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ANALYSIS OF METABOLOMIC AND GENOMIC MARKERS FOR DIAGNOSING CARDIOVASCULAR DISEASES

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Cardiovascular disease is the leading cause of death in the population. Unfortunately, cardiovascular disease and its associated risks are often difficult to diagnose due to the many factors associated with age and other comorbidities that lead to significant uncertainty in diagnostic classification and therapeutic decision making. Therefore, there is a great need to find new biomarkers for more accurate diagnosis, risk assessment and treatment recommendations for both acute and chronic cardiovascular disease. This article presents an analysis of metabolomic and genomic markers used for the diagnosis of cardiovascular disease. The study of the metabolome in combination with the genome and proteome can provide important information about both the pathogenesis of cardiovascular disease and the ability to search for and identify new cardiovascular disease biomarkers. Along with the fundamental data on new cardiovascular disease biomarkers, there is an urgent need for further research confirming their great potential for practical health care.

Keywords: metabolomic markers; genomic markers; cardiovascular diseases.

АНАЛИЗ МЕТАБОЛОМНЫХ И ГЕНОМНЫХ МАРКЕРОВ ДЛЯ ДИАГНОСТИКИ СЕРДЕЧНО-СОСУДИСТЫХ ЗАБОЛЕВАНИЙ

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Сердечно-сосудистые заболевания являются основной причиной смертности среди населения. К сожалению, сердечно-сосудистые заболевания и ассоциированные с ними риски часто трудно диагностировать из-за многих факторов, связанных с возрастом, и других сопутствующих заболеваний, которые приводят к значительной неопределенности в диагностической классификации и принятии терапевтических решений. Следовательно, существует большая потребность в поиске новых биомаркеров для более точной диагностики, оценки риска и составления рекомендаций по лечению как острых, так и хронических сердечно-сосудистых заболеваний. В данной статье представлен анализ метаболомных и геномных маркеров, использующихся для диагностики сердечно-сосудистых заболеваний. Изучение метаболома в сочетании с геномом и протеомом может дать важную информацию о патогенезе сердечно-сосудистых заболеваний и предоставить возможность поиска и идентификации новых биомаркеров этого состояния. Наряду с фундаментальными данными о новых биомаркерах сердечно-сосудистых заболеваний, остро стоит вопрос о необходимости дальнейших исследований, подтверждающих их большой потенциал для практического здравоохранения.

Ключевые слова: метаболомные маркеры; геномные маркеры; сердечно-сосудистые заболевания.

According to contemporary concepts, the search for new markers on the risk of cardiovascular diseases (CVD) is the subject of intensive study and discussion in the scientific literature. Specialists from various industries and fields are involved, and modern molecular technologies are used to solve the problem of high-quality diagnostics of CVD, which is considered nowadays

List of abbreviations

CVD: cardiovascular disease; ANP: atrial natriuretic peptide; eNOs: endothelial nitric oxide synthase; IL: interleukin; MMP: matrix metalloproteinase; NT-proBNP: N-terminal pro-b-type natriuretic peptide; TIMP-1: tissue inhibitor of metalloproteinases-1; VCAM-1: vascular cell adhesion molecule-1.

as the main cause of population mortality and disability. Currently, metabolomics and genomics represent one of the main "omic" sciences and a logical conclusion in the systemic study of biological objects.

The search for patent documents was performed using the PatSearch search engine in the arrays of published patent documents from patent offices of IP-5 countries, as well as the Russian Federation, Commonwealth of Independent States (CIS) countries, and the international patent offices of the World Intellectual Property Organization (WIPO) and the Eurasian Patent Office (EAPO) [1]. The search for scientific literature was conducted in databases, such as PubMed, CyberLeninka, Web of Science, PatentDB, Science Direct Open Access, Scopus, eLibrary, etc.

Metabolic markers of pathophysiological processes in CVD can be conditionally divided into several groups.

Group I includes markers of left ventricular function and neuroendocrine activation, including type B natriuretic peptide (BNP)/N-terminal pro-BNP (NT-proBNP), atrial natriuretic peptide (ANP), cardiac troponins hs-cTnT/hscTnI, copeptin, adrenomedullin, endothelin-1, melatonin, etc.

