Systematic Review

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Pharmacogenomics

ADME pharmacogenetics: future outlook for Russia

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This systematic review reflects the results of pharmacogenetic studies in the Russian Federation aimed at studying the genes involved in the drug biotransformation system. The works of Russian researchers found by us are mostly devoted to microsomal liver oxidation enzymes (metabolism) and membrane transporter systems (absorption and excretion). This review presents population-ethnic and associative clinical studies on the genes of the *CYP450* system, noncytochrome oxidation enzymes (*SULT1A1*, *CES1*), membrane transporter system genes (*ABCB1*, *SLCO1B1*) and warfarin biotransformation enzymes (*VKORC1*, *GGCX*). The information is structured in the form of 11 tables, divided by regions of the Russian Federation.

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In recent years, growing attention has been paid to the principles of personalized medicine in the treatment of many diseases in the Russian Federation. Although Hippocrates pointed to the importance of these principles [1]: "It is more important to know what sort of person has a disease than to know what sort of disease a person has" – their application is only now becoming possible. Fundamental knowledge accumulated during the development of evidence-based medicine showed that the genotypic and phenotypic characteristics of the patient determine the predisposition to the disease, response to the drug and effectiveness of treatment in general [2]. The use of pharmacogenetics plays an important role in eliminating the variability of the response to a drug. During preclinical studies, the main metabolic pathway of metabolism is established for each drug. Further on, it is necessary to conduct a large number of additional studies to clarify specific stages of metabolism. Identified application points in the form of transporters, receptors, enzymes, ion channels – among others, may differ by their functional capabilities, which is associated with changes in the genes that encode the listed targets. In turn, the determination of these genetic features of the patient allows prediction of response to the drug.

The Clinical Pharmacogenetics Implementation Consortium (CPIC®) accumulates all the knowledge in this field. To date, they have developed complete recommendations for dosing or prioritizing 35 drugs, taking into account the results of pharmacogenetic testing and 335 proven genes associations [3]. For a more convenient presentation of the results of pharmacogenetic testing, CPIC proposed the division of patients into phenotypic groups: normal metabolizer, rapid metabolizer, ultrarapid metabolizer, intermediate metabolizer, poor metabolizer. According to this division, further recommendations for dosing or priority selection of medicines are based.

With the accumulation of knowledge in pharmacogenetics, racial and ethnic particularities in the prevalence of genetic polymorphisms have begun to emerge. At the same time, the carriage frequency of allelic variants may vary significantly among representatives of different races and nationalities. This becomes especially important for such multinational countries as the Russian Federation, which numbers 194 different ethnic groups [4].

The objective of this systematic review was to summarize current research in the field of pharmacogenetics in the Russian Federation.

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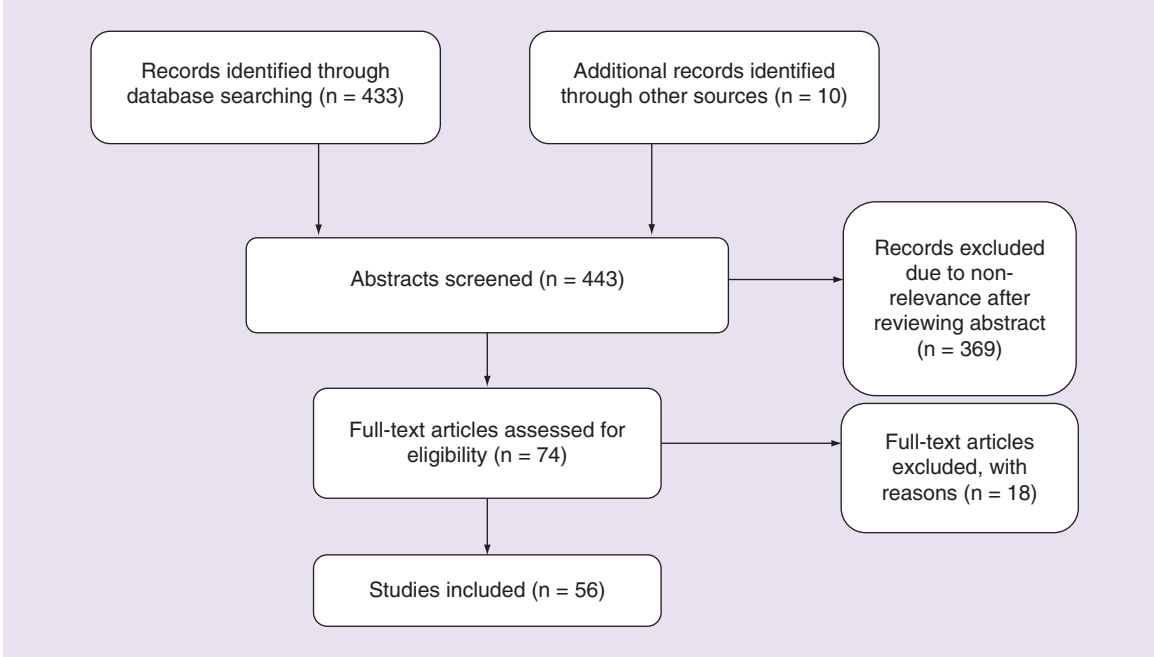

Figure 1. Flowchart of the literature selection process.

Materials & methods

Search strategy

The authors conducted an online search for articles in December 2018 using the following databases: PubMed, Google Scholar, eLIBRARY (Russian electronic library of scientific publications). The search strategy combined key terms «Russia», «Russian» with terms associated with polymorphic marker including: «P450», «CYP2C19», «CYP2D6», «CYP2B1», «CYP2B6», «CYP2E1», «CYP2C8», «CYP2C9», «CYP3A4», «CYP3A5», «CYP1A1», «CYP1A2», «CYP4F2», «CYP4F1», «ABCB1», «SLCO1B1», «VKORC1», «GGCX», «SULT1A1», «CES1», «gene», «genes», «pharmacogenetics», «pharmacogenomics», «ethnic group». A thorough review of the references in relevant articles was also completed with citations from all searches.

Systematic review

The search produced 443 articles (Figure 1). After removing duplicates, the titles and abstracts were screened for relevance based on inclusion criteria – the presence of results of pharmacogenetic testing. A total of 369 articles were excluded due to non-relevance of the inclusion criteria. After analyzing 74 full-text articles, 18 were excluded due to the inability to reproduce the results of genotyping and to calculate the prevalence rate of the alleles.

