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Pharmacogenetic testing by polymorphic markers 681G>A and 636G>A *CYP2C19* gene in patients with acute coronary syndrome and gastric ulcer in the Republic of Sakha (Yakutia)

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Abstract

Background: The focus of the study is to determine the prevalence of *CYP2C19* alleles, associated with the risk of changes in the pharmacological response to clopidogrel and proton pump inhibitors in patients with acute coronary syndrome (ACS) and gastric ulcer from Russian and Yakut ethnic groups.

Methods: The research included 411 patients with ACS (143 Russians and 268 Yakuts) and 204 patients with histologically confirmed gastric ulcer (63 Russians and 141 Yakuts). Genotyping of 681G>A and 636G>A polymorphisms was performed by using polymerase real-time chain reaction.

Results: In both ethnic groups, Hardy-Weinberg equilibrium was followed in a distribution of alleles and genotypes in the population ($p > 0.05$). The 681A allele frequency in the Yakut ethnic group was higher than in the Russian group: 17.53% vs. 8.39% ($p = 0.001$). No statistically significant difference was found in the frequency of 636A in Yakuts and Russians with ACS: 3.92% vs. 3.50% ($p = 0.840$). While comparing the frequency distribution of alleles 681A (13.49% vs. 14.54%, $p = 0.878$) and 636A (7.94% vs. 7.80%, $p = 1$) in patients with a gastric ulcer from Russian and Yakut ethnic groups, no significant difference was found in carrier frequency.

Conclusions: The results of the present study may be helpful for developing guidelines for *CYPC19* genotype-directed antiplatelet therapy for Yakut and Russian patients.

Keywords: ACS; clopidogrel; *CYP2C19*2*; *CYP2C19*3*; gastric ulcer; pharmacogenetics.

Introduction

Enzymes of the cytochrome P450 system play an important role in the biotransformation of drugs and xenobiotics. The greatest clinical importance is represented by the enzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4, participating in the metabolism of most drugs used today. CYP2C19 is one of the main representatives of the CYP2C family for its enzymatic activity.

Cytochrome CYP2C19 consists of 490 amino acids and is encoded by the *CYP2C19* gene, which is located in the chromosome 10 (10q24.1-q24.3) and is mainly present in the liver; however, it exhibits considerable activity in the intestinal wall as well. There are several allelic variants of this cytochrome. Allele *CYP2C19*1* is considered a "wild-type". Homozygotes for this allele (*CYP2C19 *1/*1*) are classified as extensive metabolizers [1]. Alleles *CYP2C19*2* (681G>A) and *CYP2C19*3* (636 G>A) are associated with a slowing of the cytochrome metabolism rate, as the translation of the protein in them terminates prematurely, which leads to the formation of a non-functional isoenzyme. *CYP2C19*2* or *CYP2C19*3* carriers (*2/*2, *2/*3, *3/*3), therefore, are classified as poor metabolizers. Heterozygotes based on alleles *CYP2C19* (*1/*2, *1/*3, *2/*17, *3/*17) are classified as intermediate metabolizers and differ in the slowed rate of exchange of cytochrome substrates, compared to wild-type homozygotes (*CYP2C19 *1/*1*). *CYP2C19*17* (806 C>T) allele (*1/*17, *17/*17) carriers are designated as ultra-rapid metabolizers due to increased expression of the isoenzyme and its activity [2].

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S-mephenytoin, clopidogrel, proton pump inhibitors (PPIs), certain tricyclic antidepressants such as imipramine, some barbiturates, certain β-adrenoceptor blockers such as propranolol, the human immunodeficiency virus protease inhibitor nelfinavir, diazepam, and the antimalarial drug proguanil are just parts of the substrates of this enzyme [3]. Simultaneous administration of these drugs may cause substrate competition. It is fraught with not only insufficient therapeutic effects but also with adverse drug events. In clinical practice, co-administration of antiplatelet agents and PPIs can be found in the therapy of acute coronary syndrome (ACS) in patients with a high risk of bleeding [4].