Group II includes inflammatory markers, such as type 1 intercellular adhesion molecule (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), E-selectin (ELAM-1), interleukins (1α, 1β, 4, 5, 6, 8, 10, 12, 13, 17, 18, 33, etc.), tumor necrosis factor (TNFα), YKL-40, C-reactive protein (CRP), soluble CD40 ligand (sCD40L), NOTCH1 transmembrane protein, growth factor GDF15, stimulating growth factor ST-2, interferon-gamma, lipoprotein-associated phospholipase A2 (Lp-PLA2), ceruloplasmin, myeloperoxidase, etc.

Group III includes markers of the hemostasis system (coagulation factors), including fibrinopeptide A, P-selectin, tissue plasminogen activator t-PA, fibrinogen, homocysteine, von Willebrand factor, endothelin, thrombomodulin, etc.

Group IV includes markers predictors of lipid metabolism disorders, such as total cholesterol, high and low-density lipoproteins, apolipoprotein A1 (Apo A1), apolipoprotein B (Apo B), lipoprotein (a), triglycerides, very-low-density lipoproteins, retinol-binding protein 4, leptin, homocysteine, paraoxonase (PON), etc.

Group V includes markers of myocardial fibrosis, as well as galectin-3, tissue inhibitor of metalloproteinases-1 (TIMP-1), TIMP-2, procollagen type I carboxyterminal propeptide, matrix metalloproteinase 9 (MMP-9), MMP-3, stimulating growth factor ST-2, NT-proBNP, total cholesterol, low and high-density lipoproteins, triglycerides, fatty acids, type IV collagen, etc.

Group VI includes markers of myocardial necrosis, such as creatine phosphokinase and its MB fraction, as well as troponin.

Group VII includes markers of endothelial dysfunction, including homocysteine, asymmetric dimethylarginine, endothelin-1, soluble sVCAM-1, ICAM-1, sICAM-1, VCAM-1, endothelial nitric oxide synthase (eNOs), etc.

The simultaneous determination and analysis of several markers provide a complete presentation of the pathogenesis of CVD since they reflect various pathophysiological aspects. Many studies confirm the importance of the multimarker strategy. For example, the level of markers reflecting the reaction of the acute phase, pro-inflammatory pathways, and activation of endothelial cells and vascular function was simultaneously determined compared with classical risk factors [2, 3]. Inflammatory markers CRP and IL-6 had limited predictive value as risk factors for cardiovascular events (although each of them individually was significantly associated with risk), whereas the inclusion of NT-proBNP increased the quality of the predictive model [4–6].

Other important markers of CVD are ceruloplasmin, myeloperoxidase, and PON [7]. An inverse relationship has been revealed between ceruloplasmin concentration and oxidative stress in acute coronary syndrome [7, 8]. In the development of acute coronary syndrome, increased myeloperoxidase concentrations are associated with a high risk of recurrent events and poor outcomes [9–11]. PON, participating in protection against oxidation of high and low-density lipoproteins, reduces the risk of atherosclerotic lesions. The blood plasma level of PON1 is decreased in patients with a history of myocardial infarction [12].

Despite the variety of biomarkers that was proposed for CVD diagnostics, high diagnostic efficacy has not been revealed in all of them, and not all biomarkers are still available for widespread use in clinical practice due to insufficient

test systems with marketing authorization, which enable laboratories to accurately and reliably issue results as soon as possible, in the territory of the Russian Federation [13].

Many patent documents that are published over the past 10 years simultaneously cover several metabolomic markers, which are expressed as alternatives or variants and refer to several different metabolomic marker groups. The data obtained were analyzed by determining the percentage of each marker group from the indicated seven groups to the total sample of CVD marker-related documents (Fig. 1).

The largest number of patent documents in the field of metabolomic CVD markers refers to myocardial fibrosis (31%) and inflammatory markers (26.71% of documents found). The smallest number refers to endothelial dysfunction markers (4.06% of the documents found), which indicates the need for further study of the main cardiovascular continuum components using metabolic profiling and diagnostic significance confirmation.

The use of contemporary molecular biological methods in genetic cardiology analyzes the genomic CVD components, which more accurately determines the molecular mechanisms underlying them [14].

Microribonucleic acids (miRNAs) are most significant in CVD development, as they initiate mRNA degradation or translation repression at the posttranscriptional level. miR-26a-5p was determined to promote activation of myocardial cell autophagy and cardiac hypertrophy by regulating *GSK3*β. MiR26a-5p stimulates *LC3II* and decreases *p62* expression in phenylephrine-induced cardiac hypertrophy in the presence or absence of a lysosomal inhibitor [15]. A negative correlation of miRNA 126 with percutaneous coronary intervention-induced inflammatory markers, such as high sensitivity-CRP and VCAM1 was revealed [16]. Circulating miR-1 is an independent predictor of left ventricular remodeling 6 months after myocardial infarction with *ST*-segment elevation [17]. S.K. Gupta et al. [18] identified miR-22 as a plentiful and potent cardiac autophagy inhibitor.