Results & discussion

All processes associated with the pharmacokinetics of a substance in the body are described by the abbreviation ADME, where A is absorption, D is distribution, M is metabolism and E is excretion. The work of Russian researchers collated by us are mostly devoted to microsomal liver oxidation enzymes (metabolism) and membrane transporter systems (absorption and excretion). Within the framework of this systematic review, two groups were identified: clinical trials involving healthy volunteers (designated as healthy) and clinical trials in patients with a specific nosology. If the authors of the study did not indicate the ethnicity of the research participants, we marked this characteristic as 'general population'. In addition, we identified three categories of research: purely population-ethnic works, which studied only the carriage frequency of allelic variants among representatives of different ethnic groups, associative clinical studies that investigated the relationship between the carrier state of allelic variants and the change in a certain physiological parameter of research participants as well as work aimed at developing drug dosing algorithms, taking into account the results of pharmacogenetic testing. Next, Tables 1–10 will present population-ethnic data, and the subsections describe the results of associative studies. Data on the study of minor alleles are presented in Supplementary Table 1.

Table 1. Allele and genotype frequencies of *CYP2C9* gene in different ethnic groups in Russia.

Region of the Russian Federation	Ethnic group	Number of patients	Characteristics of the population	Allelic variants						Ref.
				*2			*3			
				Wt/Mt	Mt/Mt	%	Wt/Mt	Mt/Mt	%	
Dagestan Republic	Laks	46	Healthy	–	–	–	12	3	19.56	[5]
	Avars	90		–	–	–	22	3	15.55	
	Dargins	50		–	–	–	15	1	17.00	
European part of Russia:										
– Moskow	Russians	63	Atrial fibrillation	13	2	13.49	14	2	14.29	[6]
	Russians	352	Healthy	80	2	11.90	33	1	5.00	[7]
	Russians	83	B-cell chronic lymphocytic leukemia	20	0	12.04	13	0	7.83	[8]
		76	Non-Hodgkin lymphoma	9	0	5.92	15	1	11.18	
		177	Healthy	29	0	8.19	21	0	5.93	
	General population	91	Warfarin taking	17	2	11.54	18	1	10.99	[9]
– Voronezh	Russians	290	Healthy	57	2	10.51	37	1	6.72	[10]
– Saint Petersburg	General population	298	Healthy	58	4	11.07	37	1	6.54	[11]
		62	Warfarin taking	11	0	8.87	6	0	4.84	
– Ufa	Russians	319	Healthy	17	0	7.59	24	0	9.02	[12]
	Tatars	279		11	0	5.14	14	0	5.43	
	Bashkirs	144		7	0	6.14	8	0	6.15	
– Karachay-Cherkessia	Circassians	77	Healthy	–	–	–	19	0	12.30	[13]
	Karachays	125		–	–	–	58	2	24.8	
– Stavropol	Russians	25	Healthy	6	0	12.00	3	0	6.00	[14]
	Armenians	25		7	0	14.00	7	0	14.00	
	Karachays	25		2	0	4.00	5	0	10.00	
	Circassians	32		4	0	6.00	6	0	9.00	
Siberia:										
– Yakutsk	Yakuts	229	Healthy	7	1	5.05	10	1	6.74	[15]
– Cheriktei	Yakuts	88	Healthy	2	0	1.10	1	0	0.60	[16]
– Kyzil	Tuvinians	88		2	0	1.10	9	0	5.10	
– Buriatia	Buryats	88		4	0	2.30	3	0	1.70	
– Altai	Altaians	87		10	0	5.70	14	1	9.20	
– Tomsk	Russians	87		19	1	12.10	8	1	6.80	
	General population	250	Breast cancer	11	0	8.87	36	3	9.00	[17]
Far East:										
– Khabarovsk	Nanai	70	Healthy	0	0	0.00	8	0	5.70	[18]
Ural:										
– Chelyabinsk	General population	63	Cardiac patients	13	1	11.90	10	0	7.94	[19]

CYP450 enzymes

CYP2C9

Cytochrome *CYP2C9* gene has more than 60 allelic variants [20], but in clinical practice the largest role is played by alleles **2*, **3*, **5*, **6*, **8* and **11*, the carrier of which is associated with reduced function of the enzyme. CYP2C9 is involved in the metabolism of several important drugs with low therapeutic index, namely: S-warfarin, fluvastatin, S-acenocoumarol, ibuprofen, phenytoin, tolbutamide, nateglinide. Accordingly, it is necessary to take into account carriage of slow alleles of *CYP2C9* gene encoding the same name isozyme, in order to avoid adverse drug effects in the appointment of listed drugs [21]. In particular, carriage of **2*, **3*, **5* and **6* alleles are taken into account when

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Table 2. Allele and genotype frequencies of *CYP2C9, VKORC1* and *GGCX* genes in different ethnic groups in Russia.

Region of the Russian Federation	Ethnic group	Number of patients	Characteristics of the population	Allelic variants			Ref.
				Wt/Mt	Mt/Mt	%	
***CYP2C9* rs9332242**							
Kursk	General population	561	CHD	100	3	9.40	[25]
		694	Healthy	124	12	10.70	
		425	Essential hypertension	80	4	10.50	[26]
		391	Healthy	71	7	11.10	
***CYP2C9* rs4918758**							
Kursk	General population	561	CHD	257	42	30.40	[25]
		694	Healthy	302	82	33.60	
***CYP2C9* rs61886769**							
Kursk	General population	561	CHD	168	16	17.80	[25]
		694	Healthy	220	23	19.20	
***VKORC1* – 1639 G > A rs9923321**							
Yakutsk	Yakuts	89	Healthy	28	60	83.14	[15]
Moscow	Russians	63	Atrial fibrillation	24	12	38.10	[6]
Moscow	General population	91	Warfarin taking	26	20	36.26	[9]
***GGCX* rs11676382**							
Moscow	Russians	63	Atrial fibrillation	6	0	4.76	[6]

CHD: Coronary heart disease.

calculating the dose of warfarin (available on the resource WarfarinDosing.org) [22]. When identifying carriage of **8* and **11* alleles in patients of African descent, it is additionally recommended to reduce the calculated dose by 15–30% [23].

The carriage frequency of these allelic variants differs among representatives of various ethnic groups. *CYP2C9*2* is most common among Middle Eastern – 13.21%, Europeans – 12.60%, south/central Asian – 10.74%, quite rare among Americas – 6.25% and practically does not occur among representatives of African – 2.36%, African–American – 2.30% and east Asian – 0.06%. *CYP2C9*3* is common among representatives of south and central Asian – 10.17%, Middle Eastern – 9.31%, Caucasian – 7.08% but rarely occurs in the African–American – 1.17% and African population – 1.03%; **5, *6, *8* and **11* allelic variants with different frequencies occur mainly in people of African origin 0.77–6.66% [24].

At present, a large number of pharmacogenetic studies have been conducted on this gene in Russia. Cumulative information about the main characteristics of the studied population and the allele frequencies of the studied gene are presented in Tables 1 and 2.

