

Perception of Primary Care Physicians' Toward Pharmacogenetics in Jordan

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Abstract

Objective: Pharmacogenetics plays a major role in personalizing pharmacotherapy. However, it is not widely practiced in the clinical healthcare centers in many countries, including Jordan. The present study aims at assessing pharmacogenetic knowledge among primary care internist physicians from different public and private Jordanian hospitals.

Methods: A structural questionnaire, covering the basic background information and attitude toward pharmacogenetic practice, has been distributed among 300 primary care internist physicians in six hospitals in Amman, Zarqa and Karak cities and some private clinical centers in Amman between January to March 2017.

Results: The response rate has been 63.3%. The majority of internist physicians have responded that pharmacogenetics is important in reducing the unwanted drugs side effects (64.21%) and enhancing the efficacy of the treatment (62.11%). The majority of the participants (61.05%) have responded that physicians should know about pharmacogenetics and 64.73% of the participants want to know more about it. Furthermore, the majority of the respondents (80%) believe that pharmacogenetics will be relevant to the clinical practice if it is applied in Jordan. In addition, 40.52% of the participants have answered that patients should be analyzed genetically before describing the drugs. Most of the internist physicians have responded that laboratory pharmacogenetic tests are not available (48.94%), in the currently working hospitals, and not covered by medical insurances (69.47%).

Conclusion: It is concluded from the results of this study that most of the primary care internist physicians in Jordan know the clinical importance of pharmacogenetic testing but it is still not widely practiced. Further intensive studies are needed to find the possible ways of implementation of pharmacogenetic testing in Jordan.

Keywords: Pharmacogenetics; internist physicians; Jordan; perception

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Introduction

Pharmacogenetics is the study of the effect of genetic variations on drugs response.¹ Genetic

variations were estimated to account for 20 to 95% of the inter-individual variation in response to medications.² These genetic variations may affect the pharmacodynamics and kinetics of the

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drugs, depending on the role of the mutated gene in drugs response. It is found that genetic variations in drug-metabolizing enzymes, such as Cytochrome (CYP) 2C19, influenced the pharmacokinetics and associated with reduced efficacy and unwanted toxic side effects of the drugs.³ In addition, it is reported that genetic variations in genes coding for drug target proteins (such as receptors) affected the sensitivity to drug therapy.⁴ Therefore, the United States Food and Drug Administration (US FDA) recommended pharmacogenetic testing for some drug treatment, such as warfarin.⁴

Although the response of the drug is influenced by many factors, such as health status, age and gender, the variation in human gene sequence is considered a major factor explains the inter-individual variation in drug's response.⁵ In addition, the inter-ethnic variation in drug's response is observed, which depends mainly on the genetic background of the population. For example, African populations are less sensitive to β -blocker drugs than Caucasians due to genetic variation in the β -receptor gene.⁶ Furthermore; Asians are generally fast acetylators in comparison to Caucasians due to genetic polymorphisms in N-Acetyltransferase 2 gene.⁷

Generally, Jordanian population is considered genetically as Caucasian. Therefore, it is recommended to follow the medical guidelines for Caucasians in Jordan. However, the Jordanian population is actually admixture of different populations; due to its geographical location in the link between Asian, African and European continents.⁷

The pharmacogenetic testing approach is considered to be one of the most promising clinical applications with the potential to reduce adverse drug responses and improve drug efficacy.⁸ Therefore, medical education of pharmacogenetic testing was assessed in different

medical colleges. However, the clinical practice of pharmacogenetic testing is generally slow due to some reasons including lack of knowledge and guidelines, limited clinical evidence and cost-effective molecular test.⁸

Primary care physicians (family and internal medicine) play a major role in ordering pharmacogenetic testing for personalized medicine and as a source of information for patients in USA.⁸ It is estimated that primary care physicians prescribe about 25% of the outpatients with medications that contain pharmacogenetics information in their labels.⁹

Although pharmacogenetic testing is recommended in the clinical guidelines for the treatment of some diseases, it is still not applied in most on the healthcare centers in Jordan. Therefore, the present study aimed to assess pharmacogenetics knowledge among primary care internist physicians from different public and private Jordanian hospitals. Identification the knowledge, attitude and the limitations in applying pharmacogenetics will help us in understanding the current status as a first step toward implementation of pharmacogenetics in medical treatment in Jordan.

Methods

A structural questionnaire, that contains only closed-ended questions, was developed in College of Pharmacy, Al-Zaytoonah University. The resulting questionnaire was comprised of 30 questions modeled on findings from previous studies about the incorporation of pharmacogenetics into clinical practice,¹⁰ These questions cover the basic background information and attitude toward pharmacogenetics practice. The ethical approval was obtained from Al-Zaytoonah University Ethical Committee before beginning this study.

