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RESEARCH ARTICLE

Pharmacogenomics-based practice in North Cyprus: its adoption by pharmacists and their attitudes and knowledge

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Abstract

Background Pharmacogenomics is a branch of biotechnological science integrating medicine, pharmacology, and genomics techniques. Moreover, it focuses on creating drug therapies in order to analyze genetic differences in patients causing various responses to a single therapeutic regimen. *Objective* This cross sectional study aimed to examine the attitude, knowledge and adoption among pharmacists in North Cyprus and the most appropriate method to improve education among them. *Setting* Community pharmacy setting. *Method* A total of 103 out of 140 pharmacists responded to a pre-tested and validated questionnaire consisting of 25 items during July through September 2016. *Main outcome measure* Pharmacists attitude, knowledge and adoption towards pharmacogenomic tests. *Result* Data showed that most of the pharmacists in North Cyprus had positive attitude and knowledge scores with mean value of 28.3 ± 5.3 (out of 40) and 6.9 ± 0.8 (out of 10) respectively, further findings showed that there is a significant difference among age groups in their total attitude score ($p < 0.05$). *Conclusion* Even though pharmacogenomics is a field promising a variety of benefits, it is vital to implement it in clinical settings in order to improve outcomes. Our findings highlight the necessity for more education on the availability and interpretation of pharmacogenomics tests.

Keywords Attitude · Education · North Cyprus · Pharmacist · Pharmacogenomics · Pharmacy practice

Impacts on practice

- It is necessary that sufficient insight into pharmacogenomics is added to the knowledge base of community pharmacists.
- The successful implementation of pharmacogenomic knowledge in the prescribing process, will assist pharmacists to optimize pharmaceutical care for their patients, in cooperation with other health care providers.
- While the emerging field requires pharmacists to add pharmacogenomics to their knowledge base, it also presents an important opportunity to enhance their role as a member of the health care team.

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Introduction

Pharmacogenetics involves personalizing therapeutic drugs prior to their administration by identifying and considering differences in an individual's genetic makeup that influence drug disposition, metabolism, transport and efficacy, leading to individual responses to drugs [1, 2].

Pharmacogenomics (PG)-based clinical practices have been implemented successfully in many developed countries to increase personalized medicine and improve the quality of life and safety of patients [3, 4].

It is clear that the advantages of PG testing, which improves health care and further optimizes or rationalizes drug therapy, are increasing daily. The Food and Drug Administration (FDA) has further strengthened the roles of PG in optimum health care settings. The FDA recommended that pharmaceutical industries modify the labelling for various drugs to indicate the potential use of genetic testing [5]. More than 200 medications were pharmacogenomically labelled between 2005 and 2017, all of which have PG information on their FDA product label ranging from boxed warnings to information in the clinical pharmacology sections of the label [6].

The Clinical Pharmacogenetics Implementation Consortium (CPIC), an international consortium of individual volunteers, consists of Pharmacogenomics Research Network members; PharmGKB staff; and experts in pharmacogenetics, PG, and laboratory medicine who are interested in facilitating the use of pharmacogenetic testing for patient care; the CPIC have published 36 guidelines as of March 2017 on the use of drug therapy based on pharmacogenetic information [7]. Examples of commonly used FDA-labelled drugs with published CPIC guidelines include warfarin, irinotecan, carbamazepine, clopidogrel, 6-mercaptopurine, and cetuximab [8–12].

However, many barriers obstruct the application of PG in drug prescription; PG is widely used in laboratories and health centres but not in routine clinical practice. These barriers include regulatory and reimbursement issues, evidence of clinical utility and clinician perspectives, and healthcare provider education and practice [13]. The cost of testing was also identified as a barrier that impedes the clinical utilization of PG testing, although this is likely to be inaccurate, as many physicians believe that the cost of genotyping exceeds the potential benefits. For example, a recent mathematical modelling study showed that genotype-guided clopidogrel therapy in some patients was more cost-effective than prescribing this drug (or its alternative, prasugrel) to all patients [14].