Analysis of Russian works shows that the prevalence frequency of allelic variants *CYP2C9*2* and *CYP2C9*3* has its own peculiarities. Thus, **2* allelic variant prevails among Russians and Armenians as representatives of the Europoid race, and is rarely found among representatives of the Mongoloid race, namely: Yakuts, Buryats, Tuvinians. What is important, **3* allelic variant is widespread among representatives of the Caucasian peoples: Circassians, Laks, Avars and Dargins – which indicates the validity of pharmacogenetic testing in this group of patients.

The analysis of the results also revealed a specific feature of our country: the frequency of allelic variants prevalence both among Russians and in the general population changes depending on the region. This is probably due to population migration and inter-ethnic marriages.

One of the first applications of pharmacogenetic testing began in the Moscow region. Gra *et al.* studied the carriage frequency of *CYP2C9* allelic variants in Russian patients with B-cell chronic lymphocytic leukemia and Non-Hodgkin lymphoma in comparison with healthy patients. The study revealed a higher prevalence of allelic variant *CYP2C9*2* in men with B-cell chronic lymphocytic leukemia (OR = 2.38; 95% CI: 1.1–5.2), as well as a combination of *CYP2C9*2* and *CYP2C9*3* (OR = 2.09; 95% CI: 1.1–3.9) [8]. The results were used to create a biochip. Ivashchenko *et al.* studied the general population of patients taking warfarin [9]. The obtained results turned out to be comparable with data on the carriage frequency of allelic variants of this gene among representatives of the Caucasians.

Barysheva *et al.* studied the prevalence of *CYP2C9* allelic variants in cardiac patients in the Ural region [19]. Based on the results of pharmacogenetic testing, personalized selection of the warfarin dose was carried out.

Polonikov *et al.* studied rs9332242 and rs4918758 polymorphisms of *CYP2C9* and their possible role in the development of susceptibility to coronary heart disease (CHD) and essential hypertension, but the result was negative [25,26].

Pchelina *et al.* investigated individual sensitivity to warfarin in patients with atrial fibrillation and prosthetic heart valves who received this drug. The results were compared with a healthy population. An association was established between the carriage of *CYP2C9*2* and *CYP2C9*3* alleles and excessive anticoagulation [11].

In Siberia, Seredina *et al.* studied the effectiveness of neoadjuvant chemotherapy in patients with breast cancer [17]. *CYP2C9*2* was associated with neoadjuvant chemotherapy resistance (OR = 4.64; 95% CI: 1.01–20.91).

Sychev *et al.* showed the ineffectiveness of existing Acenocoumarol dosing algorithms based on *CYP2C9* genotyping for Russian patients with Atrial fibrillation [6].

In addition to cytochrome CYP2C9, other enzymes are involved in the metabolism of Warfarin. γ-Glutamyl carboxylase (*GGCX*) oxidizes vitamin K hydroquinone (the active form of vitamin K1) to vitamin K 2,3 epoxide [27]. VKORC1 returns the epoxides formed in the carboxylation reaction to the active form of vitamin K. It becomes clear that changes in the activity of these enzymes will lead to shifts in the vitamin K metabolism cycle and, as a result, changes in the effectiveness of anticoagulant therapy. Therefore, the polymorphisms of these enzymes are taken into account in the dosing regimen of anticoagulants [28].

Vasilyev *et al.* found a high prevalence of *VKORC1* – 1639G> A rs9923321 polymorphism in the Yakut population – 83.14% [15], while the prevalence among patients of the Moscow region was only 36.26% according to Ivashchenko *et al.* [9]. The work mentioned earlier by Sychev *et al.* did not show the effectiveness of existing Acenocoumarol dosing algorithms with regard to the *VKORC1* genotype as applied to the Russian population [6].

CYP2C19

Cytochrome CYP2C19 enzyme is involved in the metabolism of several important classes of drugs: benzodiazepines [29], antidepressants [30], proton pump inhibitors (PPIs) [31], mephenytoin [32] and the antiplatelet prodrug clopidogrel [33]. Currently, 35 allelic variants of the *CYP2C19* gene have been discovered [34]. In pharmacogenetic testing, three alleles are used as polymorphic markers: **2*, **3*, encoding an enzyme with reduced activity, and **17,* a change in the promoter zone, resulting in the formation of a larger amount of enzyme. It should be noted that the simultaneous presence of these two mutations is possible. In this case, the person will have increased expression of the enzyme with reduced activity [35].

The carrier rate of *CYP2C19*2* allelic variant can reach 53.9% among representatives of the Oceanian ethnic groups, common among south/central Asian – 34.3%, east Asian – 29% and is quite rare among representatives of the African–American – 18.3%, Europeans – 14.6% and Middle Eastern – 13.2%. *CYP2C19*3* allelic variant of is not so widespread in the world population: the carriage frequency among representatives of Oceania's ethnic groups reaches 14.5%, among Asians 4–5%, and is quite rare among other ethnic groups – 0.28–0.73%. The reverse trend is observed for *CYP2C19*17* allelic variant: it is rarely found in Oceania - 4.1% and east Asian – 1.31%, but is widespread in Middle Eastern – 21.6%, Caucasians – 21.3% and African–American – 21% [36].

Cumulative information about the main characteristics of the studied population and the frequency of *CYP2C19* alleles are presented in Table 3.

Analysis of the work of Russian researchers revealed a wide spread of *CYP2C19*2* and *CYP2C19*17* allelic variants in the population, while *CYP2C19*3* is less common and is mainly found in representatives of the Mongoloid race. The prevalence of the polymorphisms of this gene is consistent with global data for the respective races.

In clinical practice, pharmacogenetic testing of the *CYP2C19* gene is used to reduce adverse drug events in patients with cardiovascular diseases. Mirzaev *et al.* estimated the prevalence of alleles in Russian patients with acute coronary syndrome (ACS) in the Moscow region and Siberia. Statistically significant differences were found in *CYP2C19*3* allele frequency between the Russian ethnic group patients from eastern and central Siberia ($p = 0.001$; odds ratio = 1.05 [95% CI: 1.01–1.09]) [39]. Barysheva *et al.* used the results of pharmacogenetic testing of *CYP2C19* gene to personalize antiplatelet therapy in patients with ACS [19]. Fedorinov *et al.* studied the prevalence of alleles of this gene in Russian and Yakut patients with ACS and peptic ulcer disease in order to personalize therapy [45].

Muslimova *et al.* found association between carriage of *CYP2C19* 681A allele and a higher degree of platelet aggregation induced by Adenosine diphosphate in patients with coronary heart disease [46]. Golukhova *et al.* studied

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Table 3. Allele and genotype frequencies of *CYP2C19* gene in different ethnic groups in Russia.