The internal validity of the questionnaire was

assessed after translation the questionnaire to the Arabic language. Accordingly, some questions were revised to be more precise. The first draft of the developed questionnaire was pre-tested on a pilot group of 30 physicians noting confusing questions and ambiguous terms of the content. Then, the questionnaire was revised accordingly.

This study was conducted in six hospitals in Amman, Zarqa and Karak cities between January to March 2017 using structured questionnaires. These hospitals were: Royal Medical Service, Al-Hikma Modern, University of Jordan, Prince Hamzah, Al-Bashir and Al-Karak Governmental Hospital; the biggest hospitals in Jordan where many internist physicians prescribe some drugs, such as warfarin and clopidogrel, with pharmacogenetics impact. These hospitals were selected as they are main healthcare centers in Jordan where many of the Jordanian citizens are receiving treatment there and some of these healthcare centers have educational programs for medical students and residency. In addition, the questionnaire was distributed in some private medical centers in Amman city.

As internist are the major prescribers of drugs with pharmacogenetic labeling, the present study focused on administrating the questionnaires to primary care physicians belonging to Internal Medicine Department and internist known to be associated with programs where genetics and pharmacology were covered.

The sample size was calculated using the Raosoft online calculator (<http://www.raosoft.com/samplesize>) with a 5 % margin of error, 95% confidence level and targeted population of 1300 internist physicians. Based on

this, it was anticipated that the sample of 292 internist physicians would enable us to achieve the study objectives.

A total of 300 questionnaires were distributed among 300 primary care physicians. Every respondent provided an informed consent before questionnaires were administered. All data were summarized as frequencies and percentage.

Results

One hundred and ninety of the internist (63.33%) completed and returned the questionnaires. Among the respondents; (70%) were males and (30%) were females with age range from 27 to 53, average of 32 ± 7 SD and median of 29 (Table 1). All of the internist physicians were Jordanians.

Table 1. Demographics of sample population

Item	Category	Frequency
Age	27-37	142
	38-49	45
	50-60	3
	>60	0
Sex	Male	133
	Female	57
Province	Amman	140
	Zarqa	34
	Karak	16

Table 2 shows the source of pharmacogenetics information. It is found that colleagues, scientific conferences, and college education were the major source of the pharmacogenetics information, while only 15.58% didn't hear about it.

Table 2. Source of Pharmacogenetics information among primary care physicians in Jordan

Source of information	Not heard	Colleagues	Internet	Journals	Media	University	Conferences and seminars
% of response	15.6	18.2	9.1	13	5.2	20.8	18.2

Regarding the basic knowledge of pharmacogenetics among Jordanian Internist physicians, this study found that the majority of internist physicians responded that pharmacogenetics is important in reducing the unwanted drugs side effects (64.21%) and

enhancing the efficacy of the treatment (62.11%), as represented on Table 3. It is found that the majority of the respondents (80%) believe that pharmacogenetics will be relevant to the clinical practice if it is applied in Jordan.

Table 3. Basic Knowledge of Pharmacogenetics among primary care physicians in Jordan

	Not important Frequency (% of response)	Uncertain Frequency (% of response)	Important Frequency (% of response)
Importance of pharmacogenetics in reducing the cost of the drug	12 (6.3)	83 (43.7)	95 (50)
Importance of pharmacogenetics in enhancing the efficacy of the drug	23 (12.1)	50 (26.3)	118 (62.1)
Importance of pharmacogenetics in reducing the side effect of the drug	24 (12.6)	44 (23.2)	122 (64.2)

Table 4 provides summary of relevant pharmacogenetics teaching-related items, knowledge of pharmacogenetics laboratory testing and attitude of primary care internist physicians toward pharmacogenetic practice. Only 40.52% of the participants responded that

pharmacogenetics was part of the medical curriculum and 27.89% didn't know if pharmacogenetics was included in the curriculum. The majority of the participants (61.05%) responded that physicians should know about pharmacogenetics and 64.73% wanted to know more about it (Table 4).