PG adds further complexity to pharmacotherapy decision making regarding individualized optimal applications and treatments, which requires physicians to allocate further time to maintain competency in both pharmacotherapy and their field of medicine [15–18].

Thus, there is a lack of leadership in implementing and utilizing PG in the clinical setting, which is a role that pharmacists within research settings, multidisciplinary settings and community pharmacies are well suited to carry out [19–23].

A pharmacist is the only health professional whose training and educational activities focus on medication use, and because of this, a pharmacist may serve as both a patient educator and a provider of PG testing. In addition, as pharmacists work in a range of clinical settings, they may be well suited to deliver PG testing at different time points during clinical care to both assure proper dosing and avoid prescribing drugs to those who do not respond to the drug or those who may suffer adverse effects [22–25].

Multiple studies have demonstrated that incorporating PG into community pharmacy practice is viable in many settings [26, 27]. A community pharmacy-based programme in Canada reported community pharmacists to be ideally suited to both offer personalized medication services and interpret PG results on a broad scale. An ineffective response to therapy, the occurrence of an adverse reaction or guiding the initiation of therapy were the main reasons why community pharmacists reported carrying out a PG test, and an average of 1.3 drug therapy problems directly related to PG testing were identified per patient, with recommendations reported back to the prescribers [25]. However, globally, many pharmacists are reportedly sceptical toward sharing the results of PG testing with other healthcare professionals due to the debate about the perceived benefits of PG testing [28–31]. Pharmacists should be well educated in PG at both the undergraduate and postgraduate levels [32]; however, a study indicated that 80% of the responding pharmacists disagreed that PG was an integral part of the curriculum at the pharmacy institutes they had attended. Furthermore, it was determined that, like other healthcare providers, pharmacists in developed countries feel that their PG education was insufficient [13, 14, 33, 34].The limited use of PG in pharmacy practice is thus the case in most countries [35].

In the state hospitals of North Cyprus, pharmacists working in hospital pharmacies are responsible for supplying drugs to inpatients and thus do not provide core pharmaceutical services, such as patient education and counselling. Community pharmacists also do not provide counselling services, except upon request [36]. However, the introduction of proactive pharmacists in these settings has improved therapeutic outcomes in different patient groups, indicating the potential for improvement in the provided care [36–39].

Both the healthcare and educational systems in North Cyprus (being mostly Turkish-inhibited) are closely associated with Turkey. In terms of pharmacogenetic education, universities in North Cyprus affiliated with the Turkish Higher Ministry of Education (as well as Turkish universities) offer either ‘Personalized Medicine’ as a course in the undergraduate curriculum or ‘Molecular Genetics’ or ‘Genetics and Molecular Biology’ courses that discuss PG instead [40].

In Turkey, pharmacogenetic research in practice has grown and become more powerful, yet the translation of knowledge from research into clinical practice has been limited. Relatively few laboratories offer pharmacogenetic testing services, and a limited number of tests are requested. Studies have been carried out on different drugs including warfarin, other anticoagulants and antiplatelets [41, 42]. Pharmacogenetic testing has also been introduced into psychiatric practice, cardiology, oncology, and adult and paediatric medicine [42–47]. However, in clinical practice in both Turkey and North Cyprus, routine testing is still mainly utilized in oncology settings only [47].

Aim of the study

This study aimed to examine the attitude and knowledge among pharmacists in Northern Cyprus (NC) of PG testing, their adoption of PG testing, and the most appropriate method to improve their education.

Ethics approval

Ethical approval for this study was obtained from the Institutional Review Board (IRB) of Near East University Hospital (Ref YDU/2016/39-311). Research was conducted in accordance with the Declaration of Helsinki.