Region of the Russian Federation		Ethnic group	Number of patients	Characteristics of the population	Allelic variants									Ref.
					*2			*3			*17			
					Wt/Mt	Mt/Mt	%	Wt/Mt	Mt/Mt	%	Wt/Mt	Mt/Mt	%	
Dagestan Republic		Laks	46	Healthy	11	1	14.13	2	0	2.17	17	1	20.65	[5]
		Avars	90		20	1	12.22	0	0	0.00	30	3	20.00	
		Dargins	50		5	0	5.00	0	0	0.00	22	1	24.00	
European part of Russia	Moscow	Russians	59	Gastric or duodenal peptic ulcer	13	2	14.40	1	0	0.84	19	1	17.79	[37]
		Russians	971	Gastric or duodenal peptic ulcer	245	14	14.00	10	1	0.62	399	66	27.34	[38]
		Russians	352	Healthy	84	4	13.10	–	–	–	–	–	–	[7]
		Russians	83	B-cell chronic lymphocytic leukemia	18	0	10.84	–	–	–	–	–	–	[8]
			76	Non-Hodgkin lymphoma	12	0	7.89	–	–	–	–	–	–	
			177	Healthy	33	5	12.14	–	–	–	–	–	–	
		Russians	81	ACS	13	0	8.00	0	0	0.00	23	1	15.40	[39]
		General population	94	Pre-PCI patients	24	3	15.95	–	–	–	–	–	–	[40]
		General population	21	Alcohol withdrawal	3	0	7.14	1	0	2.38	9	1	26.19	[41]
		General population	124	IHD	43	0	17.33	–	–	–	–	–	–	[42]
		General population	55	Stable CHD	14	2	16.36	–	–	–	–	–	–	[43]
	Kursk	General population	561	CHD	106	7	10.70	–	–	–	–	–	–	[25]
			694	Healthy	130	21	12.40	–	–	–	–	–	–	
		General population	425	Essential hypertension	80	4	10.40	–	–	–	–	–	–	[26]
			391	Healthy	74	11	12.30	–	–	–	–	–	–	
	Voronezh	Russians	290	Healthy	56	5	11.37	2	0	0.34	–	–	–	[10]
	Kazan	Tatars	130	Healthy	n.d.	n.d.	11.90	–	–	–	n.d.	n.d.	21.20	[44]
	Karachay-Cherkessia	Circassians	77	Healthy	19	5	18.80	–	–	–	–	–	–	[13]
		Karachays	125		31	2	14.00	–	–	–	–	–	–	
Siberia	Surgut	Russians	87	ACS	22	2	14.90	1	0	0.50	28	15	33.33	[39]
	Novosibirsk, Kemerovo		222		39	0	11.50	0	0	0.00	62	7	17.10	
	Irkutsk		122		14	1	10.60	5	1	2.80	43	6	22.20	

ACS: Acute coronary syndrome; CHD: Coronary heart disease; IHD: Ischemic heart disease; n.d.: Not determined for the study population by the PCI: Percutaneous coronary intervention.

Table 3. Allele and genotype frequencies of *CYP2C19* gene in different ethnic groups in Russia (cont.).

Region of the Russian Federation		Ethnic group	Number of patients	Characteristics of the population	Allelic variants									Ref.
					*2			*3			*17			
					Wt/Mt	Mt/Mt	%	Wt/Mt	Mt/Mt	%	Wt/Mt	Mt/Mt	%	
	Yakutsk	Russians	143	ACS	22	1	8.39	10	0	3.50	–	–	–	[45]
			63	Gastric or duodenal peptic ulcer	17	0	13.49	10	0	7.94	–	–	–	
		Yakuts	268	ACS	90	2	17.53	21	0	3.92	–	–	–	
			141	Gastric or duodenal peptic ulcer	41	0	14.54	22	0	7.80	–	–	–	
		Yakuts	229	Healthy	59	12	18.12	14	0	3.05	–	–	–	[15]
	Cheriktei	Yakuts	88	Healthy	27	7	23.30	8	0	4.60	–	–	–	[16]
	Kyzil	Tuvinians	88		24	1	14.80	4	0	2.30	–	–	–	
	Buriatia	Buryats	88		31	3	21.00	10	1	6.80	–	–	–	
	Altai	Altaians	87		20	3	14.90	7	0	4.00	–	–	–	
	Tomsk	Russians	87		16	2	12.20	0	0	0.00	–	–	–	
		General population	249	Breast cancer	109	4	23.49	5	0	1.01	–	–	–	[17]
		General population	166	IHD	39	3	13.55	–	–	–	–	–	–	[46]
Far East	Khabarovsk	Nanai	70	Healthy	28	3	24.30	12	0	8.60	3	0	2.10	[18]
Ural	Chelyabinsk	General population	63	Cardiac patients	19	2	11.50	–	–	–	41	3	23.50	[19]

ACS: Acute coronary syndrome; CHD: Coronary heart disease; IHD: Ischemic heart disease; n.d.: Not determined for the study population by the PCI: Percutaneous coronary intervention.

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residual platelet activity in patients receiving dual antiplatelet therapy. The frequency of the *CYP2C19*2* allele carriage in the high residual platelet reactivity group was significantly higher when compared with the group with normal platelet reactivity (40.0 vs 20.3%; p = 0.0035) [40]. Golukhova *et al.* studied sensitivity to clopidogrel in patients undergoing percutaneous coronary intervention (PCI). Platelet reactivity is higher in patients with heterozygous and homozygous carriers of *CYP2C19*2* versus common genotype [43]. Bokeria *et al.* used pharmacogenetic testing for the selection of antiplatelet therapy in patients with coronary artery disease [42]. Polonikov *et al.* found that *CYP2C19* rs4244285 GG was associated with an increased risk of essential hypertension (OR: 3.34; 95% CI: 1.48–7.51; p = 0.004) [26]. The same authors have tried to evaluate the association between the *CYP2C19* gene polymorphism and risk of coronary heart disease in Russian population, but the results were negative [25].

Pharmacogenetic testing is also used to improve the effectiveness of therapy in patients with diseases of the gastrointestinal tract. Sychev *et al.* found that the high frequency of *CYP2C19* genotypes associated with modified response to proton pump inhibitors in Russian patients with peptic ulcers [38]. Denisenko *et al.* found a connection between particular *CYP2C19* genotypes and urine metabolic ratio of Omeprazole in Russian peptic ulcer patients [37].

Zastrozhin *et al.* studied the relationship between carriage of alleles of various allelic variants of the *CYP2C19* gene and the development of adverse drug events in patients with alcohol withdrawal syndrome, taking Bromdihydrochlorphenylbenzodiazepine (Phenazepam®) [41].

Seredina *et al.* applied pharmacogenetic testing to increase the effectiveness of neoadjuvant chemotherapy in patients with breast cancer [17], and Gra *et al.* – for a personalized approach to therapy for patients with chronic lymphocytic leukemia and non-Hodgkin's lymphoma [8].