Table 4. Relevant pharmacogenetics teaching-related items, knowledge of pharmacogenetics laboratory testing and attitude of primary care physicians in Jordan toward pharmacogenetic practice

	Response		
	Yes Frequency (% of response)	No Frequency (% of response)	Unaware Frequency (% of response)
Relevant pharmacogenetics teaching-related items			
Do medical courses contain pharmacogenetics subject during your study	77 (40.5)	60 (31.6)	53 (27.9)
Do you think that medical students should know about Pharmacogenetics	116 (61)	31 (16.3)	43 (22.6)
Do you want to know more about pharmacogenetics	123 (64.7)	12 (6.3)	55 (28.9)
The knowledge of pharmacogenetic laboratory testing			
Is pharmacogenetics laboratory test available in the hospital, where you are working?	16 (8.4)	93 (48.9)	81 (42.3)
Is the cost of genetic tests available in your hospital?	8 (4.2)	79 (41.6)	103 (54.2)
Do you think that genetic tests are included in the Medical insurance	8 (4.2)	132 (69.5)	50 (26.3)
The attitude of primary care physicians in Jordan toward pharmacogenetic practice			
Do you think that pharmacogenetics help you in prescribing of the medicines	131 (68.9)	39 (20.5)	20 (10.5)
Do you think that patients should do the genetic tests before prescribing of the drug	77 (40.5)	60 (31.6)	53 (27.9)
Do you think that physicians should order the genetic test before prescribing certain drugs?	66 (34.7)	81 (42.6)	43 (22.6)

Most of the internist physicians responded that laboratory pharmacogenetics tests are not available (48.94%) or unaware (42.55%) in the healthcare centers in the hospitals where they work. In addition, only 4.21% responded that the cost of laboratory analysis tests for pharmacogenetics is available and 41.57% of the participants responded that the pharmacogenetic testing cost is not available or

unaware (54.21%) about the availability of the pharmacogenetic testing cost for publics and physicians. Furthermore, the majority of the internist physicians were aware (69.47%) that pharmacogenetic testing is not covered by medical insurance (Table 4).

Regarding the attitude toward practicing of pharmacogenetic testing, is also shown in the current report that 40.52% of the participants

responded that patients should be analyzed genetically before describing the drugs and 34.73% responded that physicians should order the pharmacogenetic test before prescribing the appropriate drug.

Discussion

Pharmacogenetics plays a major role in personalizing the medicine. However genetic based pharmacotherapy is widely practiced in many countries, such as Holland and Thailand,^{11, 12} it is still clinically unpracticed in Jordan, except in the treatment of some cancer cases. To the best of our knowledge, this is the first report regarding the perception of primary care internist physicians toward the application of pharmacogenetics testing in the clinical treatment. It is found from this study that primary healthcare internist physicians have generally a good knowledge of the principles of the pharmacogenetics but they believe that it is not applied in Jordan due mainly to the absence of pharmacogenetic laboratory testing in general hospitals and medical insurances covering the pharmacogenetic test. The impact of this study is through identification of the barriers in applying pharmacogenetics in medical treatment, which can be overcome in order to increase the widespread using of pharmacogenetics in Jordan.

In the current study, the knowledge of the primary care internist physicians was tested using some questions regarding the basic knowledge in pharmacogenetics. It is found that the majority of the physicians had the basic knowledge regarding the influence of the genetic variation on drugs response through alteration of the drugs kinetics and dynamics. In addition, most of the respondents received their knowledge of pharmacogenetics through university education and scientific conferences.

These results indicate that primary care internist physicians in Jordan are aware of the importance of the genetic-based pharmacotherapy. However, pharmacogenetics is still not significantly applied in the healthcare centers, where the respondents practice the pharmacotherapy. This study didn't ask directly the practice of pharmacogenetics among internist physicians in Jordan. But it was concluded from Table 4 that most of the responded (91.5%) don't know if genetic analytic methods are available for testing pharmacogenetics in Jordan which might reflect the low rate of pharmacogenetics practice.

It is observed from the internist's response in the current study that pharmacogenetic analysis tool is absent in most public healthcare centers in Jordan. Therefore, it is necessary to find a cost-effective and fast genotyping method for Jordanian patients which may encourage the physicians to apply the genetic-based medicine.¹³ Genetic tests are usually done through different molecular analysis techniques. The golden method for genotyping is DNA sequencing.¹⁴ However, it is expensive. In Jordan, most of the pharmacogenetics researches used Polymerase Chain Reaction-Fragment Length Polymorphism (PCR-RFLP) for genotyping analysis.^{7,15,16} Although PCR-RFLP is the cheapest genotyping tool in Jordan, it takes longer time and the rate of false positive results are higher in comparison with other genotyping methods.¹⁷

Most of the Jordanian population are on medical insurance. Unfortunately, many of the genetic analysis tests aren't included in the medical insurance and are expensive. Therefore, physicians depend on observing the phenotype of the drug treatment (efficacy and side effects) for personalizing of the medicine,

rather than ordering the genotyping test. Pharmacogenetic analysis tests are included in the medical insurance in some countries, such as Thailand, but still excluded in many countries, such as USA and UK.¹⁸ This suggests that excluding of pharmacogenetics from medical insurance is the major barrier of applying pharmacogenetics in the clinical field.

