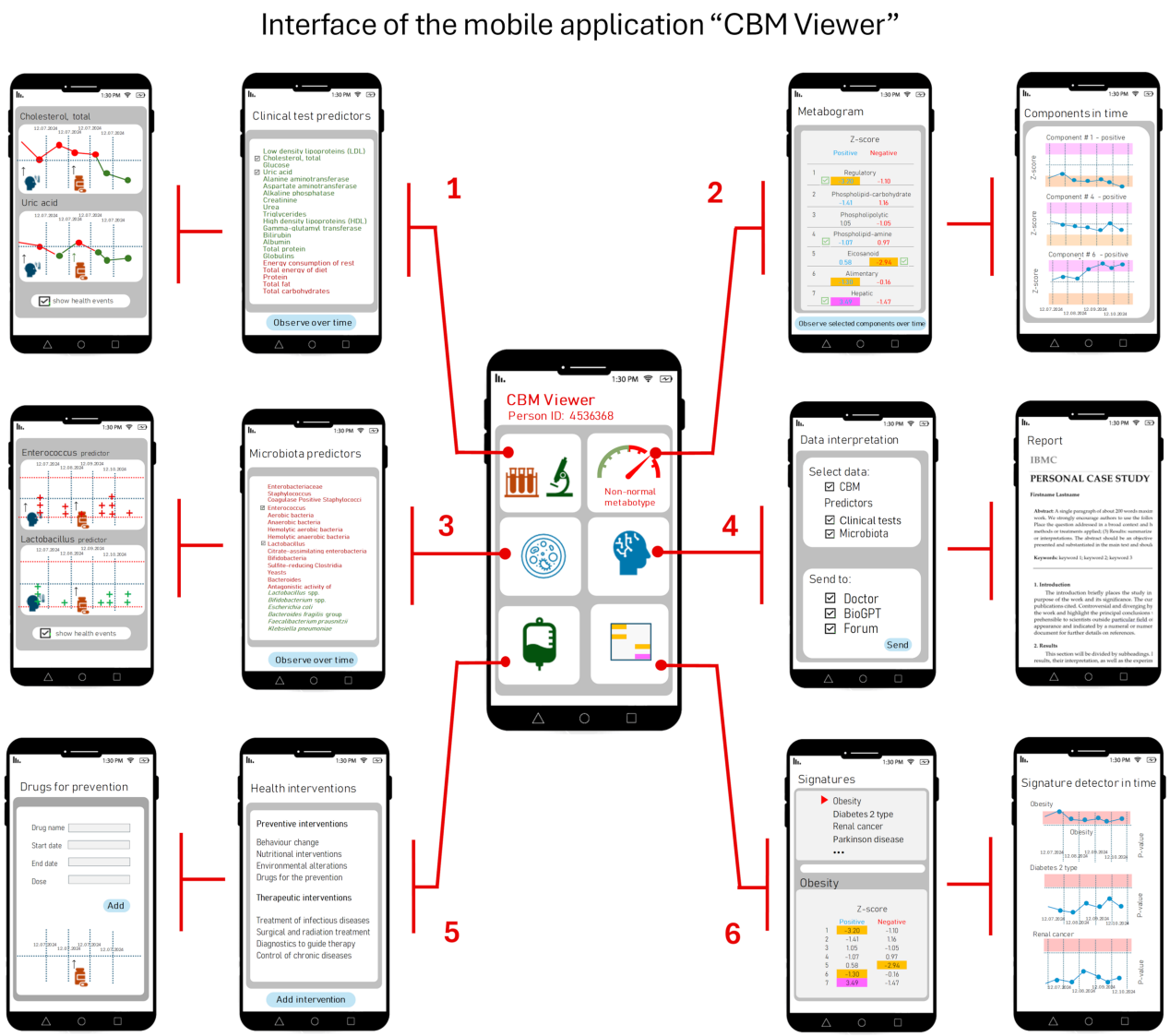

Figure 9. Interface of the CBM Viewer mobile application for viewing the clinical blood metabogram (CBM).
1 – List of clinical laboratory tests for which the results are predicted from the blood metabolome data. By selecting the tests, the change in their values over time can be viewed.
2 – Current values of the clinical blood metabolome. By selecting the metabolome components, their change over time can be viewed.
3 – List of intestinal microbiota tests for which the results are predicted from the blood metabolome data. By selecting the microorganisms, their values on the graph can be viewed along with the previously obtained data.
4 – Selecting data to send for interpretation (CBM data, predicted blood tests and microbiota). Formatted data is sent to a physician, to a specialized forum or artificial intelligence (BioGPT), the results of which can be presented in a publication format (with sections “introduction”, “methods”, “results and discussion”).
5 – Health event tracking, which allows registering the impact of these events on the blood metabolome.
6 – Disease signatures known at the moment. By selecting a disease signature, it can be overlayed on metabolomic data obtained at different times.
The mobile application interface shown has been simplified to adapt to the publication format.

health is obtained, and an opinion of artificial intelligence is obtained. The network nature of the CBM service allows, on the basis of informed consent, to permanently supplement the statistical models of the CBM with personal data, which will improve the accuracy of diagnostics and acquire new diagnostic competencies.