CYP2D6

From the standpoint of pharmacogenetics, the cytochrome CYP2D6 enzyme is a rather complex object of study due to the high polymorphism of its gene. The number of studied allelic variants reached 113, but not all of them are significantly associated with a decrease in the function of the enzyme [47]. In addition, this gene is characterized by an increase in the number of its copies, which increases the expression level of the enzyme [48]. Another feature of this enzyme is quite a wide range of changes in the activity. Statins, being a substrate of another isoenzyme, can reduce activity of CYP2D6 cytochrome that has been demonstrated *in vitro* study [49]. But what is more significant, the substrates of this isoenzyme can change its activity in the process of its metabolism, therefore, the effectiveness of the drug may suddenly decrease after some time from the start of treatment [50]. These subtle patterns of pharmacokinetics must be taken into account, since this cytochrome metabolizes 25% of drugs used nowadays [51].

Currently the **4* allele of this gene is the most studied is due to its high prevalence among representatives of the European race – 18.17%. The prevalence frequency among other populations: American – 10.76%, south/central Asian – 7.87%, Middle Eastern – 7.8%, African–American – 6.39%, African – 3.34%, Oceanian – 2.48% and east Asian 0.65% [52].

The analysis of the work of the Russian researchers showed a high prevalence of the allelic variant *CYP2D6*4* both in the general population and in individual ethnic groups. The highest prevalence was observed in Russians (17–20%), the lowest in the Mongoloid race (Nanai – 1.7%).

Cumulative information about the main characteristics of the studied population and the allele frequencies of the studied gene are presented in Tables 4 and 5.

Due to the broad class of drugs metabolized by CYP2D6 pharmacogenetic testing finds application in various diseases.

Ivanova *et al.* have reported an association between carriage of polymorphic variant 1846G>A *CY2D6*4* and genotype A/A of *CYP2D6* gene (responsible for debrisoquin-4-hydroxylase synthesis) with limbotruncal tardive dyskinesia in patients with schizophrenia receiving antipsychotics for a long time [62]. Sychev *et al.* found a statistically significant association between extrapyramidal disorders development and heterozygous *1846GA* genotype and *1846A* allele carrier frequency among all schizophrenic patients and among those of Tatars [60]. Zastrozhin *et al.* discovered that the lower efficacy and safety of Fluvoxamine in patients with depressive disorder and comorbid alcohol use disorders with *GA* genotype in *CYP2D6 1846G>A* polymorphic marker [55] and used test results to personalize therapy in patients with alcohol withdrawal syndrome [41]. Sychev *et al.* showed the correlations between the activity of CYP2D6 isozyme and the efficacy and safety of Haloperidol in patients with alcohol addiction [53,56].

Table 4. Allele and genotype frequencies of *CYP2D6* gene in different ethnic groups in Russia.

Region of the Russian Federation	Ethnic group	Number of patients	Characteristics of the population	Allelic variants									Ref.
				*3			*4			*10			
				Wt/Mt	Mt/Mt	%	Wt/Mt	Mt/Mt	%	Wt/Mt	Mt/Mt	%	
Dagestan Republic	Laks	46	Healthy	_	_	_	17	0	18.47	_	_	_	[5]
	Avars	90		_	_	_	23	0	12.77	_	_	_	
	Dargins	50		_	_	_	19	0	19.00	_	_	_	
European part of Russia:													
– Moscow	Russians	352	Healthy	6	0	0.90	91	14	17.00	_	_	_	[7]
	Russians	83	B-cell chronic lymphocytic leukemia	1	0	0.60	24	3	18.07	_	_	_	[8]
		76	Non-Hodgkin lymphoma	1	0	0.65	20	3	17.10	_	_	_	
		177	Healthy	4	1	1.69	49	8	18.36	_	_	_	
	General population	70	Alcohol addiction	_	_	_	n.d.	n.d.	12.14	_	_	_	[53]
	General population	81	Arterial hypertension	_	_	_	_	_	_	74	7	54.32	[54]
	General population	45	Depressive disorder and comorbid alcohol use disorder	_	_	_	17	0	18.89	_	_	_	[55]
	General population	69	Alcohol use disorder	_	_	_	17	0	12.32	_	_	_	[56]
	General population	21	Alcohol withdrawal	_	_	_	4	0	9.52	_	_	_	[41]
– Saint Petersburg	Russians	1230	Healthy	n.d.	n.d	1.30	n.d	n.d	17.70	_	_	_	[57]
	Russians	181	Acute myocardial infarction	0	3	1.66	54	3	16.57	8	1	2.76	[58]
	General population	17	Acute myocardial infarction + depression	3	0	8.82	5	0	14.70	_	_	_	[59]
– Voronezh	Russians	290	Healthy	6	0	1.03	87	9	18.10	22	1	4.13	[10]
– Kazan	Russians	37	Schizophrenia	_	_	_	12	3	24.30	_	_	_	[60]
	Tatars	42		_	_	_	10	0	11.90	_	_	_	
– Kursk	General population	215	Asthma	_	_	_	64	7	18.14	_	_	_	[61]
		214	Healthy	–	–	–	62	6	17.29	–	–	–	
– Karachay-Cherkessia	Circassians	77	Healthy	_	_	_	19	2	15.00	_	_	_	[13]
	Karachays	125		_	_	_	38	7	20.80	_	_	_	
Siberia:													
– Kemerovo and Chita	General population	475	Schizophrenia	8	1	1.05	86	11	11.36	_	_	_	[62]
– Yakutsk	Russian	93	CHD	_	_	_	20	0	10.75	30	0	16.13	[63]
	Yakuts	108		_	_	_	22	0	10.19	35	0	16.20	
– Novosibirsk	Tundra Nentsi	102	Healthy	_	_	_	n.d	n.d	7.00	_	_	_	[64]
	General population	96		_	_	_	n.d	n.d	20.00	_	_	_	
Far East:													
– Khabarovsk	Nanai	70	Healthy	_	_	_	2	0	1.40	_	_	_	[18]

CHD: Coronary heart disease; n.d.: Not determined for the study population by authors.

Table 5. Allele and genotype frequencies of *CYP2D6* gene in different ethnic groups in Russia.

Region of the Russian Federation	Ethnic group	Number of patients	Characteristics of the population	Allelic variants			Ref.
				Wt/Mt	Mt/Mt	%	
CYP2D6*2							
Saint Petersburg	Russian	1230	Healthy	n.d.	n.d	35.7	[57]
CYP2D6*5							
Voronezh	Russian	290	Healthy	15	0	2.58	[10]
Saint Petersburg		1230		n.d.	n.d.	1.60	[57]
CYP2D6*6							
Voronezh	Russian	290	Healthy	7	0	1.20	[10]
Saint Petersburg		1230		n.d.	n.d.	1.00	[57]
CYP2D6*7							
Saint Petersburg	Russian	1230	Healthy	n.d.	n.d.	0.04	[57]
CYP2D6*41							
Saint Petersburg	Russian	1230	Healthy	n.d.	n.d.	7.60	[57]

n.d.; Not determined for the study population by authors.

