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An exploratory study of pharmacogenetics in Palestine: A qualitative evaluation of attitudes and practicesof physicians, Ministry of Health and pharmaceutical companies

By

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An exploratory study of pharmacogenetics in Palestine: A qualitative evaluation of attitudes and practices of physicians, Ministry of Health and pharmaceuticalcompanies

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ABSTRACT

Background: The inter-individual variations to drug response is often unpredictable.Several factors can causethis variation including age, weight, diet, drug-drug interactions,drug microbiota - interactionsand genetics polymorphisms. In general, the genetic makeup of a patientis considered one of the most significant factors that account for inter-individual variability in drug response.Such variations can lead to lower treatment efficacy or undesiredadverse effects of drugs.So, pharmacogenetics(PGt) is an emerging medical field that seeksto improve the efficacy and reduce the toxicity of drugsin order to enhance the practice of precision medicine.The presence of several obstacles facing the implementation of pharmacogeneticsin clinical practice promote us to perform this study in order to explore the current situation of pharmacogenetics in Palestine.

Methods: A questionnaire was developed targeting specialists, residents and general physicians working in several hospitals and clinics inthe West Bank.The data was collected from September to October 2019. Also, the Ministry of Health (MOH) website was explored to investigate the presence of pharmacogenetics guidelines, legislations and awareness programs.A total of 100drugs leaflets of 49drugs available in the Palestinian market under different brand nameswere screened for pharmacogenetics informationthat is in compliance with the FDA pharmacogenetics recommendations.

Results: The findings showed that 71% of physicians had positive attitude toward the importance of genetic variations in drug selection and dosing.Nevertheless, ٩٦.5% of physicians did not order pharmacogenetic tests. Furthermore, 74.4 % of physicians consider

that the Ministry of Health bears a greatresponsibility to adopt and force guidelines that aims to control thepharmacogenetics practice. Of the addressed physicians, 84% consider that pharmaceutical companies must be involved in developing this discipline by adopting a clear pharmacogenetics drug labeling on drug leaflets that require pharmacogenetic testing. Although 48% of physicians received education about PGt in universities during their study to gain medical degree, they showweakness in practical application of pharmacogenetic testing. High percentage of them 50.9% used self-learning sources, such as internet, to get information about PGt. Out of the addressed physicians 230, only 6answered the question related to the name of pharmacogenetic tests. All addressed physicianshad misconception between genetic tests and pharmacogenetic tests. On the other hand, the study revealed an absence of awareness guidelines and legislations control practical application of PGton MOH website. Also, the results of investigation into the presence of pharmacogenetics information in drugs leafletsfor a 49drugs showed that only 2 drugs leaflets contains pharmacogenetics information that comply with the FDA recommendations.

Conclusion and recommendations: The Palestinianphysicians showed a positive attitude and interest in pharmacogenetics discipline and its importance in maximizing drug efficacy and minimizing adverse toxicity . However, theyrequire specialized educationaland training programs as well as approved pharmacogenetics guidelines from the MOH. So, in the light of thesefindings, the study recommended the necessity of establishing national pharmacogenetics initiatives to enhance the translation pharmacogenetics into clinical practice to ensure maximum drug efficacy and minimum toxicity.

دراسة تقييمية لواقع الصيدلة الجينية في فلسطين من خلال تقييم توجهات الأطباء ودور وزارة الصحة التوعوي والتنظيمي ودور شركات الدواء التعريفي بهذا الحقل الطبي المُستجد

بيسان عبد عبد المعطي أبو سنينه

ملخص

خلفية الدراسة: غالبا ما تكون الاختلافاتالفردية في الاستجابة للأدوية غير متوقعة، كماتسببالكثير من العوامل اختلافا في الاستجابة للأدوية بين الأفراد مثل: العمر والوزن والغذاء والتفاعلات بين الأدوية وتعدد الأشكال الوراثية الجينية. يعتبر التركيب الجيني للفرد مسؤولاً أساسياعن الاختلاف في الاستجابة للأدوية . مثل هذه الاختلافات تؤديإلى تقليل فعالية الدواء أو ظهور الأعراض الجانبية. لذلك فإن علم الصيدلة الجيني هو مجال طبي ناشئ يسعى من أجل تحسين فعالية الدواء وتقليل سميّته من أجل تحسين تطبيق الطب التشخيصي .إن وجود عدة عوائق تواجه تطبيق علم الصيدلة الجيني في المجال العملي شجعنا لإنشاء هذه الدراسة لتقييم الوضع الحالي لعلم الصيدلة الجيني في فلسطين.

الطرائق المستخدمة في الدراسة: تم تطوير استبانه أجريت على أطباء الاختصاص والمقيمين والأطباء العامّين الذين يعملون في عدة مستشفيات وعيادات ومراكز صحية في الضفة الغربية. تم تجميع المعلومات ما بين شهري أيلول - تشرين أول من عام ٢٠١٩.كماتماستكشافموقعوزارةالصحةعلىالإنترنتللتحققمنوجودالإرشاداتوالتشريعاتوبرامج التوعيةالخاصة بعلم الصيدلة الجيني.تم جمع٣٦نشرة دواء من ١١ دواء متاحين في السوق الفلسطيني تحت أسماء تجارية مختلفةوتحتويعلى معلومات الصيدلة الجينية وفقًالإدارةالغذاءوالدواءللتحقيقفيوجودمعلومات الصيدلة الجينية فينشرتها .

النتائج: أشارت النتائج إلى أنه لدى ما نسبته71% من الأطباء موقف إيجابي حول أهمية الاختلافات الوراثية في اختيار الدواء. لكن لا يقوم ما نسبته96.5% من الأطباء بطلب عمل فحوصات الصيدلة الجينية. علاوة على ذلك، يعتبر ما نسبته 74.4% من الأطباء أن وزارة الصحة تتحمل المسؤولية الأكبر في فرض تشريعات تحكم تطبيق الصيدلة الجينية. ويعتبر ما نسبته84% من الأطباء المعالجين أنه يجب على شركات الأدوية الانخراط في تطوير هذا النظام من خلال اعتماد معلومات واضحة عن الصيدلة الجينية في نشرات الأدوية التي تتطلب فحوصات صيدلة جينية. على الرغم أن ما نسبته48% من الأطباء صرّحوا بأنهم تلقّواتعليماً عن الصيدلة الجينية خلال دراستهم في الجامعات، لكن أظهرت النتائج أن أقل من ٣% منهم فقط قد يلجأ لأجراء فحوصات صيدلة جينية تساعد في تحديد نوع وجرعة الدواء. وكما وأظهرت الدراسة أن نسبة عالية 50.9% من الأطباء المشمولين يستخدمون مصادر تعلم ذاتية مثل الانترنت للحصول على معلومات حول حقل الصيدلة الجينية. من مجموع الأطباء المعالجين، ٦ فقط أجابوا عن السؤال المتعلق بأسماء فحوصات الصيدلة الجينية . وجميعهم لديه خلط بين الفحوصات الجينية وفحوصات الصيدلة الجينية.من ناحية أخرى، أظهرت الدراسة غياب برامج التوعية والتشريعات التي تحكم التطبيق العملي للصيدلة الجينية على موقع وزارة الصحة. أيضا،

أظهرت نتائج البحث عن وجود معلومات الصيدلة الجينية في100نشرة دواءلمجموع 49دواء، وجود معلومات الصيدلة الجينية فقط لنشرتين دوائيتين وعدم وجود أي معلومات أو قواعد إرشادية لها علاقة في الصيدلة الجينية في نشرات الأدوية المتبقية.

الخلاصة والتوصيات: أظهر الأطباء موقف ايجابي واهتمام بموضوع الصيدلة الجينية وأهميته في تحقيق أقصى فعالية من الدواء وتقليل الأعراض الجانبية. ومع ذلك يحتاجون إلى برامج تعليمية وتشريعات وقوانين معتمدة من وزارة الصحة. لذلك في ظل هذه النتائج توصي الدراسةبضرورة تأسيس مبادرة وطنية للصيدلة الجينية وذلك لتعزيز ترجمة التطوراتالعلمية في هذا المجال للتطبيق الاكلينكي من أجل ضمان أقصى نجاعة وأقل سمية من العلاج .

DECLARATION

I declare that the Master Thesis entitledAn exploratory study of pharmacogenetics in Palestine: A qualitative evaluation of attitudes and practices of physicians, Ministry of Health and pharmaceutical companiesis my own original work, and hereby certify that unless stated, all work contained within this thesis is my own independent research and has not been submitted for the award of any other degree at my institution, except where due acknowledgment is made in the text.

Name and signature :

Date

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In presenting this thesis in partial fulfillment of the requirements for the joint Master's degree in Biotechnology at Palestine Polytechnic University and Bethlehem University, I agree that the Library shall make it available to borrowers under rules of the Library. Brief quotations from this thesis are allowable without special permission, provided that accurate acknowledgment of the source is made.

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Date

DEDICATION

I dedicate this Thesis to my parents, who have always been a source of support and have encouraged me to achieve my goals throughout my years of study.Because of their unconditional love and prayers, I have the chance to complete this thesis.

To my husband Dr. Hamed for his unconditional love, support and patience. Without his constant encouragement and belief in me I would never have reached my dreams.

To my brothers and sisters for their generous support they provided me throughout my entire life and particularly through the process of pursuing the master's degree.

My friends who encourage and support me.