E.V. Privalova et al. [19] demonstrated the need to determine the MMP-3 and TIMP-1 markers in the blood to assess the degree of fibroblast generation, which largely determines the clinical course of hypertrophic cardiomyopathy.

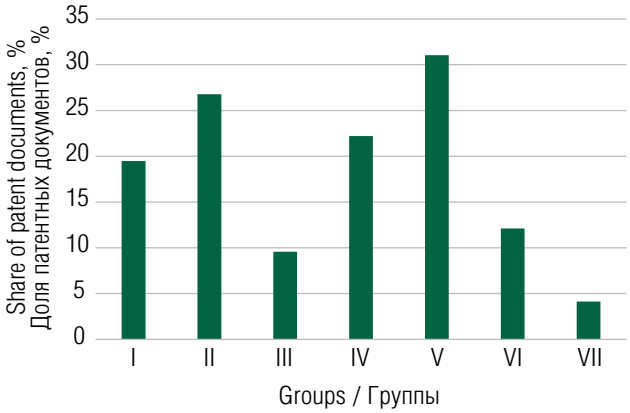

Fig. 1. The share of patent documents of a certain group of markers in the total sample. Here and in Fig. 3: group I — markers of left ventricular function and neuroendocrine noisy activation; group II — inflammatory markers; group III — markers of the hemostasis system (factors of coagulation); group IV — markers predictors of impairment lipid metabolism; group V — markers of fibrosis for the myocardium; group VI — markers of myocardial necrosis; group VII — markers of endothelial dysfunction

Рис. 1. Доля патентных документов определенной группы маркеров в общей выборке. Здесь и на рис. 3: группа I — маркеры функции левого желудочка и нейроэндокринной активации; группа II — воспалительные маркеры; группа III — маркеры системы гемостаза (факторы коагуляции); группа IV — маркеры-предикторы нарушений липидного обмена; группа V — маркеры фиброза миокарда; группа VI — маркеры некроза миокарда; группа VII — маркеры эндотелиальной дисфункции

The detected association of the MMP-3 1171 polymorphism with the TIMP-1 marker indicates a genetically mediated enhancement of proteolytic processes in patients with hypertrophic cardiomyopathy.

The main factors influencing the synthesis and secretion of ANP and BNP are identical, as well as the cardiovascular effects. Expression of the *ANP* gene is revealed mainly in the atria, whereas the main site of BNP synthesis is the ventricular myocardium [20].

The hereditary burden of arterial hypertension was associated with the "mutant" allele of the *AG* gene (polymorphism *M268T*) and the A1666C allele of the *AGTR1* gene. "Mutant" alleles of the angiotensinogen gene (*AGT*) of the *M268T* polymorphism and the "mutant" allele A1666C of the angiotensinogen receptor gene (*AGTR1*) were revealed in 50% of young people with masked arterial hypertension and 50% with stable arterial hypertension [21].

Genetic variability in lipid regulatory genes, especially *APOE*, significantly influences the risk

