Pharmacogenetic Tests in Ukraine: Economic Aspect

Ukrayna'da Farmakogenetik Testler: Ekonomik Bakış

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ABSTRACT

Background: A key approach in modern medicine is the use of tactics of choosing drugs and their doses based on the specific characteristics of the individual patient, as well as determination of treatment regimens based on the genetic traits of the organism. This approach is part of personalized medicine and is based on pharmacogenetic testing. To study the real possibilities of conducting pharmacogenetic tests the questioning of the population of Ukraine has been performed for the first time, and the economic aspect of carrying out DNA tests has been studied.
Methods: Field investigations were used in this work. The students of pharmaceutical, medical and biological specialties of higher schools of Ukraine, the medical staff, as well as persons having no relevance to the field of medicine or pharmacy were questioned. In our study 3143 respondents took part.
Results: It has been determined that one third of the males and females interviewed in different occupational groups are ready at the moment to pay for testing depending on the cost of treatment. It has been shown that more than half of the respondents (71.8% males and 78.6% females) consider it possible to conduct DNA tests in Ukraine although it requires a significant investment.
Conclusion: The opportunities of conducting pharmacogenetic testing in Ukraine taking into account the economic aspect have been studied. The studies have shown that it is necessary to raise the awareness of the population of Ukraine about pharmacogenetics with the purpose of further introduction of pharmacogenetic testing into clinical practice.

Key Words: Pharmacogenetics, pharmacogenetic testing, personalized medicine, Ukraine, cost-effectiveness

Received: 11.11.2016 **Accepted:** 12.20.2016

ÖZET

Amaç: Modern tıpta anahtar bir yaklaşım;bireysel hastanın spesifik özelliklerine dayalı olarak ilaç ve doz seçim taktiklerini kullanmak ve organizmanın genetik özelliklerine dayalı tedavi rejimlerini belirlemektir. Bu yaklaşım, bireysel tıbbın bir parçasıdır ve farmakogenetik testlere dayanmaktadır. Farmakogenetik testlerin yürütülmesinin gerçek imkanlarını incelemek için Ukrayna nüfusunun araştırılması ilk kez gerçekleştirildi ve DNA testlerini gerçekleştirmenin ekonomik boyutu da incelendi.
Yöntem: Bu çalışmada saha araştırmaları yapılmıştır. Ukrayna'da Eczacılık, Tıp ve Biyoloji gibi yüksek öğretimde öğrenim gören öğrenciler ile Tıp ya da Eczacılık alanıyla ilgisi olmayan kişiler de sorgulandı. Çalışmamızda 3143 katılımcı yer aldı.
Bulgular: Farklı meslek gruplarında görüşülen erkek ve kadınların üçte birinin tedavinin maliyetine bağlı olarak test için ödeme yapmaya hazır olduğu tespit edilmiştir. Katılımcıların yarısından fazlasının (%71.8 erkek ve %78.6 kadın) önemli bir yatırım gerektirmesine rağmen Ukrayna'da DNA testleri yapılabileceğini düşündüğü saptanmıştır.
Sonuç: Ukrayna'da ekonomik açıdan dikkate alınarak farmakogenetik test yapma fırsatları incelenmiştir. Çalışmalar, klinik uygulamaya daha ileri farmakogenetik testlerin getirilmesi amacıyla Ukrayna nüfusu için farmakogenetik testler hakkındaki farkındalığının arttırılması gerektiğini gösterdi.

Anahtar Sözcükler: Farmakogenetik, farmakogenetik test, bireysel tıp, Ukrayna, maliyet etkinliği

Geliş Tarihi: 11.11.2016 **Kabul Tarihi:** 20.12.2016

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doi:http://dx.doi.org/10.12996/gmj.2017.24

INTRODUCTION

The introduction of a huge number of innovative drugs into medical practice does not reduce the relevance of effective and safe pharmacotherapy. Thus, pharmacoepidemiological studies indicate low efficacy of drugs for various diseases: according to the WHO data drugs are not effective for approximately 40% of patients (1).

Throughout the world there is a high frequency of adverse drug reactions and side effects, including the severe ones, which can lead to disability, and in some cases even death. Unwanted drug reactions in some countries take the 4-5th place among all causes of death (2).