My homeland Palestine.

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To my mother, a strong and gentle soul who thought me to trust in Allah, to believe in hard work and that so much could be done with little.

My father for earning an honest living for us and for supporting and encouraging me to believe in myself.

I owe profound gratitude to my husband, Dr. Hamed, whose constant encouragement, limitless giving and great sacrifice, helped me to accomplish my degree.

I would like to take this opportunity to say warm thanks to my beloved sisters and brothers, who have been so supportive along the way of doing my thesis.

Last but not least, deepest thanks go to all people who took part in making this thesis real.

List of Abbreviations

Abbreviations	Full Form
PGx	Pharmacogenomics
PGt	Pharmacogenetics
PK	Pharmacokinetic
PD	Pharmacodynamic
G6PD	Glucose-6-Phosphate Dehydrogenase
CNV	Copy Number Variation
SNP	Single Nucleotide Polymorphism
ns SNPs	Non-Synonymous Single Nucleotide Polymorphisms
CYP450	Cytochrome P450
EM	Extensive Metabolizer
IM	Intermediate Metabolizer
UM	Ultrarapid Metabolizer
PM	Poor Metabolizer
NSAIDs	Non Steroidal Anti-Inflammatory Drugs
TPMT	Thiopurine Methyl Transferase
ABCB1	ATP-Binding Cassette Sub-family B member 1
gp	Glycoprotein
DPD	Dihydropyrimidine Dehydrogenase
NAT	N-Acetyltransferase
GSTs	Glutathione Transferases
MDR1	Multidrug Resistance Protein 1
ADRB1	β_1-Adrenergic Rreceptor
GRK5	G-Protein Receptor Kinase5
ACE	Angiotension Converting Enzyme
TD	Tardive Dyskinesia
5-HT	5-Hydroxytryptamine
FDA	Food and Drug Administration
PharmGKB	Pharmacogenomics KnowledgeBase
CPIC	Clinical Pharmacogenetics Implementation Consortium
HLA	Human Leukocyte Antigen
VKORC1	Vitamin K Epoxide Reductase Complex Subunit 1
ALL	Acute Lymphoblastic Leukaemia
AZA	Azathioprine
6-MP	6-Mercaptopurine
6-TG	6-Thioguanine
5-FU	5-Fluorouracil
CRC	Colorectal cancer
SSRIs	Selective Serotonin Reuptake Inhibitors
SERT	Serotonin Transporter
CHRs	Cutaneous Hypersensitivity Reactions
DIHS	Drug Induced Hypersensitivity Syndrome
SJS	Stevens-Johnson Syndrome
TEN	Toxic Epidermal Necrolysis
PB	Phenobarbital
PHT	Phenytoin

CBZ	Carbamazepine
LTG	Lamotrigine
LABA	Long-Actingβ2-Agonist
EMA	European Medicines Agency
PMDA	Pharmaceuticals and Medical Devices Agency
ADRs	Adverse Drug Reactions
APDs	Antipsychotic Drugs
BP	Blood Pressure
ESPT	European Society of Pharmacogenomics and Personalized Therapy
eMERGE	Electronic Medical Records and Genomics.
NIH	National Institutes of Health
PGRN	Pharmacogenomics Research Network
TPP	Translational Pharmacogenomics Program.
PCP	Primary Care Physician
MOH	Ministry of Health
U-PGx	Ubiquitous Pharmacogenomics
UK	United Kingdom
PI	Package Insert
PCI	Percutaneous Coronary Intervention

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CHAPTER 1:INTRODUCTION

1.1 Principles of pharmacology (Overview)

Pharmacology is the study of drug action on the biological system and body response to the drug. It has two main branches: pharmacokinetics and pharmacodynamics[1]. Pharmacokinetics describes the pathway of drugs in the body including absorption, distribution, metabolism and excretion, these processes depends on several physiochemical properties[2]. While Pharmacodynamics is the second branch of pharmacology that describes how drugs bind to their targets to give the desired therapeutic effect.These targets could bedifferent types of molecules such asreceptors or enzymes [3]. For most drugs, the concentration at the site of the receptor determines the intensity of a drugs effect (Figure1.1).

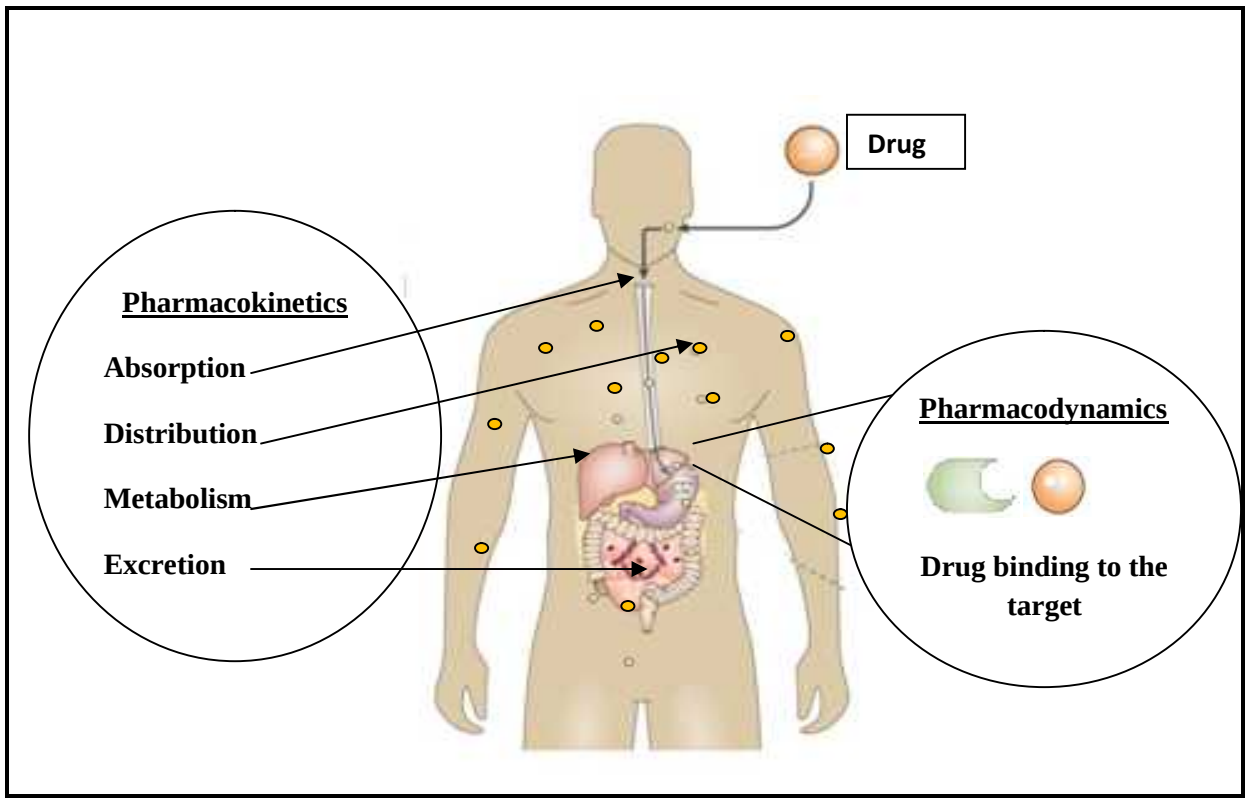

Figure 1.1: Drug journey in human body.This figure represents the pharmacokinetics processesabsorption, distribution, metabolism and excretion (ADME)from the time of drug administration to excretion from the body. And also it represents the binding of the drugs on its target which is called pharmacodynamics.

1.1.1 Relation between pharmacogenetics and pharmacokinetics

There are several clinically relevant polymorphisms in the genes responsible for pharmacokinetic mechanism, especially in the metabolism. The major metabolizing family of enzymes that have genetic variants is cytochromes P450 (CYP450)family which is responsible for metabolizing high percentage of drugs and xenobiotics, particularly the 1^{st},2^{nd} and 3^{rd} sub-families of CYP450. The most polymorphic enzymes of this family are CYP2C9, CYP2C19 and CYP2D6[4]. Some of these polymorphismscan lead to enhancement or reduction in the activity of the metabolized substance .

According to the type of variation in the metabolizing enzyme, individuals can beclassified into four different types phenotype: extensive metabolizers (EM) who is a person carrying two homozygous normal alleles; intermediate metabolizers(IM) who is a person with one functional allele and one deficient alleles; poor metabolizer (PM)who is a personwith two non-functional alleles, and an ultrarapid metabolizer (UM) who is a personthat carries alleleswith extra activity above the normal level [5]. In general, reduced activity of enzyme decreases the clearance of medication from the body, while increased activity of enzyme increases the clearance of the medication from the body. Such abnormal rates of metabolism can cause toxic accumulation of drugs or their metabolites or insufficiency of effective concentration of the active drug [6].

CYP2D6 gene is the most common polymorphic metabolizing enzyme with more than 100 allelic variants that differ between ethnic groups. CYP2D6 polymorphisms affect the efficacy and safety of tricyclic antidepressants (TCAs), such as nortriptyline and amitriptyline. The recommended starting dose of amitriptyline or nortriptyline does not need adjustment for those with genotypes of CYP2D6 normal metabolism. A 25% reduction of the recommended dose may be considered for CYP2D6 intermediate metabolizers. While CYP2D6 ultrarapid metabolizers have a higher probability of failing amitriptyline or nortriptyline pharmacotherapy due to sub-therapeutic plasma concentrations, and alternate agents are preferred. Also, alternate agents are preferred in CYP2D6 poor metabolizers due to elevated tricyclic plasma concentrations which lead to adverse effects. [7].