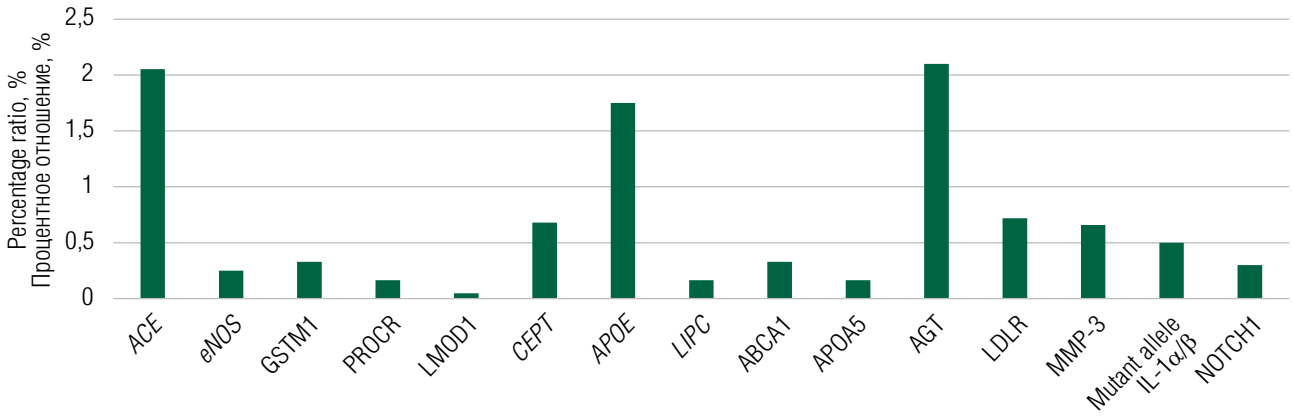

Fig. 2. Genomic markers
Рис. 2. Геномные маркеры

of coronary heart disease. The presence of the APOE4 allele is a significant risk factor for severe coronary stenosis (>70%) [22, 23].

eNOS is involved in many physiological regulatory functions of the cardiovascular system, such as nitric oxide synthesis. A significantly higher proportion of the eNOS T894 allele was revealed in patients with acute coronary syndrome compared with controls ($p = 0.006$) and patients with stable angina pectoris ($p = 0.005$) [24]. The rs1799983 eNOS Glu298Asp polymorphism in patients with chronic kidney disease is associated with relevant subclinical cardiac remodeling [25].

As in the case of metabolomic markers, the analysis of the data obtained was performed by determining the percentage ratio of each genomic marker to the total sample of documents related to CVD markers.

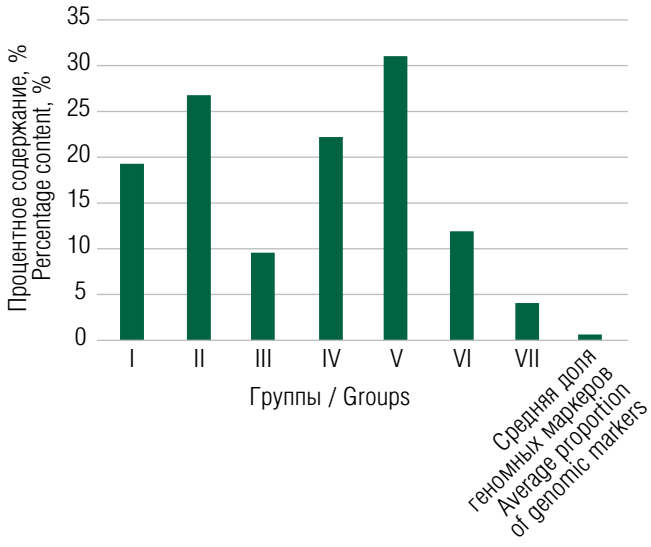

Fig. 3. Comparison of metabolomic and genomic markers
Рис. 3. Сравнение метаболомных и геномных маркеров

Concurrently, no documents related to genes *14q23-q24*, *PECAM1*, *SREBFs*, *USF1*, *ANP*, and *BNP* were revealed in the used sample.

The percentage ratio of each genomic marker to the total sample of documents related to CVD markers is presented in Fig. 2.

As noted in the metabolomic marker discussions, certain mutant variants of IL-1α, IL-1β, and NOTCH1 are also used as genomic CVD markers, which is illustrated in Fig. 2.

The largest number of patent documents refer to the use of *AGT* (2.11%), *ACE* (2.05%), and *APOE* (1.76%) genes as genomic CVD markers, whereas the smallest number refers to the use of *LMOD1* (0.01%), *APOA5* (0.14%), and *LIPC* (0.15%).

The percentage comparison of seven groups of metabolic markers in the total sample of documents related to CVD markers with the average percentage for genomic markers is presented in Fig. 3

According to the presented data, inventors show a noticeably greater interest in metabolic CVD markers than the genomic ones, which is evident from the higher percentage of metabolomic markers relative to genomic ones in the sample of patent documents related to CVD markers.

The analysis of patent activity over the past 10 years in the field of inventions related to metabolic and genomic CVD markers demonstrated stable increased patent documents published almost throughout the entire period under study (Fig. 4).