Sometimes, it is possible to observe variability in pharmacological response in therapy with clopidogrel, as an inhibitor of $P2Y_{12}$ receptors. This is a consequence of individual differences in the speed of two-step hepatic transformation of clopidogrel from an inactive prodrug to active metabolites by cytochrome P450 isoenzymes (CYP2C19, CYP3A4). *CYP2C19*2* and *CYP2C19*3* allelic variants encode enzyme isoforms with low enzymatic activity, which will lead to the deceleration of clopidogrel's active form formation. While prescribing the pharmaceutical drug in a standard dose, the efficiency of pharmacotherapy will be insufficient, which can be a premise to thrombotic complications [5]. Allelic variant *CYP2C19*17* encodes isoenzyme with high activity, which leads to the increase of the level of an active metabolite of clopidogrel in plasma and increases the risk of bleeding [6].

In turn, PPIs are well tolerated in standard doses [7]. However, the recommended dosages do not always lead to the expected therapeutic response. Thus, approximately 10%–20% of patients taking PPI do not respond to therapy because of insufficient antisecretory effect [8]. Wide interindividual and interethnic differences in pharmacological response to PPI can also be explained by genetic polymorphisms of cytochrome CYP2C19 [9]. A connection between particular *CYP2C19* genotypes and urine metabolic ratio of omeprazole in Russian peptic ulcer patients was found [10]. Some authors attributed this to the carriage of *CYP2C19*17* associated with ultra-rapid metabolism of substrates [11].

The effect of clopidogrel and PPI co-administration on the pharmacokinetics and metabolism remains controversial [12, 13]. Therefore, currently, there is no proven algorithm for dosing these drugs in patients who are carriers of *2 or *3 alleles of the *CYP2C19* gene. Current recommendations made by the Clinical Pharmacogenetics Implementation Consortium (CPIC) only allow switching of clopidogrel to prasugrel or ticagrelor in carriers of *2 and/or *3 alleles, but does not solve the problem of clopidogrel dosing and PPI co-administration [14]. Nevertheless, one should bear this in mind and control the treatment of these patients especially in the absence of pharmacogenetic testing results. This is why the knowledge of genetic profile of the population in any region will allow forecasting of possible side effects or lack of therapeutic effect of the newest or already known pharmaceutical drugs in clinical practice.

The focus of the study was to determine the prevalence of polymorphic genetic markers 681G>A and 636G>A, which are associated with changes in the pharmacological response to clopidogrel and PPIs among the Russian and Yakut patients with ACS and gastric ulcer.

Unlike other ethnic studies of cytochrome CYP2C19, this study included a population not of healthy volunteers but patients with diseases for which drugs were prescribed, including substrates of this isoenzyme: clopidogrel and PPIs. An earlier study of *CYP2C19* polymorphism frequency in Russians with ACS and peptic ulcer did not include the Yakut population [15, 16].

Materials and methods

The research was conducted in accordance with ethical principles of the World Medical Association Declaration of Helsinki and was approved by the local Ethics Committee at Federal State Budgetary Institution "Yakut Science Centre of Complex Medical Problems". The objectives of the study and its possible complications were explained to the patients in a manner that they could understand. Written informed consent was obtained from all participants prior to entering the study.

Study population

The study consisted of two parts. The first one included 411 patients with ACS with an average age of 64 ± 8.5 years, who were in Republican Hospital No. 3 in Yakutsk and had treatment with clopidogrel in the recommended dosage (initial dose – 300 mg, maintenance dose – 75 mg). A total of 143 (34.79%) patients were Russian (84 [58.74%] men and 59 [41.26%] women) and 268 [65.21%] patients were Yakut (153 [57.09%] men and 115 [42.91%] women). There were no significant differences between the sex groups ($p = 0.755$).

The second part included 204 patients with a histologically confirmed gastric ulcer, who were in Republican Hospital No. 3 in Yakutsk and had treatment with PPIs. A total of 63 (30.88%) patients were Russian (21 [30.33%] men and 42 [66.77%] women) and 141 (69.12%) patients were Yakut (49 [34.75%] men and 92 [65.25%] women). There were no significant differences between the sex groups ($p = 0.875$).

The ethnicity of the participants in the study was established using the method of self-determination. The inclusion criterion was self-determination in at least two generations, with both parents representing a single ethnic group.