For example; in the USA, costs for alleviation of complications after taking drugs comprise over 3 billion $ per year. In this regard, individual approaches to treatment (personalized/individualized medicine) are particularly topical. Under personalized pharmacotherapy the pharmacogenetic approach to the use of drugs is meant. The principle of pharmacotherapy taking into account the individual approach is that the patient should receive the right drug in the right dose and in the right site. The relevance of pharmacogenetic testing is stipulated by occurrence of side effects of treatment when underestimating the genetic polymorphism of the systems involved in the metabolism of drugs. Side effects related to genetic differences between people are especially evident in the treatment of cancer (3).

In this regard, in recent years, pharmacogenetic information is purposefully included in the specification to common drugs. In the USA the Food and Drug Administration (FDA) is engaged in this procedure (4). Pharmacogenetic testing is especially required when using highly effective drugs, such as oral anticoagulants; warfarin is the most used of them (5).

The research on personalization of medicine is conducted abroad (5-19). The impact of the genotype in treatment regimens is recognized in Europe and the USA since 2000.

However, at present, even in countries with advanced medicine, the use of individual treatment approaches with application of pharmacogenetic tests is not widespread (1).

There are a few studies based on individual approach in Ukraine. At the present time, personalized medicine has not been formed within the healthcare system of Ukraine yet since its introduction into clinical practice is limited by the level of development of research and social factors in the country. One of the complicating factors of the practical use of personalized medicine is also poor awareness of doctors and patients about the benefits of this approach.

For carrying out pharmacogenetic testing it is necessary to have standards for its conduct, and for interpreting the results the trained medical staff is required. Currently this staff does not have enough knowledge for the correct dose selection of drugs in most cases. The DNA tests in Ukraine are seldom used in practice because of ineffective interaction of pharmacists with colleagues (medical practitioners, genetic consultants). The pharmacist and the physician play an important role in introduction of pharmacogenetics into clinical practice (4, 20).

In addition to the lack of knowledge when introducing pharmacogenetic testing into clinical practice, there are financial (21), evidence-based barriers, the ethics of conducting DNA test (22) other important aspects (11), which are still studied.

Financial barriers are directly the cost of pharmacogenetic testing itself. If the cost of pharmacotherapy is more than the cost associated with pharmacogenetic testing, it makes economic sense to consider the possibility of using genomic testing. Evidence-based barriers include the absence of randomized controlled data documentation of clinical trials, advantages of the pharmacogenetic approach to treatment, "genetic exclusivity" for genetic and pharmacogenetic tests.

At the moment Ukraine is experiencing a crisis due to the military conflict in the Eastern Ukraine. In these conditions conducting of pharmacogenetic tests in Ukraine is complicated.

The aim of our work is to study some economic aspects of conducting pharmacogenetic tests in Ukraine.

MATERIALS and METHODS

The students of pharmaceutical, medical and biological specialties of higher schools of Ukraine, the medical staff (medical practitioners, medium-level medical personnel), as well as persons having no relevance to the field of medicine or pharmacy were questioned. Most respondents were the young population of Ukraine.

Collection of the personal information was carried out taking into account ethical requirements when working with a human in accordance with the Helsinki Declaration (World Medical Association Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects). All the participants of the study gave informed consent to anonymous questioning. The relationship between qualitative characteristics was evaluated using the criterion χ^2. The conclusion concerning statistic hypotheses was made at a significance level of $p \leq 0.05$. The database was formed in Microsoft Excel. The calculations were performed in Microsoft Excel and Statistica 6 software.

The questionnaire consisted of two parts: socio-demographic characteristics and the main part. The socio-demographic part of the questionnaire contained the information about gender, age, place of residence, level of education, occupation of the respondent and the presence of persons working in the healthcare system in his/her family. The main part of the questionnaire comprised the questions aimed at understanding the role of genetic factors in pharmacocorrection and the cost effectiveness of pharmacogenetic tests conducting. For the current analysis only some of the issues from the main part of the questionnaire were used.

The survey was conducted in the period from April 2014 to January 2015. The sample consisted of 3143 questionnaires. Because of the fact that not all questionnaires were filled in correctly, part of the questionnaires was rejected. The analysis of the material was conducted based on questioning of 2920 respondents.

The sample was biased towards female due to the specificity of the student population and the medical staff. Thus, among the respondents there were 2432 females (83.3%) and 488 males (16.7%).

The age distribution of the respondents by gender is presented in Table 1.