From 2010 to 2017, across all the arrays, a steady increase in published patent documents, related to metabolomic and genomic markers of

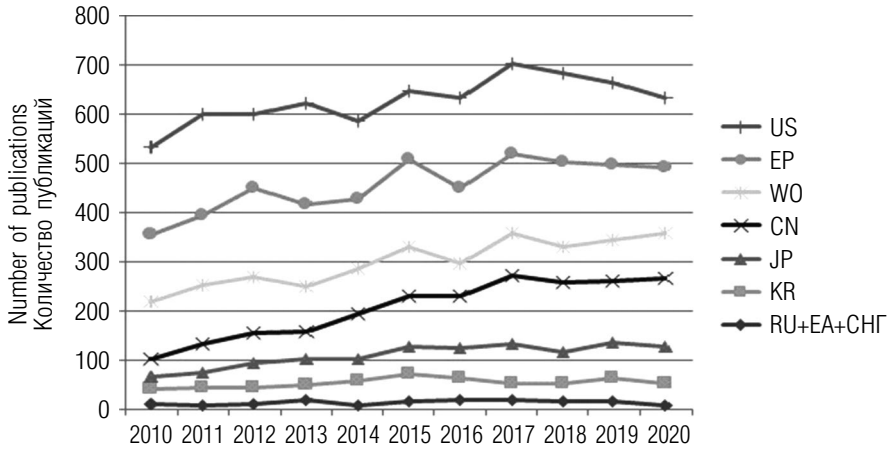

Fig. 4. Dynamics of publications of patent documents for markers of cardiovascular diseases in 2010–2020 by country. US — United States of America; EP (EPO) — European Patent Office; WO (WIPO) — World Intellectual Property Organization; CN — China; JP — Japan; KR — South Korea; RU+EA+CIS — Russia + Eurasian Patent Office + Commonwealth of Independent States

Рис. 4. Динамика публикаций патентных документов на маркеры сердечно-сосудистых заболеваний за 2010–2020 гг. по странам. US — Соединенные Штаты Америки; EP (ЕПВ) — Европейское патентное ведомство; WO (ВОИС) — Всемирная организация интеллектуальной собственности; CN — Китай; JP — Япония; KR — Южная Корея; RU+EA+СНГ — Россия + Евразийское патентное ведомство + Содружество Независимых Государств

CVD has been reported. Since 2017, an insignificant decline in patent activity in this field is found in most patent offices, except for Japan, the People's Republic of China, and WIPO.

Publication ratio analysis of patent documents related to inventions in the field of metabolic and genomic CVD markers at the beginning and end of the study period revealed the distribution of inventive activity by country over the last decade (Fig. 5).

The inventors of the United States of America and Europe are the most active, and the filing of international applications under the PCT system is also of interest to inventors, as one of the most convenient opportunities for submitting applications to the national offices of the countries of interest. By 2020, China has reached almost the same level as the USA and Europe in terms of the number of published patent documents in this field. A relatively small segment is made up of patent documents designated in the figures as "RU + EA + CIS," which include arrays of patent documents of the EAPO and the CIS countries, including the Russian Federation, which indicates a developing technology market.

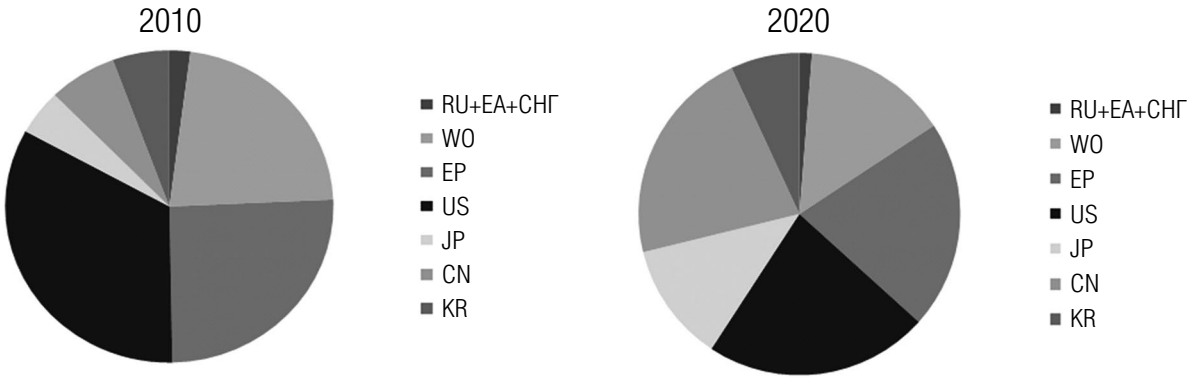

Fig. 5. Ratio of publications of patent documents for markers of cardiovascular diseases by country for 2010 and 2020. RU+EA+CIS — Russia + Eurasian Patent Office + Commonwealth of Independent States; WO (WIPO) — World Intellectual Property Organization; EP (EPO) — European Patent Office; US — United States of America; JP — Japan; CN — China; KR — South Korea