Genotyping

Venous blood samples (4 mL) of patients were collected into ethylene diamine tetra-acetate (EDTA) tubes. The study was conducted on 4 mL of venous blood of patients collected into EDTA vacutainer tubes (Vacuette®; Greiner Bio-One, Austria). DNA extraction from whole blood leukocytes was done using a set of laboratory reagents for DNA extraction from whole blood "DNA-EXTRAN-1" (CJSC "Sintol", Moscow, Russia). Polymorphism frequencies *CYP2C19*2* (681G>A; rs4244285), *CYP2C19*3* (636G>A; rs4986893) were performed by using allele-specific real-time polymerase chain reaction (real-time PCR). Primers for PCR were selected using the Primer Select program 4.05© 1993-2000 DNASTAR Inc. and synthesized by CJSC "Sintol" (Russia). Primers 5′-GATATGCAATAATTTTCCCACTATCATTG-3′ and 5′-GGTGTTCTTTTACTTTCTCCAAAATATCAC-3′ were used to amplify the sequence of *CYP2C19*2* in exon 5; for *CYP2C19*3*, we used 5′-CACCCTGTGATCCCACTTTC-3′ and 5′-ACTTCAGGGCTTGGTCAATA-3′. The sequence of the G allele-specific probe was 5′-FAM-TTATTTCCCGGGAACC-3′, and the sequence of the A allele-specific probe was 5′-VIC-ATTATTTCCCAGGAACC-3′. The genotypes were determined with a TaqMan® Single Nucleotide Polymorphism Genotyping Assay kit and a TaqMan Universal PCR Master Mix (Applied Biosystems, Foster City, CA, USA) following the manufacturer's instructions using Detecting Amplifier CFX96 TouchTM Real-Time PCR Detection System (Bio-Rad, Hercules, CA, USA). All PCR reactions were carried out in a 10-μL reaction volume containing genomic DNA 10 ng, oligonucleotide primers 0.5 pM, 1 μL 10×PCR buffer, deoxynucleotides 250 μM, magnesium chloride 3 mM and DNA polymerase 0.25 U. The cycling program involved preliminary denaturation at 95 °C for 10 min, followed by 30 cycles of denaturation at 95 °C for 30 s, annealing at 60 °C for 60 s and elongation at 72 °C for 60 s, followed by a final elongation step at 72 °C for 7 min. The primers and probes for these assays are commercially available.

Statistical analysis

Statistical analysis was done in the program IBM SPSS Statistics 22.0. The average indicators are represented as mean ± standard deviation. For the indication of differences in the presence of minor allelic variants among Russians and Yakuts, the exact Fisher test (two-tailed p) was used. The frequency of each allele in the study population is given together with the 95% confidence interval. In order to keep Hardy-Weinberg equilibrium, the same test was applied. The differences were statistically significant if $p < 0.05$.

Results

In both ethnic groups, Hardy-Weinberg equilibrium was followed in the distribution of alleles and genotypes in the population ($p > 0.05$), which gives evidence about the accordance in the frequency distribution of alleles and genotypes in studied groups of statistical population and data sample.

Patients with ACS

While comparing the frequency distribution of alleles *CYP2C19*2* and *CYP2C19*3* in patients with ACS from Russian and Yakut ethnic groups, it was found that the frequency of *CYP2C19*2* in the Yakut ethnic group was higher than that in patients from the Russian ethnic group (17.53% vs. 8.39%, $p = 0.001$). Comparing the frequency distribution of allele *CYP2C19*3* in Yakuts and Russians with ACS, no statistically significant difference in the carrier frequency was found (3.92% vs. 3.50%, $p = 0.840$) (Table 1).

Patients with gastric ulcer

While comparing the frequency distribution of alleles *CYP2C19*2* (13.49% vs. 14.54%, $p = 0.878$) and *CYP2C19*3*

Table 1: Polymorphism frequencies of gene *CYP2C19* in Yakut and Russian ethnic groups with ACS.