Table 1. The age distribution of respondents

No.	Age, years	The number of the people surveyed, (%)					
		Males		Females		In total	
		n	%	n	%	n	%
1	15-20	303	62.1	1524	62.7	1827	62.6
2	21-25	101	20.7	502	20.6	603	20.7
3	26-30	16	3.3	109	4.5	125	4.3
4	31-35	9	1.8	84	3.5	93	3.2
5	36-40	18	3.7	81	3.3	99	3.4
6	41-45	14	3	43	1.7	57	2
7	46-50	12	2.5	39	1.6	51	1.7
8	51-55	5	1	20	0.8	25	0.8
9	56-60	5	1	20	0.8	25	0.8
10	61-65	4	0.8	6	0.3	10	0.3
11	over 66	1	0.1	4	0.2	5	0.2
In total:		**488**	**16.7**	**2432**	**83.3**	**2920**	**100**

Note: χ^2=59.52, v=56, p>0.05.

The youngest participant of the study was 15 years old, and the oldest was 71. The age of most respondents ranged from 15 to 20 years. These individuals constitute a potential group of consumers of pharmacogenetic services. At the age of 15 to 20 years 62.6% of respondents were interviewed, of them there were 62.1% of males and 62.7% of females. The study surveyed respondents from all regions of Ukraine. A small number of respondents were from neighboring countries and beyond.

Among the respondents 98% of males and 99.1% of females lived in Ukraine (the rest respondents lived in Russia, Kazakhstan, Turkmenistan, Ecuador, Cyprus and were in Ukraine only temporarily).

The majority of respondents lived in the Eastern part of Ukraine – 60.5% of males and 58.1% of females, of them 217 males (46.4%) and 991 females (41.5%) were from Kharkov and the Kharkov region.

Other respondents were from the Central part of Ukraine – 19.4% of males and 19.4% of females, from the North-West – 11.1% of males and 13.6% of females, from the South-East – 2.8% of males and 2.6% of females, from the southern part – 1.5% of males and 2.8% of females, from the South-West – 0.6% of males and 0.9% of females. Residents of Russia amounted to 2.1% of males and 2.3% of females. In total, the respondents from the neighboring countries were 3.8% of males and 2.6% of females. The respondents of other foreign countries comprised 0.3%. Our previous studies have demonstrated the multiethnic composition of different populations of Ukraine (23-25).

Among males 55.4% of them lived in the largest cities with a population of over 1 million people, 28% – in large cities (with a population of 250-500 thousand) and cities (with a population of 100-250 thousand), and 16.5% – in towns (up to 50 thousand people) and rural areas. Among the females interviewed 51.2% of them lived in the largest cities, 27.8% – in large cities and cities, and 21% – in towns and rural areas (Table 2).

Table 2. Distribution of respondents by place of residence

Gender	The largest cities with a population of over 1 million people		Large cities (with a population of 250-500 thousand) and cities (with a population of 100-250 thousand)		Towns (up to 50 thousand people) and rural areas		In total, persons	
	The number of respondents, persons N (%)							
	n	%	n	%	n	%	n	%
Male	265	55.4	134	28	79	16.6	478	16.6
Female	1229	51.2	668	27.8	502	21	2399	83.4
In total	1494	52	802	27.9	581	20.1	2877*	100

Note: χ^2=5.18, v=2, p>0.05.
*The number of respondents who indicated their place of residence.

The majority of respondents had incomplete higher education since they were the senior students, among them there were 340 males (68%) and 1578 females (63.2%). The higher education was in 10.4% of respondents (14.6% of males and 9.5% of females among them), specialized secondary education – 14 males (2.8%) and 170 females (6.8%), secondary education – 6.6% of males and 8% of females, incomplete secondary education – 7.6% of males and 12.4% of females.

Most respondents were students of the pharmaceutical higher school – 47.4% of respondents. Students of the medical higher school were 20.4% of respondents, the paramedical personnel – 7.3% of respondents, physicians – 3.5%, students of the biological higher school – 3% of respondents. And 6% of males and 3% of females do not belong to the professionals of the medical or pharmaceutical branch.

The relation of the respondents to medicine or pharmacy is presented in Table 3.