It is found in the current study that most of the internist physicians in Jordan know that genetic variation is important in personalizing of the medicine. However, only 39% of the respondents believed that pharmacogenetics should be applied in the treatment. This may be due to the absence of sufficient clinical evidence of the influence of genetic variation on many drug's responses. Some studies found that genetic variations affected on the drugs activity by *in vitro* but not clinically.¹⁹ Furthermore, the clinical effect of some genetic variations is still not validated.²⁰ On the other hand, genetic variations in CYP2C9 and Vitamin K Epoxide Reductase genes are approved by the US FDA to be analyzed before prescribing warfarin therapy.²¹ However, the approved genetic variations by US FDA are still not analyzed before prescribing the drugs in Jordan.

Although this study described generally the internist physicians knowledge in

pharmacogenetic, it is planned to study the practice of the pharmacogenetics in US FDA approved drugs among hematologists, cardiologists and oncologists who prescribe drugs which the pharmacogenetics impact is known, such as warfarin and imitinib.

This study has some limitations. Firstly, the study was conducted in some cities and didn't cover all Jordanian cities, such as northern cities Irbid and AlMafrq. Secondly, the present study didn't include the family medicine specialists whom can practice the pharmacogenetic testing for drug prescription. Thirdly the data analysis of this study was conducted in a small number of samples (190 samples); due to the low response rate to the questionnaire.

Conclusion

It is concluded from the results of this study that physicians have generally good knowledge regarding the basic principles of pharmacogenetics but it is still not widely practiced in Jordan due to the absence of cost-effective genotyping tests and medical insurance in Jordan. Intensive efforts are needed to implement the practice of pharmacogenetics in Jordan.

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إدراك أطباء الرعاية الأولية نحو علم الوراثة الدوائي في الأردن

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الملخص

الهدف: علم الأدوية الجينية يلعب دوراً رئيسياً في العلاج الدوائي للأشخاص. ومع ذلك، لا يُمارس على نطاق واسع في مراكز الرعاية الصحية السريرية في العديد من البلدان، بما في ذلك الأردن. لذا، هدفت الدراسة الحالية إلى تقييم المعرفة بعلم الأدوية الجيني بين الأطباء الباطنيين في الرعاية الأولية من مختلف المستشفيات الأردنية العامة والخاصة.

المنهجية: تم توزيع استبانة، يغطي المعلومات الأساسية والموقف والرأي تجاه التطبيق الطبي لعلم الأدوية الجيني في العلاج، على 300 من أخصائيي الباطنية في ست مستشفيات في مدن عمان والزرقاء والكرك وبعض المراكز السريرية الخاصة في عمان بين يناير ومارس 2017. **النتائج:** كان معدل الاستجابة 63.3%. أجاب غالبية الباطنيين بأن علم الوراثة الدوائي مهم في الحد من الآثار الجانبية للأدوية غير المرغوب فيها (64.21%) وزيادة فعالية العلاج (62.11%). أجاب غالبية المشاركين (61.05%) أن الأطباء يجب أن يعرفوا عن علم الأدوية الوراثة و 64.73% يريدون معرفة المزيد عن ذلك العلم. علاوة على ذلك، يعتقد أغلبية المشاركين (80%) أن علم الأدوية الوراثة سيكون ذا تأثير في الممارسة السريرية إذا تم تطبيقه في الأردن. بالإضافة إلى ذلك، أجاب 40.52% من المشاركين أنه ينبغي تحليل المرضى وراثياً قبل وصف الأدوية. وأجاب معظم الأخصائيين الباطنيين بأن الاختبارات المخبرية الوراثة غير متوفرة (48.94%)، في المستشفيات التي يعملون فيها حالياً، ولا تشملها التأمينات الطبية (69.47%).

الخلاصة: خلصت نتائج هذه الدراسة إلى أن معظم الأطباء الباطنيين المشاركين في هذه الدراسة من الأردن يعرفون الأهمية السريرية لعلم الأدوية الجيني وتطبيقاته. لكن، لا يزال علم الأدوية الجيني لا يُمارس على نطاق واسع. هناك حاجة إلى مزيد من الدراسات المكثفة للعثور على الطرق الممكنة لتطبيق علم الأدوية الجيني في علاج المرضى في الأردن.

الكلمات الدالة: علم الوراثة الدوائي، طبيب باطني، الأردن، الإدراك.