Genotypes and alleles, n (%)	All patients with ACS	Russians	Yakuts	p-Value
Number of patients, n	411	143	268	
*CYP2C19*2* (681G>A), n (%)				
GG	296 (72.02)	120 (83.92)	176 (65.67)	<0.05
GA	112 (27.25)	22 (15.38)	90 (33.58)	<0.05
AA	3 (0.73)	1 (0.70)	2 (0.75)	1
*CYP2C19*3* (636G>A), n (%)				
GG	380 (92.46)	133 (93.00)	247 (92.16)	0.846
GA	31 (7.54)	10 (7.00)	21 (7.84)	0.846
AA	0	0	0	
Allele frequency, % (95% CI)				
681A		8.39 (5.18–11.60)	17.53 (14.31–20.75)	0.001
636A		3.50 (1.37–5.63)	3.92 (2.28–5.56)	0.840

*CYP2C19*2* c.G681A (rs4244285); *CYP2C19*3* c.G636A (rs4986893). p-Values were calculated using two-sided Fisher's exact test.
CI, confidence interval.

Table 2: Polymorphism frequencies of gene *CYP2C19* in Yakut and Russian ethnic groups with gastric ulcer.

Genotypes and alleles, n (%)	All patients with GU	Russians	Yakuts	p-Value
Number of patients, n	204	63	141	
*CYP2C19*2* (681G>A), n (%)				
GG	146 (71.57)	46 (73.02)	100 (70.92)	0.867
GA	58 (28.43)	17 (26.98)	41 (29.08)	0.867
AA	0	0	0	
*CYP2C19*3* (636G>A), n (%)				
GG	172 (84.31)	53 (84.13)	119 (84.40)	1
GA	32 (15.69)	10 (15.87)	22 (15.60)	1
AA	0	0	0	
Allele frequency, % (95% CI)				
681A		13.49 (7.53–18.45)	14.54 (10.43–18.65)	0.878
636A		7.94 (3.22–12.66)	7.80 (4.67–10.93)	1

*CYP2C19*2* c.G681A (rs4244285); *CYP2C19*3* c.G636A (rs4986893). p-Values were calculated using two-sided Fisher's exact test. CI, confidence interval; GU, gastric ulcer.

(7.94% vs. 7.80%, p = 1) in patients with gastric ulcer from Russian and Yakut ethnic groups, no significant difference in the carrier frequency was found (Table 2).

Discussion

The carrier frequency of allelic variants of the gene that encodes the CYP2C19 isoenzyme can vary in different races and nationalities: *CYP2C19*2* (Caucasian race has allele frequency 12%–18%, Negroid race has 30%–35% and Mongoloid race has 45%–50% [17–19]), *CYP2C19*3* (Mongoloid race has allele frequency not more than 4%, Caucasian and Negroid races have <1% [20]) and *CYP2C19*17* (Mongoloid race has allele frequency not more than 5%, both Caucasian and Negroid races have not more than 25% [2, 21]).

This information should be considered in clopidogrel prescription. Moreover, it is crucial to take into account the question about the priority of implementation of pharmacogenetic testing in any region of multinational countries, such as the Russian Federation. According to the population census in 2010, there are 194 different nationalities in this country [22]. In addition, the proportion of indigenous people in several regions is predominant. Thus, in Sakha Republic, the proportion of Yakuts (Mongoloid race) is 49%, whereas the proportion of Russians (Caucasian race) is 37% [23].

Yakuts are distinctive representatives of the Mongoloid race. A small group of migrants from the Cis-Baikal Region and a small number of women from various South Siberian regions assimilated till the XV century and formed the population of Yakutia. For the last five centuries, there were no significant genetic changes in gene pool caused by population waves and genetic drifts [24].

The implementation of pharmacogenetic testing should be considered by the example of a particular region, rather than the country as a whole. When creating the biobank of the Russian Federation, the genogeography of individual regions was analyzed. Not only the stages of the formation of the population of Yakutia were established, but also the interrelationship of the gene pools of various regions of the country [25]. In the course of the extensive work on the analysis of genomes obtained in the general population of Russia, five relatively independent subpopulations were isolated, the gene pools of which are mixed to a small extent. According to the data, Russians in the Republic of Sakha and Russians from the central part of Russia belong to two different subpopulations, which explains the difference in the carrier frequency of polymorphic markers of the *CYP2C19* gene in these groups [26].

Study of the frequency of allelic variants *CYP2C19* is conducted among different nationalities in the Russian Federation. Thus, Gaikovitch et al. [27] studied about Russian healthy volunteers. Comparing the results of this study and the results of the current study, it is possible to admit that the differences in *CYP2C19*2* are statistically insignificant (11.40% vs. 8.39%, p > 0.05) in contrast to *CYP2C19*3* (0.32% vs. 3.50%, p < 0.05).