CYP2C9 is another important enzyme thatmetabolizes many medications, such aswarfarin, tolbutamide, phenytoin, losartan, diclofenac and celecoxib. It also possesses nearly 33 variants, associated with the efficacy and side effects of multiple drugs innonsteroidal anti-inflammatory drugs(NSAID) family and anti-diabetic drugs. Many studies pointed out to the

importance of CYP2C9 variants in warfarin therapy because of its narrow therapeutic window as anticoagulant drug[8].

Thiopurine methyl transferase (TPMT) is another metabolizing enzyme in the 2nd phase metabolism process, it has an important role in transformation of the 6-mercaptopurine into inactive by product. With patients who take the azathioprine drug, these metabolites can accumulate in the blood causing toxicity and bone marrow suppression as a result of polymorphism in TPMT gene[9] (Table 1.2).

Table 1.2: Examples of genetic polymorphisms in drug metabolizing enzymes and their effects[10].

Phase (1) enzymes	**Substrate (Drug)**	**Consequences of polymorphisms**
CYP2C9	Warfarin, phenytoin, tolbutamide.	Anticoagulant effect of warfarin.
CYP2C19	Omeprazole, phenytoin, propranolol, mephenytoin.	Peptic ulcer response to omeprazole.
CYP2D6	β blockers, antidepressants, antipsychotics, codeine, debrisoquin, dextromethorphan.	Tardive dyskinesia from antipsychotics, narcotic side effects, efficacy and dependence.
Phase (2) enzymes	**Substrate (Drug)**	**Consequences of polymorphism**
Dihydropyrimidine dehydrogenase (DPD)	Fluorouracil.	Neurotoxicity of fluorouracil.
N-acetyltransferase (NAT2)	Isoniazid, hydralazine, sulfonamides, amonafide, procainamide, dapsone, caffeine.	Hypersensitivity to sulfonamides, amonafide toxicity, hydralazine induced lupus, isoniazid neurotoxicity.
Glutathione transferases (GSTs)	Several anticancer agents.	Decreased response in breast cancer; more toxicity and worse response in AML
Thiopurine methyltransferase (TPMT)	Mercaptopurine, thioguanine, azathioprine.	Thiopurine toxicity and efficacy, risk of second cancers.
UDP-glucuronosyl-transferase (UGT1A1)	Irinotecan, bilirubin.	Irinotecan glucuronidation.

In another way in pharmacokinetic, the ATP-dependent membrane efflux drug transporters is considered as an important factor that helps in absorption regulation, distribution and excretion of medications. The most popular family is glycoprotein (gp), a lot of studies have

been made to identify more than 50 genetic variants in the ATP-binding cassette sub-family B member 1(ABCB1) gene,whether SNP or insertion and deletions [11].

Many drugs bind to these transporters in order to get the desired effect, one example is digoxin which is glycoside drugs with narrow therapeutic window. A C3435T SNP in exon 26 of ABCB1 gene have a significant role in the pharmacokinetic of digoxin.Homozygous wild-type subjects (CC) show high intestinal P-gp expression and low digoxin plasma concentrations.In contrast, homozygous subjects with (TT) show low intestinal P-gp expression and potentially toxic digoxin plasma concentrations [12].

1.1.2Relation between pharmacogenetics and pharmacodynamics

One of the most used types of drugs in hypertension treatment is β_1-adrenergic receptor blocker. Its efficacy varies according ethnicity. Some Africanpeople complain from the low activity of these medications,which is likely due to this genetic variant NP_000675.1:p.Gly389Arg in β_1-adrenergic receptor *(*ADRB1*)* and an amino acid substitution ($Gln^{41}Leu$) of G-protein receptor kinase5 *(*GRK5*)* gene[13].

Angiotension converting enzyme inhibitors(ACE inhibitors) are the most widely used medication in hypertension and cardiovascular diseasetreatment. Although millions of patients are using it for its high efficacy, a lot of them discounted it because its side effects, particularly the dry cough. The most common polymorphism in this gene insertion or deletion is 287-bp sequence of DNA in intron 16, that gives three genotype homozygous DD, homozygous II and heterozygous ID. Studies revealed that ACE activity levels in DD carriers are twice the level that was found in II genotype individuals while subjects with the ID genotype had intermediate levels, so it affects the level of ACE enzyme and drug efficacy [14].

In addition to the variations in drug metabolism and drug targets, pharmacogenetics also covers the area of adverse drug reactions which may involve an exaggerated drug responses that help in avoiding toxicity and side effectsby linking it with the genetic of individuals.That appears in schizophrenic patients who are taking antipsychotic drugs, and are predispose to Tardive dyskinesia (TD),some studies revealed the association between the polymorphism in the5-hydroxytryptamine receptors(5-HT2C) and TD[15].

1.2Genetic variants in pharmacogenetics

The human genome is composed of 3 billion nucleotides with approximately 0.5% of these nucleotides differing among individuals. Human genetic variationsare the differences in DNA sequence within the genome of individuals. The nucleotides that differ from one person to another affect the majority of human phenotypic differences, from eye color and height to disease susceptibility and response to drugs[16, 17].

Multiple types of genetic variations are evaluated in pharmacogenetics studies, includingnucleotide insertion, deletion, tandem repeat, copy number variation (CNV) and chromosomal translocation. Presently, the most common variation is single nucleotide polymorphisms (SNPs) which means substitution of single base in gene sequence, it can be synonymous and non-synonymous (nsSNPs) in coding region, and it also appears in non-coding region. If the genome of any two individuals are compared, nearly one SNP in every kilobase of DNA sequences will appear over the genome. The presence of polymorphisms in the genes encoding drug receptors, drug transporters and metabolizing enzymes have an important role in drug efficacy and toxicity [18, 19].

1.3Pharmacogenetics history and development

In 1950s, Hughes and his colleaguesnoticed that some of the patients who were treated with an antituberculosisdrug isoniazid showedunexpected neurological disorders. Later, it was found that this phenomenon is due to deficient activity of the N-acetyltransferase metabolizing enzyme which leads to poor metabolism of theantituberculosisisdrug causing its toxic accumulation of it in the blood. Such observations were the very preliminary building block in pharmacogenetics[20].The first scientist who pointed out to the relation between the mood of inheritance in genes and pharmacology science was Arno Motulsky in 1957. Two years after, Friedrich Vogel combined between both the sciences of genetic and pharmacology in one term “pharmacogenetics”.Later on, the research in this field expanded to become an important part in drug development and therapy[21]. At present,several national and international organizations and networks have been working with healthcare authorities and pharmaceutical industry to provide information and to establish a solid evidence-based guidelines to regulate this emerging critical field of the precision medicineera[22].

1.4Pharmacogenetics and Pharmacogenomics (Two sides of the same coin)

The terms pharmacogenetics(PGt) and pharmacogenomics (PGx)represent the junction between the pharmacology and the genetic variability in individuals in order to determine their response to any given drugs.Pharmacogenetics is the field of study dealing with the differences of responses to medications due to variability in single gene, while the pharmacogenomicsexplores multiple genes and variations rather than just one single gene.Both of them deal with pharmacokinetic (PK) and pharmacodynamics (PD) of drugs; in other words,how the drugsget metabolized and how do they exert their biological effects to achieve the maximum therapeutic efficacy and minimum undesired adverse effects[9]. Although there are many factors that participate in the individuals' responses to drugs such as age, gender, diet, environment, lifestyle and health status, the genetic makeup is considered the gold key in healthcare sector and will open the doors tothe field of drugsdevelopment and personalized therapy.

1.5Pharmacogeneticselectronicresources

Currently, several open access of electronic resources are constantlyproviding pharmacogenetics information and publishupdatedguidelinesto help clinicians to understand and practice PGx.For example, the Clinical Pharmacogenetics Implementation Consortium (CPIC),which is an organization that was established in 2009 asa joint project betweenPharmGKB and Pharmacogenomics Research Network (PGRN), publishesupdated guidelines thathelp doctors in understanding the available pharmacogenetic test results in order to use them in therapy management. Table 1.3 provides example of pharmacogenetics drug (ondansetron) which hasguidelines in CPIC for dosing management.

Table 1.3 : CPIC dosing recommendations for ondansetron based on CYP2D6 genotype.

Phenotype	Implication	Therapeutic recommendation
CYP2D6 Ultrarapid Metabolizer (UMs)	The metabolism of ondansetron in UMs is increased to less active compounds comparing to NMs. Hence, that decreases the response to ondansetron.	Change the drug to another one not metabolized by CYP2D6. Such as (granisetron).
CYP2D6 Normal Metabolizer (NMs)	Normal metabolizer.	Start therapy with normal recommended dose.
CYP2D6 Intermediate Metabolizer (IMs)	Very limited data available for CYP2D6 IMs.	Start therapy with normal recommended dose. Because there are deficient evidence regarding clinical impact based on CYP2D6 genotype.
CYP2D6 Poor Metabolizer (PMs)	Very limited data available for CYP2D6 PMs.	Start therapy with normal recommended dose. Because there are deficient evidence regarding clinical impact based on CYP2D6 genotype.