Рис. 5. Соотношение публикаций патентных документов на маркеры сердечно-сосудистых заболеваний по странам за 2010 и 2020 гг. RU+EA+СНГ — Россия + Евразийское патентное ведомство + Содружество Независимых Государств; WO (ВОИС) — Всемирная организация интеллектуальной собственности; EP (ЕПВ) — Европейское патентное ведомство; US — Соединенные Штаты Америки; JP — Япония; CN — Китай; KR — Южная Корея

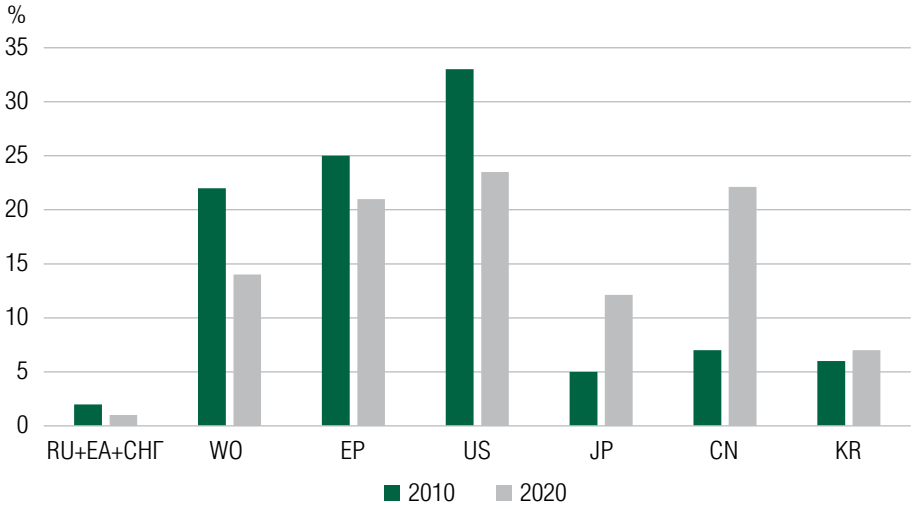

Fig. 6. Publication activity in the field of markers of cardiovascular diseases by country in 2010 and 2020. RU+EA+CIS — Russia + Eurasian Patent Office + Commonwealth of Independent States; WO (WIPO) — World Intellectual Property Organization; EP (EPO) — European Patent Office; US — United States of America; JP — Japan; CN — China; KR — South Korea

Рис. 6. Публикационная активность в области маркеров сердечно-сосудистых заболеваний по странам в 2010 и 2020 гг. RU+EA+СНГ — Россия + Евразийское патентное ведомство + Содружество Независимых Государств; WO (ВОИС) — Всемирная организация интеллектуальной собственности; EP (ЕПВ) — Европейское патентное ведомство; US — Соединенные Штаты Америки; JP — Япония; CN — Китай; KR — Южная Корея

Attention should be paid to the change in publication activity in 2010 and 2020 as a percentage of the total number of publications of patent documents for the selected countries for analysis (Fig. 6).

A slightly decreased interest in this field in several countries, which are most active in the patenting of metabolomic and genomic CVD markers, is noteworthy, namely the activity decreased from 33% in 2010 to 23% in 2020 in the USA and from 25% to 21% in Europe; the number of international applications also decreased from 22% to 14%. The publication activity analysis of the patent offices of the CIS, including the Russian Federation, as well as in the EAPO, revealed that the number of publications of patent documents on this subject in the CIS countries has been halved. However, activity has sharply increased from 7% in 2010 to 22% in 2020 in the People's Republic of China and from 5% to 12% in Japan, as well as the number of publications in the Republic of Korea from 6% to 7%.

Thus, the study of metabolomic and genomic markers of CVD is of high practical importance. The integration of metabolomics data with other orthogonal technologies, such as genomics and proteomics will provide an even deeper understanding of the main biological pathways and mechanisms of disease development, particularly CVD. Analysis of the array of patent documents over the past 10 years concluded a rather stable situation with the patenting of inventions in the field of CVD diagnostics related to new metabolomic and genomic marker identifications of these pathologies. The increased patent activity in the Oriental countries indicates a clear interest of the inventors of the People's Republic of China, the Republic of Korea, and Japan and stable research funding in this field; therefore, this field can be attributed to investment-attractive under conditions of the developing technology market.

Conflict of interest. The authors declare no conflict of interest.

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