Mirzaev et al. [28] compared the distribution of *CYP2C19*2* in healthy Russian volunteers and patients with ischemic heart disease (IHD) who had therapy with clopidogrel. Comparing the results of the study mentioned above and those of the current one, it is possible to state that differences in *CYP2C19*2* are statistically insignificant among healthy volunteers (13.42% vs. 8.39%, p > 0.05) and

patients with IHD (15.0% vs. 8.39%, $p > 0.05$). Makeeva et al. published the results of their research about the carriers of clinically significant allelic variants of *CYP2C19* gene among various ethnic groups of the Russian Federation. This study included representatives of Tuvinians, Buryats, Altaians, Yakuts and Russians [29]. We used Pearson's χ^2 to calculate the differences between the groups. The calculation was based on the original data from the article. In comparison with the data from the current study, only differences in the allele *CYP2C19*3* frequency in Yakuts were statistically insignificant (4.60% vs. 3.92%, $p > 0.05$).

From the latest research conducted on healthy volunteers, it is relevant to distinguish the work of Vasilyev et al. [30]. The results obtained from the study mentioned above showed that there are no statistically significant differences compared to the current research about Yakuts: *CYP2C19*2* – 18.12% vs. 17.53% ($p > 0.05$), *CYP2C19*3* – 3.06% vs. 3.92% ($p > 0.05$). All available information about the prevalence of *CYP2C19* gene alleles among the Yakuts is presented in Table 3.

The study of the distribution of allelic variants of *CYP2C19* was conducted among different nationalities of Russian Federation [31], such as Tatars [32, 33], Kalmyks [32], Chechens [32], Karachays [34], Cherkess [34], Ingush [32], Laks, Avars and Dargins [35]. All the latest research can be helpful for creating full maps of the prevalence of the most important genetic markers associated with contravention of pharmacological response on the most commonly used medicines in each federal subject of Russia.

As seen in Table 4, the frequency distribution of alleles *CYP2C19* in Yakuts is more similar with the representatives of Mongoloid and Indo-Asiatic races; in Russians, it is similar to the representatives of the Caucasian race. All in all, the frequency distribution of alleles *CYP2C19* in Yakuts is between that in the representatives of Mongoloid and Caucasian races, which can be explained by the history of forming the population of this particular region.

Table 3: Allele frequencies of gene *CYP2C19* in Yakut ethnic group.

Ethnic group	Sample size	Frequency of alleles *CYP2C19*		References
		*2%	*3%	
Yakuts (ACS)	268	17.53	3.92	Current study
Yakuts (GU)	204	14.54	7.80	Current study
Yakuts (healthy)	88 (*2); 87 (*3)	23.30	4.60	Makeeva et al. [29]
Yakuts (healthy)	229	18.12	3.06	Vasilyev et al. [30]

GU, gastric ulcer.

Table 4: Frequency of *CYP2C19* alleles in the representatives of different ethnic groups.

Ethnic group	Sample size	Frequency of alleles *CYP2C19*		References
		*2%	*3%	
Yakuts (ACS)	268	17.53	3.92	Current study
Yakuts (GU)	204	14.54	7.80	
Russians (ACS)	143	8.39	3.50	
Russians (GU)	204	13.49	7.94	
Caucasian race				
Americans	92	15.8	0	Brackbill et al. [36]
Portuguese	95	14.2	0	Teixeira et al. [37]
Danes	239	16	0	Bathum et al. [38]
Germans	328	15.9	0.2	Aynacioglu et al. [39]
Italians	360	11.1	0	Scordo et al. [40]
Mongoloid race				
Chinese	295 (*2) 405 (*3)	63.9	11.1	Wang et al. [41]
Koreans	103	20.9	11.7	Roh et al. [42]
Japanese	217	27.4	10.8	Takakubo et al. [43]
Indo-Asiatic race				
Indians	120	8.3	35	Tantray et al. [44]

GU, gastric ulcer.