CPIC membership now spans 12 countries and includes over 100 members from 58 institutions and multiple observers from the National Institutes of Health (NIH) and the FDA [23].

On the other hand,a governmental organization such as Food and Drug Administration(FDA) provides pharmacogenetics information in drug labeling and approved biomarkers related pharmacogenetic testing.It appears in different sections (e.g.dosing information, clinical pharmacology, etc.)[24].For example,astable 1.4 shows some FDA approved pharmacogenetics biomarkers related to commonly prescribed drugs in multiple therapeutic areas.

Table 1.4: Pharmacogeneticsbiomarkers in FDA drug labels for most commonly prescribing drugs.

Drug	Therapeutic area	Biomarker	Labeling section
Carbamazepine	Neurology	HLA-B	Boxed Warning, Warnings and Precautions.
Carvedilol	Cardiology	CYP2D6	Drug Interactions, Clinical Pharmacology
Celecoxib	Rheumatology	CYP2C9	Dosage and Administration, Use in Specific Populations, Clinical Pharmacology
Clopidogrel	Cardiology	CYP2C19	Boxed Warning, Warnings and Precautions, Clinical Pharmacology.
Codeine	Anesthesiology	CYP2D6	Boxed Warning, Warnings and Precautions, Use in Specific Populations, Patient Counseling Information.
Duloxetine	Psychiatry	CYP2D6	Drug Interactions.
Esomeprazole	Gastroenterology	CYP2C19	Drug Interactions, Clinical Pharmacology
Fluorouracil	Oncology	DPYD	Warnings and Precautions, Patient Counseling Information
Fluoxetine	Psychiatry	CYP2D6	Precautions, Clinical Pharmacology
Glimepiride	Endocrinology	G6PD	Warnings and Precautions, Adverse Reactions.

Also, European Medicines Agency (EMA) provides important information about pharmacogenetics and how these information can be used for the improvement of drug therapy[25]. In Japan, the Pharmaceuticals and Medical Devices Agency (PMDA) provides pharmacogenetics labeling for many drugs available in the market, additionally, the PMDA introducedprograms including collaboration with drug companies in order to integrate pharmacogenetics in drug development[26].

Many databases have been created to manage pharmacogenetics data.These databases help researchers and healthcare professionals obtain genetic information quickly and conveniently. The Pharmacogenetics Knowledge Base (PharmGKB) is a public database that contains genotype and phenotype information related to pharmacogenetics[27].This data iscollected from different sources. Until now, on Sep 10,2020 PharmGKB website states 23,940 variant annotations. Figure 1.5shows examples of drugs with the level of pharmacogenetics biomarkers in drug label annotations part on PharmGKB.

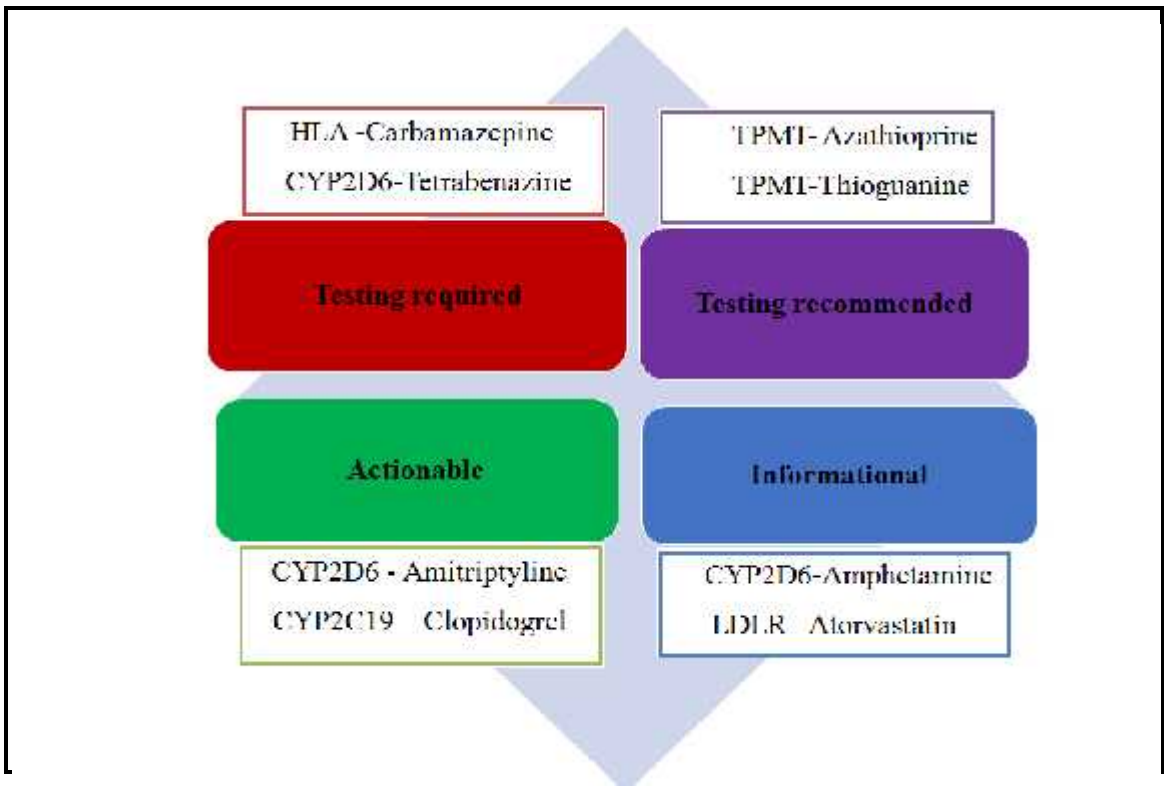

Figure 1.5. PharmGKB PGx biomarkers levels.

Testing required:The label states or implies that some sort of gene; protein or chromosomal testing, including genetic testing, functional protein assays, cytogenetic studies, etc., should be conducted before using this drug. This requirement may only be for a particular subset of patients (e.g.HLA -- carbamazepine and CYP2D6 – tetrabenazine**).**

Testing recommended:The label states or implies that some sort of gene, protein or chromosomal testing, including genetic testingis recommended before using this drug. That may only be for a particular subset of patients**(**e.g.TPMT marker for azathioprine**,** thioguanine).

Actionable PGx:The label may contain information about changes in efficacy, dosage, metabolism or toxicity due to gene/protein/chromosomal variants or phenotypes (e.g. "poor metabolizers"). Or the label may mention contraindication of the drug in a particular subset of patients with particular variants/genotypes/phenotypes**.** (e.g.CYP2D6-amitriptyline, CYP2C19 – clopidogrel).

Informative PGx: The label contains information stating that particular gene/protein/chromosomal variants or metabolizer phenotypes do not affect a drug's efficacy, dosage, metabolism or toxicity. Or, the label states that particular variants or phenotypes affect a drug's efficacy, dosage, metabolism or toxicity, yet this effect is not "clinically" significant. (e.g.CYP2D6– amphetamine, LDLR– atorvastatin).

Furthermore, other updated databases can provide valuable pharmacogeneticsinformation to scientists, physicians, regulatory agencies and industries such asCYP- allele database, NAT-allele database, PMT database[28].

1.6Use of pharmacogenetic testing in clinical practice

Pharmacogenetic testingis becomingan increasingly important practice in choosing the suitable drug for patient. PGttesting also helps physicianstо determine the effective dose and gives indication to potential adverse effects. For example is thePGt test to determine variations within CYP2C9 and VKORC1genes, which are important in warfarin dosing management. Additionally, determining certain variants in CYP2D6 gene is very important to avoid lethal adverse effects of codeine in children and nursing mothers[29].

Currently, several approaches are used in clinical settings to deliver PGttesting services, but it is not yet clear if one model will dominate the delivery of PGttesting. The most effective model will depend on several factors including necessity for immediate treatment, severity of event potentially prevented by testing, and availability of clinical expertise to ensureappropriate use of PGtinformation when treatment is required. The most available delivery models of PGt are point-of- care (POC), preemptive and direct to consumer pharmacogenetic testing. Table1.6 describes the advantages and disadvantages ofthe different method.

Table1.6: Comparisons of delivery approaches of PGt testing in clinical practice [30].

Delivery models of PGttesting	Advantages	Disadvantages
Point of care	Rapid turnaroundtime	It is still not established that

	pharmacogenetic testing. Point-of-care PGx testing can be ordered in almost any clinical setting and by any clinician.	this testing strategy results in better clinical outcomes. Potential delay in treatment.
Preemptive	Fewer genetic tests are required, which save money and resources. No delay in treatment.	The results of a preemptive test ordered by a primary care physician(PCP) in one practice setting may not be available to a specialist in another practice setting.
Direct to consumer	Increases public awareness of genetics' influence on medication response among other clinical phenotypes. Patients receive their results directly, may have access to experts for further review and counseling, therefore, they are empowered with their findings, which may lead to better health-related life-style choices.	The results may be misleading in many instances. Moreover, these reports tend to be very long (i.e., 20 – >100 pages) depending on the combination of genes and medications, and this can be very overwhelming to patients who may have ordered the tests on their own without their doctor's supervision.