Methods

A prospective cross-sectional study was conducted between July and September 2016 in NC using a pretested, modified questionnaire [4]. Prior to the study, verbal consent was obtained from all participants. The questionnaire was translated from English into Turkish by an expert, and then two independent native Turkish speakers translated the questionnaire back to English to keep the equivalence of the questionnaire in the target language. The questionnaire was completed by face-to-face interviews that allowed the data collector to explain any ambiguous items. A pilot study was conducted in NC with 15 pharmacists to determine the applicability of the questionnaire, and the Cronbach's alpha coefficient was calculated to determine the internal consistency of the questionnaire [48].

Sampling

All community pharmacists in the major cities of NC were invited to participate (n = 202). Raosoft software (Raosoft. Inc., Seattle, USA) was used to calculate the minimum sample size required for the study [49]. Assuming a 95% confidence level, a 5% margin of error and a 50% response distribution, at least 133 pharmacists needed to participate in the survey out of 202 pharmacists in NC.

The modified questionnaire consisted of 25 questions and was divided into five sections.

The respondent demographics section consisted of four items on the respondent's gender, age, and years of experience and the location of the school the respondent attended. The knowledge section consisted of five different items to measure the respondent's knowledge regarding PG and to verify whether any further education was needed; the knowledge score was between 5 and 10 and involved the use of two answers (agree and disagree).Three items in the section assessed genetic variability and the metabolic drug response, and one item tested the PG information on the FDA label for warfarin. The last item assesses the availability of PG testing for drugs. The attitude section was assessed with a score between 8 and 40 using a 5-point Likert scale of strongly disagree, disagree, normal, agree and strongly agree. To measure the respondent's thoughts on financial support for PG testing and the respondent's concern about confidentiality and discrimination, 8 items were required. The adoption section was intended to measure the level of evidence required to recommend PG testing, and the education section focused on the sources of PG information used by the participants for items with more than one answer.

Data analysis

Statistical methods were used to analyse the data, including the calculation of descriptive statistics such as the frequency and percentage for categorical variables, the weighted mean, the median, the standard deviation (SD), and the minimum and maximum for the continuous variables. The Kolmogorov-Smirnov test of normality was applied, and since the data did not support parametric assumptions, the Kruskal–Wallis test and the Mann–Whitney U test were performed when applicable. For multiple group comparisons, Bonferroni correction was applied, and the results were evaluated accordingly. To evaluate the associations between categorical variables, a Pearson Chi square test was performed. The level of significance was defined as $\alpha = 0.05$. All calculations and analyses were carried out with the SPSS (Statistical Package of Social Sciences Demo Version 22.0) program.

Prior to the initiation of the study, all study procedures were approved by the Institutional Review Board (IRB) of Near East University Hospital.

Results

Demographics of the respondents

One hundred forty survey instruments were distributed to community pharmacies in North Cyprus. One hundred and three (68.7%) pharmacists completed the survey instrument. Most of the respondents were female (60.2%) as opposed to male (39.8%). The age distribution of the respondents showed that 20.4% of the pharmacists were more than 30 years old and that 65% of the respondents had 1–5 years of working experience. The majority of the respondents graduated from universities in Cyprus (51.5%) and Turkey

(32%). The respondents' demographics are presented in Table 1.

Most of the pharmacists who had 1–5 years of experience graduated from universities in North Cyprus (77.6%), and those who had more than 11 years of experience graduated from universities in other countries. Twenty-eight percent of the respondents who graduated from other universities had more than 11 years of experience($x^2 = 52.57$, $p < 0.05$).

The choice of the internet as a source of PG information was dependent on the years of experience, with 42.9% of the pharmacists who had more than 10 years of experience choosing the internet as a reliable source, while 28.4% of those who had 1–5 years of experience relied on the internet as a PG information resource ($x^2 = 10.29$, $p < 0.05$).

More than half (66.7%) of the pharmacists who graduated from universities in North Cyprus reported asking doctors for knowledge when they needed to know about PG, while 20% of those who graduated from universities in Turkey asked doctors for information about PG ($x^2 = 4.07$, $p > 0.05$). In contrast to lab testing, pharmacists who studied in Turkey relied less on genetic lab tests than those who studied in North Cyprus (63.3% and 20%, respectively).