Thus, the CBM dissemination can potentially have an impact on disease prevention, lifestyle modification by people, raising public awareness of their health, improving health literacy, helping people acquire skills in monitoring their health, diet and exercise parameters, as well as the ability to optimize them using accessible and objective health parameters provided by CBM.

9. REGULATORY FRAMEWORK FOR CBM

In many countries, especially with an innovative form of economy, there is a simplification of registration requirements for LDTs [15]. For example, in the United States, the FDA has historically viewed LDTs as tests that pose less risk to patients than most commercial testing kits, and has therefore exempted them from almost all regulatory requirements under the Federal Food, Drug, and Cosmetic Act (FD&C Act). The exact number of organizations that use LDT is unknown, because reporting to the FDA is voluntary.

In Russia, in 2021, Federal Law no. 128-FZ of April 30, 2021 ("On Amendments to the Federal Law "On the Fundamentals of Protecting the Health of Citizens in the Russian Federation" and Articles 12 and 22 of the Federal Law "On Licensing Certain Types of Activities") was adopted, which effectively established a model for special regulation of medical devices with the LDT status: medical devices for diagnostics manufactured and used in a medical organization were exempted from the registration procedure. This means that all regulations governing unregistered medical devices apply to LDT:

- Order of the Ministry of Health of Russia dated 02.11.2021 no. 1031n "On approval of the Procedure for the manufacture, storage, use, disposal or destruction of unregistered medical devices for *in vitro* diagnostics" (came into force on March 1, 2022, valid until March 1, 2028);
- Rules on unregistered medical devices for *in vitro* diagnostics (RF Government Resolution dated 24.11.2021 no. 2026). The rules are valid from March 1, 2022 to March 1, 2028.

Russian requirements for LDT-type medical devices:

- lack of analogues;
- manufacture by an organization exclusively for its own use (i.e. the organization that manufactured the LDT cannot transfer them to another organization, and the latter cannot provide services using such medical devices);
- at least one of the following requirements must also be met: 1) the LDT is intended for the diagnosis of rare diseases; 2) the cost of technical and clinical trials for the purpose of registration exceeds the cost of materials for the manufacture of such products.

In addition, a medical organization must have a license for services that use such products. Thus, the use of CBM in the LDT format became possible without registration as a result of the adoption of Federal Law no. 128-FZ.

CONCLUSIONS

Clinical laboratory diagnostics has faced an existential challenge. Monomarker laboratory tests, which dominate in clinical practice and old intentions in developing new tests, are unable to solve the problem due to the multitude of nosologies and the huge variety of their course. As a result, diagnostic errors that lead to severe consequences require urgent and effective measures in clinical laboratory diagnostics. Science suggests moving to panoramic measurements, especially of low-molecular substances in the blood. The CBM is the result of these efforts in Russia. The fundamental principles that formed the basis for the creation of the CBM determined its sensitivity to all significant deviations in the body for health, which include diseases and more, and the multiparametric nature of CBM — high specificity of detection of these deviations. The implementation of the CBM in the LDT format will allow its massive introduction into practical healthcare, changing its appearance.

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COMPLIANCE WITH ETHICAL STANDARDS

This article does not contain any research involving humans or the use of animals as objects.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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КЛИНИЧЕСКАЯ МЕТАБОЛОМИКА: ТЕКУЩЕЕ СОСТОЯНИЕ И ПЕРСПЕКТИВЫ В РОССИИ

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Используемые сегодня в науке аналитические технологии позволяют измерять всё разнообразие молекул даже в небольшом количестве биологического образца. В частности, метаболомные технологии сделали возможным одномоментный анализ тысяч низкомолекулярных веществ в одной капле крови. Такая аналитическая эффективность открывает новые возможности для клинико-лабораторной диагностики, в которой до сих пор используют измерение лишь ограниченного числа клинически значимых веществ. Однако на пути внедрения метаболомики в клиническую практику существует ряд объективных трудностей. Институт биомедицинской химии (ИБМХ), консолидируя усилия ведущих научных и медицинских организаций, добился успехов в данном направлении, разработав клиническую метабограмму крови (КМК). С её использованием открываются возможности получения обзорной информации по состоянию организма с детализацией индивидуальных метаболических характеристик пациента. В ряде научных исследований показано, что КМК является действенным инструментом по контролю состояния организма, а на основе паттернов, формируемых КМК (сигнатур), можно осуществлять диагностику и контроль лечения многих заболеваний. На сегодняшний день создание КМК определяет текущее состояние и перспективы клинической метаболомики в России. Данная статья, приуроченная к 80-летнему юбилею ИБМХ, является обзором этих достижений с обсуждением их внедрения в клиническую практику.

Полный текст статьи на русском языке доступен на сайте журнала (http://pbmc.ibmc.msk.ru).

Ключевые слова: клиническая метаболомика; клиническая метабограмма крови; диагностика заболеваний; масс-спектрометрия

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