1.6.1 Point- of- care pharmacogenetic testing (POC)

Many PGttests take between 3 to 7 days to be completed, which might be considered as an unacceptable length of time which causestreatmentdelay.Many cases need rapid interpretations of the pharmacogenetic testing, so POC pharmacogenetic tests reduce the turnaround time for obtaining the results because they areperformed at the site of treatment[31]. (RAPID GENE) trial was the first POC test aimed to identify the CYP2C19*2 variants in cardiac patients with Percutaneous Coronary Intervention (PCI) before beginning the clopidogrel therapy [32].

1.6.2 Preemptive pharmacogenetic testing

This approach depends on screening patients for all genetic variations then enter it in electronic health record (EHR). This approach allows the availability of the pharmacogenetics information to clinicians so they can refer to it before drug prescription. Also, it can determine most of pharmacogenetically high-risk drugs[33].

1.6.3 Direct to consumer

This type of pharmacogenetic testing could be sold directly to the consumer via internet or any other media tools/platforms without any interventions from health care professionals. The patients buy the test kit, send the sample to the company for testing, and then they receive the results via email [33, 34].

1.7Applications of Pharmacogenetics

Various studies have demonstrated applications of pharmacogenetics in the treatment of various forms of cancers, hypertension, respiratory system diseases like asthmaand central nervous system disorders.

1.7.1 Cancer

Pharmacogenetics contributes strongly in individualizing anticancer drugs, which typically have narrow therapeutic index and unpredictable efficacy[35].Usingpharmacogenetic testing in cancerhas been demonstrated to reduce incidences of toxicity related tochemotherapeutic drugs aswell as to reduce thecost of cancer treatment[36]. The prediction of cancer treatment outcome that is based on determining clinically relevant genetic variants is becoming a reality for several classes of anticancer drugs[37].The most clinically significant examples are thiopurines drugs (azathioprine AZA, 6-mercaptopurine 6MP and 6-thioguanine 6TG)which are widely used in gastroenterology, dermatology, rheumatology and in acute lymphoblastic leukaemia (ALL). These drugs are metabolized by thiopurine S-methyltransferase (TPMT) enzyme. Its activity depends on the genetic polymorphisms of TPMTgene[38].

An adverse effect of thiopurines drugs therapy is bone marrow suppression.Patients who carry two nonfunctional TPMT alleles can experience a life-threatening myelosuppression when treated with mercaptopurine.Patients who carry one nonfunctional TPMT allele may also be unable to tolerate conventional doses of mercaptopurine[39].Also, the presence of C677T polymorphism in methylenetetrahydrofolate reductase gene increases the response rate of 5-fluorouracil (5-FU) drug [40, 41].

Irinotecan is anticancer drug used for the treatment of metastatic colorectal cancer (CRC).It is a pro-drug that is metabolically activated in the body to 7-ethyl-10-hydroxycamptothecin

(SN-38). Diarrhea and neutropenia are major limiting factors for irinotecan, with up to 36% of patients experiencing severe, potentially life-threatening toxicities[42].

Mostof genetic variants associated to irinotecan toxicity are found in the UDP-glucuronosyltransferase gene(UGT1A1).Previous studies revealed a link between UGT1A1*6 and *28and irinotecan toxicity specifically diarrhea and neutropenia.Patients homozygous for UGT1A1*28 havea significantly greater risk of grade IV neutropenia compared topatients with at least one wild-type allele [43],[44].

1.7.2 Hypertension

Hypertension (HTN) is one of the most serious diseases worldwide and it is also considered as a complex disorder arises from combining multiple genetic and environmental factors. It leads to myocardial infarction, heart failure, stroke, and atherosclerosis[45].Several pharmacogenetics studies revealed that individuals with distinct genotypes have different response to treatments[46]. Despite the several types of drugs to treat HTN (diuretics, β-blockers, ACE inhibitors, calcium channel blockers, angiotensin II blockers, α-blockers), the rates of control blood pressure (BP) are less than 50%.Also, the interindividual variability of BP response to different antihypertensive drugs is high[47].

For example, the α-adducin which is a cytoskeleton-associated protein that modulates ion transport, encoded by the ADD1 gene, is associated with antihypertensive responses of thiazide diuretics.It was found that the presence of(rs4961) polymorphism in the ADD1 gene leads to a better response to hydrochlorothiazide treatment. Another important gene in hydrochlorothiazide response is GNB3, the patient who carriers T allele for C825T (rs5443) polymorphism in this gene hasalso betterresponse for hydrochlorothiazide[48]. Another frequently prescribed treatment category for hypertension management are β-blockers drugs.This is achieved throughtheir ability to block β1-adrenergic receptor that is encoded by ADRB1 gene.Studies showed (Ser49Gly and Arg389Gly) are two common single nucleotide polymorphisms (SNPs) in the β_1-adrenergic receptor gene *(*ADRB1*)*thathave a significant role in controlling β-blockers activity[49].

Angiotensin-converting enzyme inhibitors (ACEI) target the renin-angiotensin system, as the insertion of (I) or the deletion (D) variation in ACE gene have been associated to hypertension.However, hypertensive patients who have D/D genotype conferred a greater

blood pressure lowering response to ACEIs (lisinopril and enalapril).Since this genotype has been associated with increased ACE serum levels and higher ACE activity thus leading to more potential for inhibition [50].

1.7.3 Antipsychotic drugs

Antipsychotic drugs (APDs) are the golden therapy for schizophrenia and other psychotic disorders and mentaldisorders. However, many patients suffer from APDs side effects with large variability in patients' response to these medications[51, 52].

The selective serotonin reuptake inhibitors (SSRIs) are one of the most prescribed drugs in psychiatric disorders, it is safe for patients but the problem lies in the adverse reaction of these drugs which is intolerable for some patients. The serotonin transporter (SERT) is the primarytarget for SSRIs, most studies focused on polymorphic promoter region SLC6A4 gene and relation with adverse effects of SSRI drugs[53].

Additionally, previous studies showed reduction in psychotic symptoms in patients having141C Ins allele in Dopamine 2 receptor gene. Similarly, Gly 9 allele (Ser 9 Gly) of the dopamine D3 receptor was found to be associated with better response to typical antipsychotic drugs[54].

The response and adverse effects of antiepileptic drugs (AEDs) vary widely among epilepsy patients. Some AEDs are associated with increased risk of cutaneous hypersensitivity reactions (SCR) such as drug induced hypersensitivity syndrome (DIHS), stevens-johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), including CBZ, PB, PHT, and LTG[55]. A number of recent studies suggest a strong association between HLA-B*1502 and CBZ-induced SJS[56].

CYP2C9 polymorphisms are important determinants of the rate of phenytoin metabolism.Astudy of cases with phenytoin-related severe cutaneous adverse reactions and 412 population controls from Taiwan discovered a cluster of 16 single nucleotide polymorphisms in CYP2C genes at 10q23.33. Direct sequencing of CYP2C9 identified missense variant rs1057910 *(*CYP2C9*3*)* as showing significant association with phenytoin-related severe cutaneous adverse reactions[57].

1.7.4 Respiratory system drugs

Asthma is a chronic inflammatory disease with heterogeneity in clinical expression and severity, therefore some scientists considered asthmaas a syndrome rather thana disease.The three main classes of drugs currently prescribed to patients with asthma are β2-agonists, both short-acting β2-agonist and long-acting β2-agonist (LABA). Pharmacogenetics studies of these drugs focused onSNP in gene encoding the β2AR (ADRB2), particularly is glycine for arginine at codon 16 (rs1042713). The homozygous Arg16 variant has been associated with a decline in lung function and increase in exacerbations after regular SABA therapy in adolescent and adult asthmatic patients[58].

CHAPTER 2: LITERATURE REVIEW

Over the last decade,the translation of pharmacogenetics research into clinical practice has been developed rapidly especially after the completion of human genome project and international Hap Map project [59]. Until January 2019, more than 20,000 published papers

associated with pharmacogenetics or pharmacogenomics were found in PubMed, and some of these items were translated into clinical practice.Severalkey factors are important for an effective and successful implementation of pharmacogenetics.Among these factors arethe presence of cooperatives initiatives and organizations that aim to provide the required information related to the PGt testing.Also, the validated testing technologies in order to investigate pharmacogenetics biomarkers. Furthermore, the knowledge and awareness toward pharmacogenetics among physicians and health care workers andthe adoption of legislations that forces pharmacogenetic testing application in health care centersare very critical factors to translate PGt knowledge into daily clinical practice.

2.1Pharmacogeneticsinitiatives and organizations

Currently, various ongoing initiatives have beenlaunched around the world which aim to implement pharmacogenetic testsin the daily clinical practice. In the USA, more than 20 institutions are joint together in a program for pharmacogenetics application, some of themhave begun the work in this field since more than 10 years ago.Several consortia were initiated coinciding with the foundation of theElectronic Medical Records and Genomics (eMERGE) Network in 2007. After that, eMERGE and Pharmacogenomics Research Network (PGRN)started a collaborative study about PGtin order to test genetic variations in pharmacogenes through sequencing[60].In 2011, the PGRN launched a Translational Pharmacogenomics Program (TPP) that aimedat estimating the application of pharmacogenetic testing, dosing and drug selection through various health care systems [61].Another goals ofthis project wasto identify the barriers and suggest solutions through disseminating bestpractice guidelines [62].