Annually, the proportion of Russian population increases in Sakha Republic [23]. Being representatives of two various races, Russians and Yakuts can have different frequencies of allele *CYP2C19*2*, which was observed in patients with ACS (17.53% vs. 8.39%, $p = 0.001$). It indicates the importance of studying the prevalence of clinically significant alleles *CYP2C19* among indigenous people to make a decision about implementation of pharmacogenetic testing for patients with ACS who are being treated with clopidogrel in a standard dose for preventing possible thrombotic complications. According to the results of the current research, the highest number of slow metabolizers was found in Yakuts.

Primarily, pharmacogenetic testing should be done for patients with risk factors for thrombotic events who are planned to have percutaneous coronary intervention (PCI): unprotected left main coronary artery (LCA) intervention, bifurcation stenosis of the LCA trunk, stenosis of the coronary artery, repeat PCI, and stent thrombosis in anamnesis. It is important to remember about clinical high-risk factors: ACS, diabetes mellitus, chronic kidney disease, planned coronary artery bypass graft with a high risk of bleeding, and switching to generics.

The CPIC developed recommendations for therapy with clopidogrel for patients whose genetic profile on *CYP2C19* is defined [14]. According to these

recommendations, in the absence of contraindications, it is relevant to use the alternative antiplatelet therapy (prasugrel, ticagrelor) for patients with intermediate enzyme activity (*1/*2, *1/*3, *2/*17) and for patients who are slow metabolizers (*2/*2, *2/*3, *3/*3). The reason for that is the decrease of antiplatelet function of clopidogrel and increase of residual ability of platelets to aggregate. Moreover, all these activities mentioned before will be strongly marked in slow metabolizers [14]. In both cases, the risk of adverse cardiovascular events increases. For patients with genotypes *1/*17, *17/*17, *1/*1, it is relevant to stick to the standard recommended doses of clopidogrel.

Timely done pharmacogenetic testing will allow making a decision about the choice of inhibitors of $P2Y_{12}$ receptors of platelets or about a correction of antiplatelet therapy. Herewith, pharmacogenetic testing has high predictive value for correction of the therapy for patients with ACS compared to patients with stable IHD. In addition, recent data demonstrate that polymorphisms of genes encoding the CYP2C subfamily represent potential genetic markers of coronary heart disease susceptibility in the Russian population [45].

Antiplatelet therapy increases the risk of bleeding. This is especially true for patients with peptic ulcer disease, who are classified as having an increased risk. Such patients are recommended to take PPI together with a dual antiplatelet therapy for the prevention of gastrointestinal bleeding [14]. In case of adverse cardiovascular events, they will have to apply two drugs – substrates of CYP2C19 – at the same time for a long duration. The presence of at least one CYP2C19 polymorphism associated with a decrease in metabolic rate significantly increases the risk of adverse cardiovascular events in patients taking clopidogrel [46].

According to the Royal Dutch Association for the Advancement of Pharmacy dosing guidelines, ultrarapid metabolizers for the successful antisecretory and eradication therapy must increase dose by 100%–200% for omeprazole, 50%–100% for esomeprazole, 200% for lansoprazole and 400% for pantoprazole [47]. There is no influence of the *CYP2C19* genotype on the efficiency of rabeprazole. For another type of metabolizers, there is also no genotype impact. Utilizing a PPI metabolizer genotype or switching to a CYP2C19-independent PPI is a simple and conservative measure that may be useful in the setting of incomplete acid suppression [48].

Considering this fact, we plan to study the frequency of carriage of the *CYP2C19*17* allele in Russian and Yakut ethnic groups.

Conclusions

The results of the current study, which first established the carriage frequency of the polymorphic markers 681G>A and 636G>A of the *CYP2C19* gene in patients with ACS and gastric ulcer in Russian and Yakut ethnic groups, indicate the importance of pharmacogenetic testing in the regions of the Russian Federation. The frequency of polymorphic markers, which should theoretically differ between Russians and Yakuts as representatives of two different races, may be the same (681G>A – 13.49% vs. 14.54%, $p = 0.878$; 636G>A – 7.94% vs. 7.80%, $p = 1$). According to the history of the formation of the population of Yakutia, we should consider it as a separate genogeographical region. All data obtained during the current study can be useful for the development of recommendations for personalization of antiplatelet and PPI therapy. Furthermore, all the information obtained in this study may be helpful for risk stratification of unwanted drug reactions based on the pharmacogenetic testing in the Sakha Republic (Yakutia). The experience obtained can be used for the implementation of this method in other regions.

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