Table 3. The professional affiliation of respondents

No	Relation to medicine or pharmacy	Gender					
		Male		Female		In total	
		n	%	n	%	n	%
1.	I do not belong to the professionals of the medical or pharmaceutical branch	30	6	77	3.1	107	3.6
2.	I consider that medicine or pharmacy is my hobby	2	0.4	9	0.4	11	0.4
3.	Student of the pharmaceutical higher school	183	36.6	1239	49.6	1422	47.4
4.	Student of the pharmacy college	27	5.4	243	9.7	270	9
5.	Student of the medical higher school	161	32.2	451	18.06	612	20.4
6.	Student of the biological higher school	20	4	68	2.7	88	3
7.	Student of the medical school	11	2.2	72	2.9	83	2.8
8.	Student of the humanities higher school	2	0.4	1	0.04	3	0.1
9.	Pharmacist	10	2	48	1.9	58	1.9
10.	Physician	36	7.2	70	2.8	106	3.5
11.	Paramedical personnel	13	2.6	206	8.2	219	7.3
12.	Laboratory assistant	4	0.8	12	0.5	16	0.5
13.	Biologist	1	0.2	3	0.1	4	0.1
In total:		**500**	**16.7**	**2499**	**83.3**	**2999**	**100**

Note: χ^2=124.7, v=12, p<0.001.

Almost half of the respondents (1254 respondents, 42.2%) had the family members engaged in medical or pharmaceutical industry, namely in 47.7% of males and 41.1% of females.

Most respondents study to be a pharmaceutist/pharmacist (81.6%, among them there were 78.4% of males and 82.3% of females) or a physician – 193 persons (6.7%). The paramedical personnel consisted of 228 respondents (7.9%); 16 respondents (0.6%) work as laboratory assistants. The rest 3.25% of respondents do not belong to the field of medicine or pharmacy.

RESULTS and DISCUSSION

Our preliminary studies (7) shows the lack of knowledge in the field of pharmacogenetics among students of pharmaceutical, medical and biological specialties of higher schools in Ukraine, physicians, medical staff, and persons who are not related to the field of medicine or pharmacy. The discipline "Pharmacogenetics" should be included in the teaching and learning activities of the Ukrainian pharmaceutical and medical higher schools. For example, it is a compulsory subject to study in the Department of Clinical Pharmacology and Pharmacotherapy at the Northern State Medical University in Arkhangelsk (Russia).

Since the widespread introduction of DNA tests into clinical practice may be limited by financing of the research, the potential willingness to pay for conducting pharmacogenetic testing by respondents was studied.

Analyzing the willingness to pay for conducting pharmacogenetic testing for themselves or their family members (Fig. 1) it was shown that a third of males (31%) and females (38.9%) interviewed were currently ready to pay for the DNA tests depending on the cost of treatment. It was also shown that approximately the same number of persons, i.e. a third of males (32%) and females (31.1%), were not ready to pay for conducting pharmacogenetic tests. Among males 16.7% and among females 14.7% of persons were ready to pay for conducting pharmacogenetic tests irrespective of the cost of treatment. Therefore, most respondents are not aware that pharmacogenetic tests prior to therapy reduce the cost of treatment of side effects that may appear after taking drugs. When conducting pharmacogenetic tests the individually acceptable doses of the drug are determined, as well as indication of drugs that can be potentially dangerous for the patient is prevented.

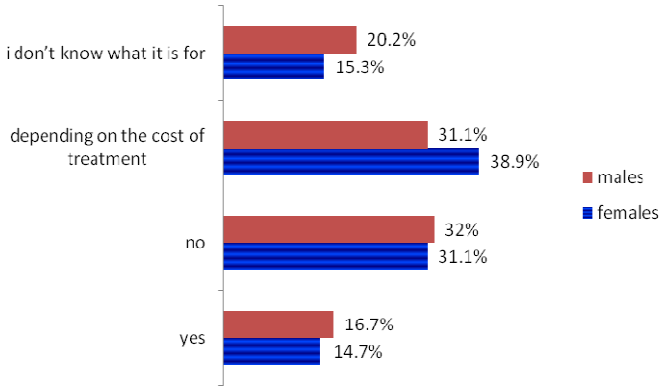

Figure 1. The distribution of willingness to pay for pharmacogenetic tests by respondents.

It is well known that pharmacogenetic tests are necessary to increase the efficiency and safety of pharmacotherapy when using certain medications in specific patient groups. For example, when taking abacavir in HIV infection the hypersensitivity syndrome develops in 50% of patients with the HLA-B*5701 allelic variant. Therefore, such patients should refuse to take this drug (10).