Often pharmacogenetic testing is necessary with the simultaneous prescribing drugs from different classes. Goryachkina *et al.* first showed that metabolism of metoprolol in patients with acute myocardial infarction (AMI) can be inhibited by the simultaneous administration of paroxetine for the treatment of depressive disorder [59]. However, even in the absence of paroxetine, metabolism of metoprolol in patients with AMI can be accelerated as a result of doubling of the *CYP2D6* gene and increased expression of the enzyme [58]. In patients with arterial hypertension, the carriage of certain alleles of this gene can increase the effectiveness of therapy with betaxolol [54].

Polonikov *et al.* first rated gene–gene and gene–environment interactions for disease susceptibility for asthma [61]. Fedorinov *et al.* revealed an association between the polymorphic marker G1846A carrier and the lower effective dose of Bisoprolol in patients with CHD [63].

CYP2D6 gene polymorphisms have also been studied to create a biochip as a tool for predictive analysis in oncohematology [8].

CYP1A1

As for the cytochrome *CYP1A1* gene, 13 allelic variants have been discovered, and 12 SNPs the gene of this isoenzyme require further study [65]. The role of this isoenzyme in carcinogenesis processes is discussed, in view of its involvement in the metabolic activation of procarcinogens (polycyclic aromatic hydrocarbons and aromatic amines) into reactive metabolites. It also participates in the metabolism of steroidal hormones including estrogens [66]. In view of the little scrutiny, it is difficult to form a reliable idea of the prevalence rate of this gene in the world population.

Cumulative information about the main characteristics of the studied population and the frequency of *CYP1A1* alleles are presented in Table 6.

As described above, most of the research is focused on oncology. Mikhailova *et al.* were the first to study this problem in Russia. The authors found no statistically significant differences in the prevalence frequency of the allelic variant *CYP1A1*2A* in patients with benign and malignant tumors compared with healthy volunteers [70].

Belogubova *et al.* have shown the association of allelic variant *CYP1A1*2* with a predisposition to the development of squamous cell lung carcinoma [69]. Gra *et al.* found that the allelic variant of *CYP1A1*2B* was more common in patients with B-cell chronic lymphocytic leukemia [8].

Pulmonology was another area that was covered in the Russian studies of CYP1A1. Polonikov *et al.* found that an absence of genotypes 462IV of the *CYP1A1* gene ($p = 0.050$) and also possessing the GSTM1-null genotype ($p = 0.023$) were significantly associated with an increased risk of asthma only in smokers [61]. Salnikova *et al.* proved that allelic variants of *CYP1A1*2A* and *CYP1A1*2B* increase the patient's sensitivity to the community-acquired and nosocomial pneumonia [68] disease and increase the risk of complications of these diseases [67].

Table 6. Allele and genotype frequencies of *CYP1A1* gene in different ethnic groups in Russia.

Region of the Russian Federation	Ethnic group	Number of patients	Characteristics of the population	Allelic variants												Ref.
				*2A			*2B			*2C			*4			
				Wt/Mt	Mt/Mt	%	Wt/Mt	Mt/Mt	%	Wt/Mt	Mt/Mt	%	Wt/Mt	Mt/Mt	%	
European part of Russia																
Moscow	Russians	352	Healthy	34	3	5.68	36	1	5.40	–	–	–	13	0	1.90	[7]
	Russians	83	B-cell chronic lymphocytic leukemia	11	0	6.62	12	0	7.89	–	–	–	7	0	4.21	[8]
		76	Non-Hodgkin lymphoma	10	0	6.57	10	0	6.57	–	–	–	4	0	2.63	
		177	Healthy	18	1	5.64	14	0	4.05	–	–	–	9	1	3.10	
	General population	341	Community-acquired pneumonia	59	1	8.94	–	–	–	33	0	4.84	–	–	–	[67]
	General population	334	Community-acquired and nosocomial pneumonia	57	1	8.83	–	–	–	32	0	4.79	–	–	–	[68]
		141	Healthy	33	0	12.31	–	–	–	8	0	2.99	–	–	–	
Kursk	General population	215	Asthma	40	1	9.77	–	–	–	33	1	8.14	–	–	–	[61]
		214	Healthy	51	1	12.38	–	–	–	30	1	7.48	–	–	–	
Saint Petersburg	General population	246	Elderly donors	49	1	10.37	–	–	–	–	–	–	–	–	–	[69]
		204	Middle-aged donors	41	2	11.03	–	–	–	–	–	–	–	–	–	
		141	Lung cancer	35	2	13.83	–	–	–	–	–	–	–	–	–	
Ufa	Russians	319	Healthy	66	3	12.63	–	–	–	28	1	4.78	–	–	–	[12]
	Tatars	279		60	8	16.38	–	–	–	27	2	6.38	–	–	–	
	Bashkirs	144		52	6	23.53	–	–	–	28	0	10.45	–	–	–	
Siberia																
Novosibirsk	General population	166	Malignant tumor	36	0	10.71	–	–	–	–	–	–	–	–	–	[70]
		170	Benign tumor	28	0	8.24	–	–	–	–	–	–	–	–	–	
		170	Healthy	40	0	11.90	–	–	–	–	–	–	–	–	–	

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Table 7. Allele and genotype frequencies of *CYP2C8* gene in different ethnic groups in Russia.

Region of the Russian Federation	Ethnic group	Number of patients	Characteristics of the population	Allelic variants			Ref.
				Wt/Mt	Mt/Mt	%	
***CYP2C8*1B* rs7909236**							
Kursk	Common population	561	CHD	210	35	25.00	[25]
		694	Healthy	239	33	22.00	
		425	Essential hypertension	151	32	25.30	[26]
		391	Healthy	118	11	17.90	
***CYP2C8*2* T805A**							
Tomsk	Common population	244	Breast cancer	1	0	0.20	[17]
***CYP2C8*3* G416A + A1196G**							
Tomsk	Common population	247	Breast cancer	44	0	8.90	[17]
***CYP2C8* rs1934953**							
Kursk	Common population	561	CHD	255	61	36.60	[25]
		694	Healthy	314	64	31.80	
		425	Essential hypertension	197	50	34.90	[26]
		391	Healthy	181	29	30.60	

CHD: Coronary heart disease.

CYP2C8

One of the poorly studied isoenzymes is cytochrome CYP2C8. Currently, 14 allelic variants of the gene of this isoenzyme have been discovered [71]. This isoenzyme is involved in the biotransformation of drugs such as amiodarone, cerivastatin, paclitaxel, repaglinide, rosiglitazone, diclofenac, ibuprofen, fluvastatin, morphine, carbamazepine, verapamil – among others. [72]. The most common is the *CYP2C8*2* allele, with its prevalence in black populations reaching 18% and about 1% in white subjects [73].