The Ubiquitous Pharmacogenomics (U-PGx) consortium is a collaborative project established in 2016 which gathers experts from 10 European countries. Its primary goal is to provide the best treatment across the whole continent of Europe, by conducting a prospective, block-randomized controlled clinical trial across multiple genes, multiple drugs, multiple ethnicities and multiple healthcare systems called Preemptive Pharmacogenomic testing for Preventing Adverse Drug Reactions (PREPARE) [22].This program performs pre-emptive genotyping of a panel of clinically relevant PGt-markers, for which guidelines are available, and will be implemented across healthcare institutions in seven European countries[63]. European Society of Pharmacogenomics and Personalized Therapy(ESPT) is a huge

networkencompass more than 1200 members divided into scientific groups, and national societiesstructured into specialized divisions: scientific and clinical implementation, education and courses, communication and external relations, congress and meetings divisions.ESPT plays a vital role in constructing links between developed and developing countries and give advice on this new field. Furthermore, it facilitates personalized treatment for patients to preserve the health of all citizens[22].

Large effort has been conducted in Asia in pharmacogenetics research and the creation of pharmacogenetics implementation strategies. The Southeast Asian Pharmacogenomics Research Network (SEAPharm) is one of the working groups established in 2012 aiming to strengthen the PGtresearch in multiple PGtcommunities. From the perspective of SEAPharm member countries, there are several key elements essential for PGtimplementation at the national level,including pharmacovigilance database, PGtresearch, health economics research, dedicated laboratories to support PGttesting for both research and clinical use, structured PGteducation and supportive national health policy[64].

On the other hand, some pharmacogenetic tests whichwere approved by FDA arenow standard health of care practice in Singapore, Thailand Hong Kong and several centers in China. The test is covered by health insurance in Thailand and Taiwan and supported for certain patients in Singapore.Additionally, Thailand offers pharmacogenetic testing for CYP2B6 enzyme and other HLA alleles for allopurinol and antiretroviral drugs. In fact, the success in pharmacogenetics application requires support from all stakeholders.For example, in Thailand, the establishment of Thailand Center of Excellence for Life Sciences, was a collaboration between the Ministry of Public Health and the Riken Institute eventually resulted in the setup of the pharmacogenomics laboratory and clinic in Ramathibodi Hospital, which offers pharmacogenomic testing and counseling [65].

2.2 Pharmacogenetics technology

At present, a variety of pharmacogenetics technologieswhich allows the identification of the genetic variations related to drug efficacy and toxicity, are available and the enthusiasm for using them is growing. Commonly used methods include gel electrophoresis-based techniques, such as polymerase chain reaction (PCR)[66]. Single SNP genotyping assays

have the longest history and many methods have been used based on PCR,for example: Invader assay which is the most common applied technique, Dynamic Allele Specific Hybridization (DASH), Pyrosequencing and TaqMan[67]. Multiplex PCR is an extension of the standard PCR protocol in which multiple loci are amplified simultaneously to save time, improves throughput and reduce the total cost of reagents[68]. Since the advent of PCR several types of multiplex approaches have been developed, suchasallele-specific oligonucleotide (ASO) dot blots or linear arrays bead-based 'Tag arrays"[69]. High throughput testing of genetic variantshas several meanings including testing hundreds of different patients' samples simultaneously, analyzing multiple genetic loci simultaneously for a single patient and obtaining results quickly. Microarray technologiesis a best-known methods high-throughput genotyping to determine the status of thousands of SNPsthat might be associated with pharmacogenomic or disease risk factors. This approach uses differential hybridization of nucleic acid oligonucleotides to determine the presence of sequence variants. Genome wide SNP array (Affymetrix Inc, Santa Clara) can probe for 906,600 individual SNPs (of over 10 million human SNPs identified). Bead array technology (Illumina Inc, San Diego, CA) can probe 1 million SNPs using a different chemistry. Both methods allow for hundreds of thousands of SNPs to be analyzed under a single set of experimental conditions with a completion time of approximately 1 day[70].

2.3Pharmacogeneticsand pharmaceutical industry

Supporting precision medicineinitiative is a major goal ofU.S. Food and Drug Administration. The first drug that was labeled with pharmacogenetics information and updated twice is warfarin, it was also called the "poster child" of pharmacogenomics. The label included information related to the impact of CYP2C9 and VKORC1 genetic variation on warfarin dosing requirements and risks. Recently, the FDA initiated proactive approach in order to estimate pharmacogenomics influence on drug efficacy and safety[71]. Indeed, over the past several years numerous genomic variants are increasingly recognized[72](Figure 2.1).

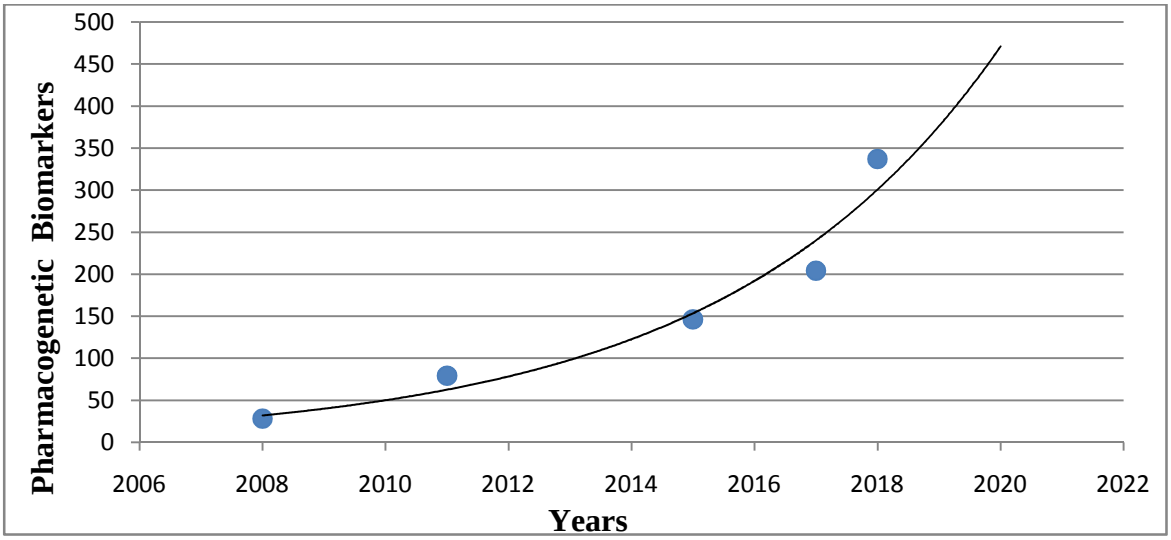

Figure 2.1. Pharmacogenetics biomarkers in FDA drug labels over the last decade. The graph show increasing in the pharmacogenetics variants through the interval 2006-2020.

In general, the labeling documents provide essential information for safety and effective use of drug. That increases the implementation in clinical practice,so, the FDA published several drug's labeling guidance for industry. In 2013, the FDA published the following guidance: "Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling" , which provides detailed information on how to consolidate clinically relevant genetic information into the most appropriate labeling section.Currently, FDA provides table of PGtbiomarkers in drug labeling, this table includes information on drugs biomarkers therapeutic areas and labeling sections that contained biomarker occurrences[73].

Drug discovery and development is considered a time consuming process because of the complexity of clinical trials and strict regulations. It includes five critical stages, stage 1: discovery and development, stage 2: pre clinical studies, stage 3: clinical research, stage 4: FDA review, and stage 5: FDA post-market safety monitoring.Additionally, the trial cost and drugs marketing is very high, and in sometimes the clinical trials are ended because the failure of the compound, so that cause financial losses for pharmaceutical companies [74].

The cause of compound failure in drug development process related to its efficacy and toxicity, which is poorly predictable in clinical trials. Now, the pharmacogenetics studies can help in increasing the predictability of safety and toxicity of drugs through its development stages. Incorporation pharmacogenetics in drug development stages trials to improve target

identification, accelerate the development process and reduce the attrition rate. So that allow the choice of the right drug for the right patient in the right disease at the right dose[75].

Recently, large number of pharmaceutical and biotech companies supporting the idea of individualized therapy. AstraZeneca drug companies was the first one promote the change in drug development process out of the model designed to deliver one-size-fits-all drug. Other companies such as Amgen, Astellas, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline (GSK), Johnson & Johnson, Merck, Novartis, Pfizer, Roche/Genentech, Sanofi-Aventis and others also supporting the pharmacogenetics principle. Although the pharmaceutical and biotech companies are now paying increased attention to personalized medicine, several challenges hinder the success in drug development. Some of these challenges reside in the way of thinking, most larger pharmaceutical companies may facing difficulty to go from big sales of drugs to smaller sales potential. Also, this future transformation will require fundamental change in the company organization and the structure of cooperation with external partners such as molecular diagnostic companies [76]. In summary, PGtenables earlier launch of a drug with less cost, representing benefit to pharmaceutical companies, patients and public as a whole.