The results of the PREDICT-1 study have shown that the screening of patients for a carrier of allelic variant of HLA-B*5701 when taking abacavir can reduce the incidence of the hypersensitivity syndrome development from 7–12% to 0–2%. Moreover, this approach has proven to be cost-effective (26). The annual cost of abacavir is ~ 6,100 £, and the cost of testing of HLA-B*5701 allelic variant is 50 £ (less than 1% of the price of abacavir). At the same time pharmacogenetic testing can be reasonable since the cost for the tests is significantly lower than the cost of the annual treatment course with this drug (13).

Analyzing the current situation in Ukraine about the real possibility of conducting such DNA tests it has been found that the pharmacogenetic testing is available in some clinical laboratories of this country, for example, in "Ecomed" center and in "Synevo" medical laboratory. The molecular genetic SNP-based study of more than 80 genes is conducted in "Ecomed" center. It is mainly polymorphisms of genes of biotransformation enzymes, in particular CYP2D6 (sensitivity to antidepressants and antipsychotics) and CYP2C9 (sensitivity to indirect anticoagulants). For example, in Ukraine currently the cost of pharmacogenetic testing of one of the genes of cytochromes 450, CYP2D6 gene, in "Synevo" laboratory is about 860$. Moreover, on the website of this laboratory there is no accurate information what types of polymorphism are included in the analysis of this gene (27).

Based on the fact that the average salary in Ukraine as of September 1, 2015, is approximately 200$ to conduct pharmacogenetic testing is currently expensive, and not every citizen of Ukraine can afford such analysis.

The study of the cost of pharmacogenetic testing are presented in the works (12, 28, 29, 30). The cost of the pharmacogenetic test for CYP2C9 and VKORC1 from 250 $ to 630 $ in 2008 was considered to be relatively inexpensive (21). For instance, the National Institute of Health and Clinical Excellence (NICE) produced four new expensive drugs for treating kidney cancer. It has been shown that pharmacogenetic tests when using these drugs are cost-effective. The economic benefits of pharmacogenetic testing were studied for warfarin dosing prior to the traditional method of treatment using the "cost-effectiveness" analysis and calculating costs per quality-adjusted life year (QALY). When doing this DNA-test for 5 days the costs per QALY were 170 000 $, being extremely expensive. In this case, to reduce the cost of the DNA test the following conditions must be met: as the result of using this test more than 32% of heavy bleedings should be prevented; besides, the period of the test performance should not exceed 1 day, and the cost of the test should be less than 200 $ (Cressey, 2009).

When studying a potential population for conducting pharmacogenetic testing most respondents (55% of males and 61.8% of females) remarked that such analyses were necessary for the entire population regardless of gender, age and clinical status. According to 15.9% of males and 12.1% of females only patients should undergo DNA tests. And 5.3% of males and 8.6% of females considered that these tests were only for pregnant females (Table 4).

Table 4. The potential population for pharmacogenetic testing (according to the respondents)

No.	Population	Gender					
		Males		Females		In total	
		n	%	n	%	n	%
1.	Males	29	5.9	101	4.2	130	4.5
2.	Females	20	4.1	81	3.3	101	3.5
3.	Children	37	7.5	144	5.9	181	6.2
4.	Elderly people	10	2	45	1.9	55	1.9
5.	Pregnant females	26	5.3	208	8.6	234	8
6.	Patients	78	15.9	295	12.1	373	12.8
7.	Healthy people	21	4.3	53	2.2	74	2.5
8.	The entire population	271	55	1501	61.8	1772	60.6
In total:		**492**	**16.8**	**2428**	**83.2**	**2920**	**100**

Note: χ^2=25.10, v=7, p<0.001.

In our previous studies it was shown that the essence of pharmacogenetics and prospects of using DNA tests were properly understood by only a small percentage of the population of Ukraine. Since the samples of males and females were comparable by the main socio-demographic characteristics, then any significant differences could be caused only by the sex-related factor (6).

It is expedient to include the issue of understanding the possibility of pharmacocorrection of hereditary diseases in the questionnaire since the genetic factor is in the basis of many atypical human reactions to drugs. The studies showed that almost half of the male respondents believed that hereditary diseases could not be corrected by drugs (48.1%). The opinions of females who believed that hereditary diseases were not corrected, and those who considered that they could be corrected by drugs were divided almost equally – 41.4% and 42.2%. Statistically significant differences between males and females in answering to this question were not found (χ^2=6.55, v=2, p<0.05).

It has been found that pharmacogenetics is differently understood by males and females (Table 5), and these differences are statistically significant (χ^2=33.2, v=6, p≤0.001).