Cumulative information about the main characteristics of the studied population and the frequency of *CYP2C8* alleles are presented in Table 7.

The allelic variants of *CYP2C8*1B* rs7909236 and *CYP2C8* rs1934953 were studied in two papers by Russian researchers. Polonikov *et al.* studied these polymorphisms from the point of view of the risk of developing coronary heart disease in the Russian population [25] and established their relationship with the risk of developing essential arterial hypertension [26].

Seredina *et al.* studied the *CYP2C8*2* T805A and *CYP2C8*3* G416A + A1196G polymorphisms from the standpoint of the effectiveness of neoadjuvant chemotherapy in patients with breast cancer, but no reliable association data was obtained [17].

Other oxidation enzymes

Besides CYP450, other enzymes are also involved in drug metabolism.

For example, the human CES1, also localized in the liver, is involved in the metabolism of dabigatran [74]. Sychev *et al.* did not confirm the effect of the *CES1* rs2244613 polymorphism Dabigatran equilibrium peak concentration in patients after total knee arthroplasty [75].

Another enzyme is SULT1A1, which is involved in estrogen metabolism [76]. Mikhailova *et al.* proved the association between the carriage of the G allele of *SULT1A1*2* with hormone-dependent cancers in women [70].

Cumulative information about the main characteristics of the studied population and the frequency of *CES1* and *SULT1A1* alleles are presented in Table 8.

Membrane transporters

In addition to the CYP450 system, membrane transporters play an important role in drug metabolism. With the help of them, the drug is transported into the cell and the drug is excreted into the extracellular space.

Cumulative information about the main characteristics of the studied population and the frequency of *SLCO1B1* and *ABCB1* alleles are presented in Tables 9 and 10.

Table 8. Allele and genotype frequencies of *CES1* and *SULT1A1* genes in different ethnic groups in Russia.

Region of the Russian Federation	Ethnic group	Number of patients	Characteristics of the population	Allelic variants			Ref.
				Wt/Mt	Mt/Mt	%	
***CES1* rs2244613**							
Saratov	General population	60	Total knee arthroplasty	21	6	27.5	[75]
***SULT1A1*2* G638A**							
Novosibirsk	General population	166	Healthy	70	28	37.50	[70]
		170	Malignant tumor	86	16	34.71	
		170	Benign tumor	60	50	47.06	

Table 9. Allele and genotype frequencies of *SLCO1B1* and *ABCB1* genes in different ethnic groups in Russia.

Region of the Russian Federation	Ethnic group	Number of patients	Characteristics of the population	Allelic variants						Ref.
				SLCO1B1 +521T>C			*ABCB1* 3435C>T			
				Wt/Mt	Mt/Mt	%	Wt/Mt	Mt/Mt	%	
Dagestan Republic	Laks	46	Healthy	7	1	9.78	21	21	67.47	[5]
	Avars	90		26	0	14.44	48	26	55.55	
	Dargins	50		8	1	10.00	21	21	63.00	
European part of Russia:										
– Moscow	Russians	50	Atrial fibrillation	_	_	_	25	15	55.00	[77]
	General population	17	Atrial fibrillation and acute stroke	_	_	_	9	3	44.12	[78]
	General population	341	Community-acquired pneumonia	_	_	_	141	66	40.38	[67]
	General population	334	Community-acquired and nosocomial pneumonia	_	_	_	140	53	36.83	[68]
		141	Healthy	_	_	_	63	31	46.64	
		21	Alcohol withdrawal	_	_	_	9	1	16.19	[41]
		100	Stage I–II hypertension (HT)	_	_	_	53	30	56.50	[79]
	Russians	1071	Hypercholesterolemia	346	60	21.76	–	–	–	[80]
	Yakuts	76		11	3	11.18	–	–	–	
	General population	50	Valvular atrial fibrillation	–	–	–	25	15	55.00	[81]
– Yaroslavl	General population	81	Statin taking	27	2	19.14	–	–	–	[82]
– Ryazan	General population	121	Statin taking	46	8	26.70	–	–	–	[83]
– Voronezh	General population	285	Colorectal cancer	_	_	_	129	70	47.20	[84]
		275	Non cancer(not healthy)	_	_	_	140	78	53.80	
– Saratov	General population	60	Total knee arthroplasty	–	–	–	29	16	50.8	[75]
Siberia:										
– Yakutsk	Yakuts	100	Healthy	12	1	14.00	–	–	–	[15]
Far East:										
– Khabarovsk	Nanai	70	Healthy	25	4	23.60	39	12	45.00	[18]

ABCB1 (MDR1, P-gp)

P-gp is a protein from the ABC family of transporters encoded by the *ABCB1* gene. This transporter is located on the membrane of enterocytes, regulating the process of absorption and release of the drug, as well as on the membrane of other cell types, for example, cells that form the blood–brain barrier [85]. The gene of this transporter has many different allelic variants, including those affecting the function of the transporter. To date, 1279 SNPs in the *ABCB1* gene region are open, 62 of which are coding [86].

In clinical studies, Sychev *et al.* established that TT genotype of rs1045642 polymorphism of the *ABCB1* gene was associated with higher dabigatran equilibrium peak concentrations and the higher risk of bleeding than the presence of CC genotype ($p < 0.008$) [75] and indicate the potential of pharmacogenetic testing for rs1045642 SNP when prescribing amlodipine for the first time in Caucasian patients with stage I–II arterial HT [79]. Osswald *et al.* found that life-long nonsmokers with an age ≥63 years who carried the 3435CC or 3435TT genotype developed more frequently colorectal cancer than others (OR = 3.9; 95% CI: 2.0–7.7) [84]. Rozhkov *et al.* revealed

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Table 10. Allele and genotype frequencies of *ABCB1* gene in different ethnic groups in Russia.

Region of the Russian Federation	Ethnic group	Number of patients	Characteristics of the population	Allelic variants			Ref.
				Wt/Mt	Mt/Mt	%	
***ABCB1* rs4148738**							
Moscow	General population	17	Atrial fibrillation and acute stroke	7	6	55.88	[78]
Saratov	General population	60	Total knee arthroplasty	25	15	45.8	[75]
***ABCB1* -129T>C (rs3213619)**							
Voronezh	General population	285	Colorectal cancer	16	0	2.80	[84]
		275	Non cancer(not healthy)	15	0	2.70	

that *ABCB1* CT and TT genotypes significantly associated with higher risk of bleeding in patients with valvular atrial fibrillation taking acenocoumarol [81]. Similar results were obtained in another study [77]. Zastrozhin *et al.* took into account the polymorphism of the gene *ABCB1* to create pharmacogenetic-guided personalization of drug dose in patients with alcohol withdrawal syndrome, due to its association with the development of adverse drug events [41]. Kryukov *et al.* found no effect of polymorphism on the pharmacokinetics of apixaban [78]. Salnikova *et al.* did not find an association of *ABCB1* gene polymorphisms with a predisposition to community-acquired and nosocomial pneumonia [68] and an increased incidence of complications [67].