2.4Pharmacogeneticsand health care workers

Several studies have been interested in evaluating the attitude and awareness of health care professionals toward PGt as they are the cornerstone in the successful application of PGt. Astudy conducted on Japanese pharmacists in 2015 shows a good awareness to the term pharmacogenetics and pharmacogenomics especiallyamong young pharmacists who have less than 10 years' experience[77]. Similar resultswere found among pharmacists in the states of Ohio and Pennsylvania(USA). The survey was distributed between December 2011 and February 2012, itrevealed high positive attitude toward the PGt and most of the addressed pharmacists were aware of the importance of pharmacogenetics in minimizing adverse drugs effects and determining the suitable dose of drugs [78]. Similarly, in 2015AlEjelat*et.al* found that 60% of Jordanian pharmacistswho are practicing in three Jordanian cities: Amman, Zarqa and Irbidagree that pharmacogenetic testing can maximize drug therapeutic effect.However, the study also showed that same pharmacists have poorawareness concerningPGtregardless of their educational level. Also, half of them agreed on their responsibility in providing pharmacogenetics information for patients, but they need more

education about PGt [79]. Conversely, in other study conducted on Ethiopians health care professionals in 2016, more than two-thirds of Ethiopians67.33% nurses, 42.86% pharmacists, and 40.27% physicians who were working at the University of Gondar Referral and Teaching Hospital in northwest Ethiopia did not know that genetic variations can account for as much as 95% of the variability in drug disposition and effects[80].

In a study conductedduring the period from January to April 2016, it included all pharmacists and physiciansworking in the six general public hospitals in Kuwait, low percentage of them learned about pharmacogenetics or even got training in order to apply pharmacogenetic testing in clinical practice. Both groups were not ready to order pharmacogenetic testing for patients because they did not know the type of drugs require pharmacogenetic tests and they can not apply the pharmacogenetic tests results in drug selection, dosing or monitoring[81]. Also, other studies in the USA,Germanyand Qatarrevealed the lack of knowledge among health care professionals in pharmacogenetics which weakenstheir self confidence in applying these tests in their job, as they can not determine when to order pharmacogenetic tests, and how to interpret the results[82-85].In a study conducted on Ethiopians physicians 61% of them, however, did not believe that they are competent enough to discuss the patients pharmacogenetics information with other health professionals[80].Anotherstudy carried in USA during September 2008on more than 10.000 physiciansshowed that physicians did not feel adequately informed when to order PGt tests[86].This knowledge gap can be addressed by providing pharmacogenetic courses in medical schools and universities.Additionally, the insertion of good training programs in medical schools and residency programs, andproviding advanced tests laboratories will help in improvingclinicians' education and thus accelerate implementation of PGtin clinical settings.De Denusand colleaguesobservedin their studiesconducted in province of Quebec(Canada) that pharmacists areinterested in combining the pharmacogenetic testing in their clinical practice if they get the adequate training[87]. Other interesting study conducted in Ohio State University Wexner Medical Center in March 2015, a group of physicians completed a survey with eight questions ontheir attitudes toward pharmacogenetic testing before and after a 1-h presentation on pharmacogenetics, that presentation was about clopidogrel, simvastatin and warfarin drugs.It has been found that the scores for all eight questions increased. Hence, the physicians' awareness toward PGt was increased[88].

In a study that was carried out in regional department of general medicine in Saguenay–Lac-Saint-Jean (SLSJ)Quebec - Canada in 2019,on some pharmacists and physicians, none of

themorder pharmacogenetic tests in their clinical practice because they havelimited knowledge about the interpretation of PGt results[89]. However, that was on the contrary to the opinions of physicians in a survey was conducted from 19 November 2010 to 15 April 2011 in North Carolina-USA asthey order at least one PGttest annually[83]. On the other hand, Staneke*t.al* found that only 12.9% of the physiciansordered pharmacogenetic testing in the past 6 months, but 26.4% said they planned to order this type of tests in the next months.That reflects the acceptance to engage this pharmacogenetic testing in clinical practice.It is worth mentioning, that survey was faxed to physicians offices across USA during September 2008.[86]. Another studywas conducted between April and August 2011revealed that 31.4% of pharmacistspracticing in the province of Quebecin Canada think thatpharmacogenetic tests should be recommended[87].In a study conducted on a group of physicians in the San Mateo, California - USA in 2011,although, the number of physicians who order pharmacogenetic tests was twice the number of them who ordered it in the last year, some of them mentioned genetic tests not related to pharmacogenetics[90].Thisindicatesthat some health care professionals have misconception between genetic tests and PGttests.

Despite this rapid progress in the field of pharmacogeneticsworldwide, the attention to it in Palestine is still very little. However, few studies attempted to study the role of genetic variants on drug toxicity and response among the Palestinian population. Nassar and colleagues in 2014 described pharmacogenetics variations associated with clopidogrel responseamong Palestinian subjects geographically originating from the West Bank and Jerusalem[91]. Furthermore, a recent study estimated the dose of warfarin depending on specific genetic variations in CYP2C9 and VKORC1 genes among Palestinians patients from five Governorates of Gaza strip[92].Moreover, in 2016 Asees *et.al* studied a particular genetic variation associated with increased platelet reactivity and risk of cardiovascular diseases among cardiovascular patients in Palestine[93]. Despite these individual research initiatives, there is a significant gap between internationally adopted guidelines on good pharmacogenetics practice and its translation to clinics and healthcare services in Palestine.

This obvious gap might possibly be due to the lack of awareness toward the importance of PGtin clinical practice and the absence of training courses and official guidelines from the responsible stakeholders in the Palestinian healthcare system. Thus, this study aimed to investigate the physicians' attitudes, knowledge and experience toward pharmacogenetics, and to inspect the main challenges facing its implementation in the Palestinian healthcare

system.Also, it examines the role of pharmaceutical companies and the Ministry of Health toward pharmacogenetics application in clinical practice. Increasing their awareness to this point will open the door to implement the pharmacogenetic tests in clinic and hospitals.We look forward not only to explore the problem but also to contribute and to help the Ministry of Health to establish a guidelines and legislation that will control the application of pharmacogenetics here in Palestine.

CHAPTER 3 : AIM AND OBJECTIVES

Statement of need and aims: Despite the rapid progress in the field of pharmacogenetics and the presence of several global regulatory organizations that have been issuing clinical guidelines to support the best pharmacogenetics practice, many physicians around the world are still using "one size fits all" approach in drug selection and dosing. And still, the impact of pharmacogenetics on daily medical practice is very weak due to several barriers, including lack of validated guidelines by many healthcare authorities, shortage in qualified professionals and the variability of available tests and their high cost. The poor health care regulatory systems status adds an extra challenge to adapt these guidelines in developing countries. All these factors prompt usto evaluate current status of pharmacogenetics in Palestine focusing on three major components that are crucial to build a good base of pharmacogenetics best practice. The first component is the practicing physicians as they are the cornerstone of the health care system. The second is the Ministry of Health as it is the main regulatory body to ensure high quality of healthcare services. And the third one is the local pharmaceutical companies as they bear responsibility to provide adequate information about drug-gene interaction.

General aim of study: To evaluate the situation ofpharmacogenetics in Palestineand the challenges facing the application of this emerging medical field.

The specific objectives of study are as follows :

1. To evaluate attitude of Palestinian physicians toward the PGt and their educational background.

2. To evaluate current situation and potential challenges of using pharmacogeneticsin therapy managementfrom the addressed physicians' point of view.

3. To explore the role of Ministry of Health in pharmacogenetics application by focusing on guidelines, legislations, awareness and training programs.

6. To explore the role of pharmaceutical companies in this field, by checking the availability of pharmacogenetics information in some drugs leaflets in the market.

CHAPTER 4 : MATERIALS AND METHODS

4.1 Physicians questionnaire

4.1.1Study design

We conducted an self administered questionnaire between the 1st of September 2019 and the 24th of October 2019.This type of surveys gives us the flexibility in explaining the questions to the participants, especially the hard questions. Furthermore, this way allows the interviewer to be sure that the questions will be answered accurately and carefully[94]. In the meanwhile, internet-based survey was sent via email to participants, which allows us to reach high percentage of population that was difficult to be contacted using other survey techniques. This questionnaire is voluntary, the participants were specialist, resident and general doctors working in hospitals and clinics in different areas in Palestine, including Al-Ahli hospital, Hebron hospital, Yatta hospital, Al-Mezan hospital, Al-Mohtasseb hospital, Al-Helal hospital, Ramallah hospital, Jericho hospital, Beit Jala, some physicians working in hospitals in the city ofJerusalem were also included. Additionally, the study covered several health care centers of the Ministry of Health in Nablus and Hebron, and private clinics as well.

4.1.2 Sample size calculation

According to the last annual report from Ministry of Health, the number of physicians working in different hospitals and clinics in West Bank is (7736) physicians[95].Depending on this population size the sample size was estimated using Cochran's sample size formula[96].To achieve a confidence interval level of 95% and a margin of error of 5%, a sample size of (367) participants wasneeded.

4.1.3 Survey development

The beginning of the questionnaire was an introductory cover letter stating the objectives of study, followed by an explanatory page that contained a brief definition about pharmacogenetics with three examples about drugs need pharmacogenetic tests in order to give the participants brief general idea about the topic of questionnaire. Then the questionnaire started with demographic questions in order to gather information about participants.

The survey contained 18 questions, include groupof fixed- answer questions and open-ended questions.The questions weredivided into four major sections, each of them is covering specific aspect. Most of the questions were constructed and refined through the analysis of the current situation of pharmacogenetics in clinical practice, while others were developed from similar studies that were undertaken in Qatar[85], Europe[97],United States [86], Netherlands[98]and Jordan[79, 99].

The first part of the survey contained four questions to measure participants' attitude to the importance of pharmacogenetics. Responses were on a 5-point Likert scale ranging between strongly agree and strongly disagree.