Knowledge of the respondents

The majority of the respondents (98.1%) believed that differences in a person's genetic profile might have an important effect on the patient's response to drugs, while 1.9% disagreed. In response to the second question in this section of the survey, 84.5% of the respondents believed that genetic factors that affect the drug response change over a patient's lifetime. Most (72.8%) of the respondents agreed that genetic differences can led to at least a 95% fluctuation in the drug's effect, while 27.2% disagreed. Furthermore, 62.1% of the respondents agreed that the warfarin leaflet label warned about metabolic differences in patients who have specific genetic variants, and the majority (55.3%) disagreed that PG testing was now available for most drugs.

Table 1 Demographic characteristics of the pharmacists (n = 103)

Characteristic	Number of respondents (n)	Percentage of respondents (%)
Gender		
Male	41	39.8
Female	62	60.2
Age		
21–25	42	40.8
26–30	40	38.8
31 and above	21	20.4
Years of experience		
1–5	67	65
6–10	22	21.4
11–15	6	5.8
16–20	4	3.9
21 and above	4	3.9
School location		
Cyprus	53	51.5
Turkey	33	32
Other	17	16.5

Attitude of the respondents

The majority of the respondents agreed that PG testing supports a reduction in the total number of unfavourable drug reactions (40.8%), while approximately half of the respondents (47.6%) believed that PG testing has contributed to decreasing the cost of creating new drugs. In response to the third question, 56.3% of the respondents agreed that PG testing helps find the optimal warfarin dose for patients in less time, and 57.3% of the pharmacists who responded to the survey believed that PG testing helps to reduce the total number of adverse drug reactions to warfarin in patients.

Nearly quarter of the respondents (21.4%) disagreed that unauthorized individuals could possibly have access to the results of a patient's PG testing, while the majority of the respondents (35%) believed that PG testing may result in discrimination by employers or/and insurance companies. Approximately one-third of the respondents (27.2%) disagreed about incorporating genetic information into determining a patient's initial warfarin dose, and 31.1% of the respondents strongly agreed that if they were the patient being placed on warfarin, they would be comfortable having their genetic information incorporated into determining the initial warfarin dose.

Adoption

Most of the respondents (87.4%) believed that a patient's genetic information affects the patient's drug therapy, and 79.6% of the respondents will order or recommend PG testing in the future. Furthermore, 62.1% of the respondents felt that they have sufficient knowledge about the availability of genetic testing and its use in therapy through drug management, and most (87.4%) would rely on FDA labels in ordering or recommending PG testing.

Education

Our findings highlighted pharmacists as the greatest information resource used by the participants to learn about PG testing (79.6%), followed by physicians and genetic labs (31.1%). Furthermore, 35.9% of the respondents preferred that PG be taught during an undergraduate education, while

Table 2 Predictors of pharmacogenomics adoption, interest in education and preferred education mode

Sources of pharmacogenomics information[a]	(n = 103)	Percentage of respondents (%)
Pharmacists	82	79.6
Genetic labs	32	31.1
Physicians	32	31.1
Internet	27	26.2
Drug labels	21	20.4
Preferred education mode[a]		
Continuing education	52	50.5
Undergraduate pharmacogenomic education	37	35.9
Postgraduate pharmacogenomic education	27	26.2
Seminars or workshops	26	25.2
Ward rounds	21	20.4
Prior pharmacogenomic education	5	4.9
Form of education of interest[a]		
Seminar or lecture	47	45.6
Ward rounds	35	34.0
All-day conference	31	30.1
Half-day conference	25	24.3
Web-based CPE	18	17.5
CPE	16	15.5

[a]Respondents could pick more than one answer (percentage summation ≠ 100%)

26.2% preferred postgraduate education, and the majority of the respondents preferred continuing education (50.5%) as the most suitable educational method. Those who had an interest in PG education preferred seminars or lectures (45.6%), ward rounds (34%), and all-day conferences (30.1%) as an education method (Table 2).