Table 5. Understanding of pharmacogenetics by the respondents

No.	What does pharmacogenetics study?	Gender				In total	
		Males		Females			
		The number of respondents, persons (%)					
1.	I don't know	76	15.4	199	8	275	9.3
2.	I've heard, but I can't say exactly	100	20.2	586	23.7	686	23
3.	Hereditary diseases	43	8.7	228	9.2	271	9.2
4.	The effects of drugs on human	35	7	160	6.5	195	6.6
5.	The impact of genes on drugs	31	6.3	132	5.3	163	5.5
6.	The possibility of mutations due to the drug administration	44	8.9	177	7.2	221	7.4
7.	The body's response to drugs depending on its genetic traits	166	33.5	993	40.1	1159	39
In total:		**495**	**16.7**	**2 475**	**83.3**	**2 970**	**100**

Note: χ^2=33.2, v=6, p<0.001.

For example, 15.4% of males and 8% of females interviewed heard nothing about pharmacogenetics, and 20% of males and 23.7% of females heard about it, but could not specify exactly what pharmacogenetics studied. More than one-third of males (33.5%) and females (40.1%) gave the correct answer about the nature of pharmacogenetics. In general, among persons, who in the future can potentially affect the safety of pharmacotherapy, it is necessary to actively improve the pharmacogenetic culture.

When studying the source of information about pharmacogenetics it was found that the majority of respondents in different occupational groups first received the information about this direction exactly at their higher school; moreover, females were more progressive in relation to pharmacogenetics (significant differences between males and females were identified: χ^2=14.76, v=5, p<0.05). According to the survey 49.90% of males and 58.46% of females casually heard about pharmacogenetics in their higher school. In addition, 18.33% of males and 14.55% of females did not have any information about this concept.

Analyzing the possibility of conducting DNA tests in Ukraine it has been shown that more than two thirds of respondents (71.8% of males and 78.6% of females) consider such analyses possible, but expensive. Unfortunately, among the respondents there are people (4.7% of males and 1.7% of females) who believe that such analyses are not carried out in Ukraine (Fig. 2).

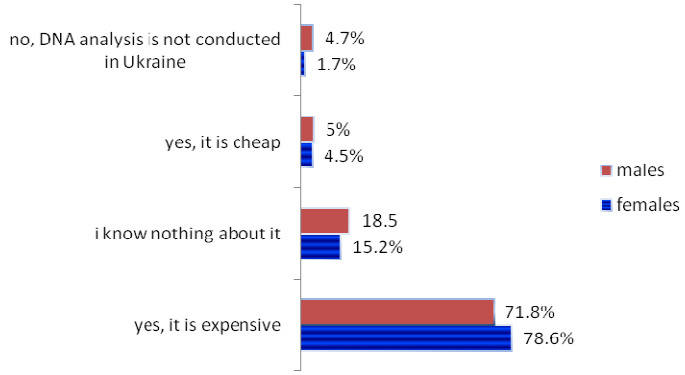

Figure 2. The possibility of conducting DNA tests in Ukraine (according to the respondents).

The analysis conducted has shown that even among future pharmacists and physicians the awareness about pharmacogenetics, genetic tests, their economic components is not satisfactory.

CONCLUSIONS

It has been determined that one third of the males (31%) and females (38.9%) interviewed are ready at the moment to pay for pharmacogenetic tests depending on the cost of treatment. It has been shown that more than half of the respondents (71.8% of males and 78.6% of females) in Ukraine consider DNA-testing to be expensive. It is necessary to raise the awareness of the population of Ukraine about pharmacogenetics with the purpose of further introduction of pharmacogenetic testing into clinical practice.

Acknowledgements

Authors are grateful to the rector of NUPh, acad. of the NAS of Ukraine, prof. V.P. Chernykh; the head of the Department of Human Physiology and Anatomy, prof. L.N. Maloshtan; the head of the Department of Pharmacology, prof. S.Yu. Shtrygol; the head of the Department of Microbiology, Virology and Immunology, prof. N.I. Filimonova; the head of the Department of Management and Marketing in Pharmacy, prof. V.V. Malyi; the director of the College at NUPh T.S. Prokopenko, as well as the head of the Department of Organization and Economy of Pharmacy and Technology of Drugs of the Ivano-Frankivsk National Medical University D.V. Semeniv for their assistance in conducting this research.

Conflict of interest

No conflict of interest was declared by the authors.

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