Of the rarer alleles, only *ABCB1* rs4148738 [32,44] and *ABCB1* -129T>C (rs3213619) [84] were studied.

SLCO1B1

SLCO1B1 is a polypeptide that transports organic anions across a cell membrane. It acquired its significance in particular due to the participation in the metabolism of statins by transporting drugs into hepatocytes [87]. Currently, the definition of genotypes for the allelic variant *SLCO1B1*5* has already been recommended for practical use by experts from the European Science Foundation [88].

The polymorphisms of this gene remain virtually unexplored for the Russian population. There are data on the frequency of the prevalence of the allelic variant *SLCO1B1* + 521T>C among Russians [80], Yakuts [15,80], Nanai [18], Laks, Avars and Darghins [5]. Khokhlov *et al.* studied the frequency of *SLCO1B1* + 521T>C in patients taking statins. Adverse drug reactions developed in 19.5% when taking Simvastatin and carriage frequency of allele was 19.14% [82]. Solodun *et al.* found a statistically significant decrease in atherogenic cholesterol fractions in carriers of *SLCO1B1*5* alleles while taking Atorvastatin [83].

Prospects for the use of pharmacogenetic testing in the Russian Federation

To date, the recommendations of professional communities regarding the use of pharmacogenetic testing are controversial and disappointing. A striking example is the recommendations of the American Heart Association and the American College of Cardiology, which contradict the position of the US FDA and the CPIC regarding the appropriateness of using *CYP2C19* pharmacogenetic testing for clopidogrel in patients with ACS [89]. Such inconsistencies are largely due to a lack of large comparative prospective clinical trials confirming the advantages of the pharmacogenetic approach to therapy as compared with the standard one, in other words, the expediency of using a marker in clinical practice.

According to the recommendations of the Evaluation of Genomic Applications in Practice and Prevention working group, clinical validity is the ability of a pharmacogenetic marker to predict the response to a drug, and clinical utility is the ability to improve clinical outcomes [90]. However, most pharmacogenetic markers overcome the barrier of clinical validity and only a few overcome the barrier of clinical utility. From these standpoints, the most clinically valid and clinically useful for therapeutic practice are gene/product pairs: CYP2C19 – clopidogrel, CYP2C9 and VKORC1 – warfarin, and SLCO1B1 – statins [91]. Pharmacogenetic testing for these markers has already been implemented in the standards of care at the University of Florida, where testing for the polymorphism of the *CYP2C19* gene is performed on all patients who have undergone cardiac catheterization since 2012, as well as at the University of Vanderbilt, where testing for the polymorphism of the *SLCO1B1* gene is performed prior to the prescription of statins [92].

Conclusion

The results of the systematic review presented in the current study indicate the importance of studying the most clinically valid and clinically useful pharmacogenetic markers (*CYP2C19, CYP2C9, VKORC1, SLCO1B1*) among different ethnic groups of the Russian Federation. For example, *CYP2C9*2* allelic variant prevails in Russians as representatives of the Europoid race, and is much rarer in Mongoloid race: Yakuts, Buryats, Tuvinians. Besides, the *CYP2C9*3* allelic variant is unusually widespread among representatives of ethnic groups of the Caucasus: Circassians, Laks, Avars and Dargins. The prevalence of *VKORC1* 1639G>A rs9923321 polymorphism in the Yakut population is two-times higher than among patients of the Moscow region – 83.14 and 36.26%, respectively. The analysis of the works of Russian researchers on the prevalence of *SLCO1B1 +521T>C* also revealed important regional ethnic features.

With the accumulation of evidence of clinical validity and clinical utility of other pharmacogenetic markers (*CES1, CYP2D6*4*, etc.), the problem of interethnic differences in the presence of clinically significant polymorphisms of these genes, identified in earlier studies in the Russian Federation, requires increasing attention.

Executive summary

CYP450 enzymes

CYP2C9 + VKORC1 & GGCX

- Fifteen studies were conducted on allelic variants of *CYP2C9*2, *3* of them: nine in the European part of Russia, three in Siberia, one in the Far East, the Urals and the Republic of Dagestan.
- In addition to healthy volunteers, associative studies were also conducted in cardiac and oncological patients.
- Minor allelic variants of *CYP2C9* rs9332242, rs4918758, rs61886769 as well as other enzymes of warfarin biotransformation (VKORC1 and GGCX) are practically not studied in the Russian population.

CYP2C19

- The most studied at the moment are *CYP2C19*2, *3, *17* allelic variants.
- Fourteen studies were conducted in the European part of Russia, six in Siberia, one in the Republic of Dagestan, the Far East and the Urals.
- Pharmacogenetic testing for this gene has found application in oncology, cardiology, psychiatry and gastroenterology.

CYP2D6

- The most significant allelic variants that are reflected in the studies are *CYP2D6*3, *4, *10.*
- Most of the investigations concentrated in the European part of Russia – 14, 3 were held in Siberia, 11 in the republic of Dagestan and the Far East.
- Much research has focused on psychiatry and narcology. Cardiology, pulmonology and oncology are covered to a small extent.

CYP1A1

- Studies of the gene of this cytochrome were conducted among patients of the European part of Russia – 7, and Siberia – 1.
- Most research is focused on oncology.

CYP2C8

- One of the poorly studied isoenzymes.
- Researches in relation to cardiology and oncology were conducted on the general population.
- The prevalence frequency of allelic variants of this gene among certain ethnic groups of the Russian Federation remains unclear.

CES1 and SULT1A1

- One of the poorly studied enzymes.
- For these genes there is a total of one study in the general population of patients.
- It is necessary to conduct population-ethnic and associative clinical studies.

ABCB1 (MDR1, P-gp)

- The allelic variant *ABCB1 3435C>T* is studied in detail.
- However, the bulk of the research was conducted on the general population of patients in the European part of Russia.

SLCO1B1

- Was studied in just six studies.
- In addition to population-ethnic studies in healthy volunteers, attempts were made to personalize statin therapy based on pharmacogenetic testing.

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In the Russian population, there are still no studies of such enzymes as uridine 5′-diphosphoglucuronosyltransferase, human flavin-containing monooxygenase, monoamine oxidases, aldehyde oxidase and such membrane transporters as SLCO1B3 and ABCG2.

These racial and ethnic peculiarities may affect the development and priority of the implementation of pharmacogenetic testing programs in different regions of the Russian Federation.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: https://www.futuremedicine.com/doi/suppl/10.2217/pgs-2019-0013

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