Based on their age groups, the respondents between 21 and 25 years old, 26–30 years old and more than 31 years old had weighted mean attitude scales of 29.4 ± 5.1, 30.7 ± 5.2 and 26.1 ± 4.2, respectively (Table 3). Accordingly, participants who were 26–30 years old had a significantly higher mean attitude score than participants older than 31 years old ($p = 0.008$). Based on the years of experience and location of the respondent's school, there were no statistically significant differences between these categorical groups in terms of both the attitude and knowledge scores. The Cronbach's alpha coefficient for the attitude score was 0.76, which shows that the data exhibited good internal consistency in the format used.

Discussion

The purpose of this particular study was to assess pharmacists' attitudes, knowledge and practice with disclosures about their limited knowledge concerning PG and pharmacogenetic testing. By partnering with other professionals, pharmacists will be well prepared to stand as leaders within

Table 3 Total attitude and knowledge scores with respect to demographic characteristics

	Total attitude score			Total knowledge score		
	Mean[b] ± SD	Median (min–max)	*p*	Mean[b] ± SD	Median (min–max)	*p*
Gender						
Male	30.1 ± 5.3	28 (18–39)	> 0.05	7.1 ± 0.9	8 (6–9)	> 0.05
Female	28.7 ± 5.0	28 (17–39)		7.1 ± 0.8	8 (6–10)	
Age						
21–25	29.4 ± 5.1	27 (18–37)	0.008[a]	7.0 ± 1.0	8 (6–10)	> 0.05
26–30	30.7 ± 5.2	31 (19–39)		7.0 ± 0.8	8 (6–10)	
> 30[a]	26.1 ± 4.2	28 (17–32)		7.1 ± 0.5	8 (7–9)	
Experience						
1–5	30.5 ± 5.2	28 (18–39)	> 0.05	6.9 ± 0.9	8 (6–10)	> 0.05
6–10	26.5 ± 4.0	27.5 (18–31)		7.3 ± 0.8	8 (6–9)	
> 10	27.1 ± 4.8	27 (17–36)		7.3 ± 0.7	8 (7–9)	
School location						
Cyprus	30.4 ± 5.3	28 (18–39)	> 0.05	7.0 ± 0.9	8 (6–10)	> 0.05
Turkey	28.2 ± 5.9	26 (17–38)		7.3 ± 0.9	8 (6–9)	
Other	28.1 ± 2.1	29 (25–31)		6.7 ± 0.5	8 (8–9)	

Kruskal–Wallis and Mann–Whitney U tests were applied where applicable

[a]$p < 0.05$ significant difference compared to the 26–30 age group

[b]Weighted mean was calculated

the field of PG research and practice [50]. Pharmacists are furnished with professional drug knowledge and are considered a valuable source of drug information; therefore, they are well positioned to play an important role in the application of PG in clinical practice. This might prevent drug-related adverse events and improve patient outcomes, despite the moral and privacy concerns and the possible consequences of lifelong genetic data availability.

The mean of the total attitude scores was significantly lower in pharmacists > 30 years old than in pharmacists 26–30 years old ($p < 0.05$), mainly because of the long time required for graduation and a lack of updated information; these results were opposite those from a study conducted in Malaysia, which showed that older health care providers had higher attitude scores [4].

Only 21.4% of the respondents in this study did not have concerns that individuals with unauthorized access could obtain the results of the patients' PG testing, which was in contrast to the study conducted in Malaysia by Bannur et al. [4], in which only 15.7% of the respondents were concerned with the privacy of the patient's pharmacogenetic testing data; although both the Turkish Cypriot and Malaysian communities are comparable in their beliefs and culture, the respondents of our study had greater fear of privacy issues than the Malaysians respondents, but almost 40% of healthcare providers in many developed countries had this concern [50]. Additionally, most of our respondents (41.7% vs. 23.3%) believed that PG testing may bring about discrimination by employers or insurance companies, which is comparable to the results of another study in which 38.7% of the respondents were concerned about discrimination by employers and insurance companies due to their genetic profile [51].

Two different studies revealed that females were significantly more concerned about discrimination than males. The researchers who conducted these studies highlighted the increased female fear for perceived risk as opposed to that in males [43], but in contrast, there was no significant difference between males and females in terms of a fear of discrimination in our study.

Approximately one-third of the respondents (41.8%) disagreed that having genetic information would help determine a warfarin starting dose, and 49.5% of the respondents strongly agreed that if they were a patient newly starting warfarin, they would agree to have genetic information assimilated into the determination of the warfarin starting dose.

A study conducted by Dodson [30] reported that 78.5% of respondents from developed countries believed that there would be fewer general adverse reactions, while 81.5% believed that adverse drug reactions to warfarin would be reduced. In contrast to our study, only 40.8% of respondents agreed that PG testing will help to decrease the total number of adverse drug reactions, while 61.2% of the pharmacists who responded to the survey agreed that PG testing may help to reduce the total number of adverse reactions experienced by patients taking warfarin [52]. In contrast to recent studies, 58.5% of the respondents believed that PG testing would help find the optimal warfarin dose for patients in less time, while 47.6% of the respondents agreed that the cost of producing new drugs would decrease once supported by PG testing, which was in contrast to the 14.1% reported by Roederer [53] for the cost of developing new drugs.

Our results on obtaining PG information were in contrast with those of the other study in Malaysia, in which only 4% of the Malaysian pharmacists who participated in the study asked physicians to obtain PG information, while in our study, physicians were the second most relied upon resources. This huge gap between the two different countries reflects difference in the health care systems of both countries and that clinical pharmacy services have successfully been established in Malaysia [4].

Although knowledge on the importance of PG in dispensing and prescribing drugs has dramatically increased in recent decades, there is still a gap between knowledge and education, and adding PG courses or workshops as part of continuing education programs for pharmacists may improve this knowledge. A study that assessed pharmacists' knowledge regarding PG before and after an educational programme showed a significant improvement in participant knowledge ($p < 0.05$) [54]. With regard to undergraduate pharmacy education, many universities and pharmacy schools around the world have adopted pharmacogenetics courses in their curriculum. The pharmacy college at Washington State University (WSU) established a mandatory PG course in 2015. Additionally, the University of California San Diego Skaggs School of Pharmacy and Pharmaceutical Sciences adopted an online course called the PG Education Program in their curriculum [54]. Although many schools have adopted a form of pharmacogenetic education, the content of these courses and syllabi still vary. In 2010, a study conducted by Murphy JE and colleagues reported that 92% of the 75 PharmD programmes in USA taught PG courses with different syllabi and contents [55, 56].

Some barriers to the application of PG into practice were described in this assessment; these contain, among others; moral issues, discrimination, incomplete knowledge of PG, price, insurance exposure, secrecy, the absence of clinical strategies, a lack of clinical suggestions, and authorization by regulatory bodies [4]. Additionally, more than half of the studies assessed had a response rate lower than 60% of the pharmacists, which may confine the generalizability of their results.

There were several potential limitations to this study. One was related to sample size, and our sample did not match the calculated sample size due to the low response rate. Another limitation of the study was that the survey was administered only to community pharmacists in NC; other health care providers (physicians and nurses) should be included to observe the gap between health care providers on PG.

Conclusions

Community pharmacists in Northern Cypus generally had a positive attitude towards the implementation of pharmacogenomics in a clinical setting, but need more training. There is still a concern among pharmacists that test results may be used to deny healthcare coverage; thus there is a need to educate healthcare professionals about privacy and legal issues surrounding genetic testing.

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