In the second part, the questions were asked to assess participants' knowledge about pharmacogenetics and their continuous learning sources about this field.

The third part included six questions to discuss the challenges facing the application of pharmacogenetics in Palestine.

The last part of the survey evaluated the participants' experience inpharmacogenetic testing, and their responsibility to describe drugs according to genetic testing results.

4.1.4 Survey pre -testing

A draft of the questionnaire was used as pilot test in a group of doctors of 10 participants, in order to get feedback about the clarity of the text, order of questions, length of questionnaire and the time needed to complete it. However, the number of questions was reduced, and we changed the phrasing of some questions to ensure the clarity. (Final questionnaire is provided in the supplementary material).

4.1.5 Survey analysis

Demographic data is expressed as frequencies and percentages. We constructed score from the 5-pointsLikert scale to estimate the attitude, there was no missing data in our survey. GraphPad Prism 8 software was used in constructing the figures.

4.2 Screening for pharmacogenetics publications by MOH

In this study wesearchedpharmacogenetics guidelines, legislations, awareness programs and educational materials on MOH website,from 2009 until March 2020.

4.3 Exploring pharmacogenetics information in drug leaflets

In order to determine the role of pharmaceutical companies in pharmacogenetics and how much PGtinformation is provided for their locally sold drugs, a group of ٤٩drugsavailable in Palestinian market from various local companies and distributors were selected. The selection of drugs were based on the FDA guidance regarding pharmacogenetics in the table of 'Pharmacogenomic Biomarkers in drug labels'.That table contains a list of drugs with pharmacogenomic information found in the drug labeling appeared in different sections[24]. The drugs leafletsincluded in this study were chosen after the search were done on thefollowing genetic termincluding "genetic", "genomic", "inherited", "hereditary", "gene", "genotype", "carrier". The selected drugs belongs to different therapeutic categories: Cardiology, Oncology,Gastroenterology, Hematology, Psychiatry, Rheumatology, Neurology and Endocrinology(Table 4.1).

Table 4.1 : List of drugs included in the study.

Drugs	Therapeutic area	Manufacturers
Amitriptyline	Psychiatry	Teva, Jepharm, Genesis
Azathioprine	Rheumatology	Aspen
Bupropion	Psychiatry	Valeant
Carbamazepine	Neurology	Desitin, Taro, Novartis
Carvedilol	Cardiology	Dexcel, Beit Jala, Teva
Ceftriaxone	Infectious Diseases	Panpharma, Birzeit, Jepharm
Celecoxib	Rheumatology	Trima, Pfizer, Jepharm, Beit Jala.
Chloroquine	Infectious Diseases	Sanofi
Escitalopram	Psychiatry	H. Lundbeck A/S/Denmark, Pharmacare.
Clomipramine	Psychiatry	Novartis
Clopidogrel	Cardiology	Sanofi, Sama, Jepharm, Birzeit, Beit Jala, Pharmacare.
Clozapine	Psychiatry	Taro
Codeine	Anesthesiology	Taro, CTS, Pharmacare, Jepharm
Dexlansoprazole	Gastroenterology	Delpharm Novara
Diazepam	Neurology	Birzeit, Teva, Jepharm, Beit Jala
Duloxetine	Psychiatry	Eli lilly
Esomeprazole	Gastroenterology	AstraZeneca, Pharmacare
Fluoxetine	Psychiatry	Eli Lilly, Teva, Pharmacare, Birzeit
Formoterol	Pulmonary	Novartis
Glimepiride	Endocrinology	Sanofi, Birzeit, Beit Jala
Glipizide	Endocrinology	Perrigo
Isosorbide Mononitrate	Cardiology	Dexcel, Jepharm

Lansoprazole	Gastroenterology	Rafa
Letrozole	Oncology	Teva
Mafenide	Infectious Diseases	Beit Jala
Meloxicam	Anesthesiology	Pharmacare, Beit Jala
Metoclopramide	Gastroenterology	Rafa, Beit Jala, Birzeit
Nitrofurantoin	Infectious Diseases	Beit Jala, Birzeit
Omeprazole	Gastroenterology	Rafa, Sama, Beit Jala, Birzeit, Jepharm, Pharmacare
Pantoprazole	Gastroenterology	Jepharm
Paroxetine	Psychiatry	GlaxoSmithKline
Ondansetron	Gastroenterology	Invamed, Novartis
Phenytoin	Neurology	Pfizer
Piroxicam	Rheumatology	Chiesi, Jepharm, Sama
Propranolol	Cardiology	Dexcel, Birzeit
Risperidone	Psychiatry	Janssen-Cilag, Jepharm, Pharmacare
Rivaroxaban	Cardiology	Bayer
Rosuvastatin	Endocrinology	AstraZeneca, Pharmacare, Jepharm.
Sulfadiazine	Infectious Diseases	Teva, Jepharm
Sulfasalazine	Gastroenterology	Pfizer
Tamoxifen	Oncology	Teva
Tamsulosin	Urology	Astellas Pharma, Invamed, GlaxoSmithKline
Thioridazine	Psychiatry	Taro
Ticagrelor	Cardiology	AstraZeneca
Tolterodine	Urology	Beit Jala
Tramadol	Anesthesiology	Birzeit, Pharmacare
Valproic Acid	Neurology	Sanofi
Venlafaxine	Psychiatry	Dexcel
Warfarin	Hematology	Taro

The medical information available in ١٠٠drugs leaflets were thoroughly studied for any pharmacogenetics related information. Then the available information was compared to the FDA pharmacogenetics recommendations on drug labeling.

CHAPTER 5 : RESULTS AND DISCUSSION

5.1Participants' characteristics

A total of 400 copies of the questionnaire were distributed throughout the period of this study, 320 were distributed in hard copies and 80 were sent as soft copies to participants' emails addresses. The final numberof collected questionnaires with positive answerwas230 and they werefrom hospitals and private clinics. The participants' demographic information is shown in table 5.1.

Table 5.1: Participants' demographic information and characteristics.

Attribute	Category	Percentage (numbers)
Gender	Female	18.3% (42)
	Male	81.7% (188)
Age	25- 34	34.3% (79)
	35-44	42.2% (97)
	45-54	17.4% (40)
	55-64	4.8% (11)
	>=65	1.3% (3)
Job Position	Specialist	54.3% (125)
	Resident	18.3% (42)
	General	27.3% (63)
Experience	1-5	30% (69)
	6-10	22.6% (52)
	10-20	38.3% (88)
	>20	9.1% (21)

The table show the highest response rate was from physicians between the ages of (35-45), those physicians in the age of work and activity. So they responded to the questionnaire easily. While physicians who are more than 45 years old responded to the survey in low percentage, most of them did not interested in this new science or they see this topic did not related to their specialties. Additionally, the physicians with (10-20) experience years responded effectively to the survey, through their long experience in hospitals and clinics they believe in the role of new fields such as PGt in solving the problems associated with drug efficacy and toxicity.

The overall response rate was 57.5 %. The relatively low response rate can be mainly ascribed tothe lack of interest in the topic. It is worth mentioning that the response rate for the

online questionnaires was 0%,that is might be because some participants don't comfortable with electronic communication .Although we conducted (400) questionnaires which are more than the exact sample size (367), the response rate was low. The low response rate is one of limitations that we faced in this study and that may not fully represent the views of physicians toward PGt . It is estimated that the response rate in online surveyson average is approximately 11%, which is a lower rate than in other survey modes[100].In general, some factors can increase the response rate of mail survey such as invitation designs, pre-notification and reminders and incentive approaches.

5.2 Attitude towardpharmacogeneticspractice

Of the investigated Palestinian physicians, 71.3% agreed on the importance of testing the genetic variations for the patients in order to choose the suitable drug with less side effects. These percentages were nearly similar to the number of participants agreed that genetic variation in patients play a vital role in determining the dose of drug 71.7%.But it is really interesting to know that 10.8% of physicians are still not confident about the role of PGt in minimizing the adverse effects of drugs, while 9.6% of them not sure about the importance of PGt in drug efficacy. This disagreeing might be refer to that some of physicians in their opinions see PGt not important in their job. Also, some questionnaires were answered in arbitrary way.(Table 5.2).

Table 5.2: Physicians' attitude toward the importance of PGt practice.

Questions	Strongly agree	Somewhat agree	Neutral	Somewhat disagree	Strongly disagree
Do you think it is important to test your patient for certain genetic variations in order to avoid adverse drug reaction?	**70 (30.4%)**	**94 (40.9%)**	**41 (17.8%)**	**21 (9.1%)**	**4 (1.7%)**
Do you think it is important to test your patient for certain genetic variations todetermine the most effective therapeutic dose of drugs?	**72 (31.3%)**	**93 (40.4%)**	**43 (18.7%)**	**17 (7.4%)**	**5 (2.2%)**
Do you think the Ministry of Health should force obligated guidelines specific for drugs that show its effects depending on the genetic variations?	**94 (40.9%)**	**77 (33.5%)**	**39 (17%)**	**11 (4.8%)**	**9 (3.9%)**
Do you think the drug companies should add clear labeling pharmacogenetic information in drug leaflet?	**131 (57%)**	**56 (24.3%)**	**27 (11.7%)**	**10 (4.3%)**	**6 (2.6%)**

Although most of the participated physiciansexpressed their conviction of the importance of the topic, 96.5% of them did not orderanypharmacogenetic tests for their patients (Figure5.3).

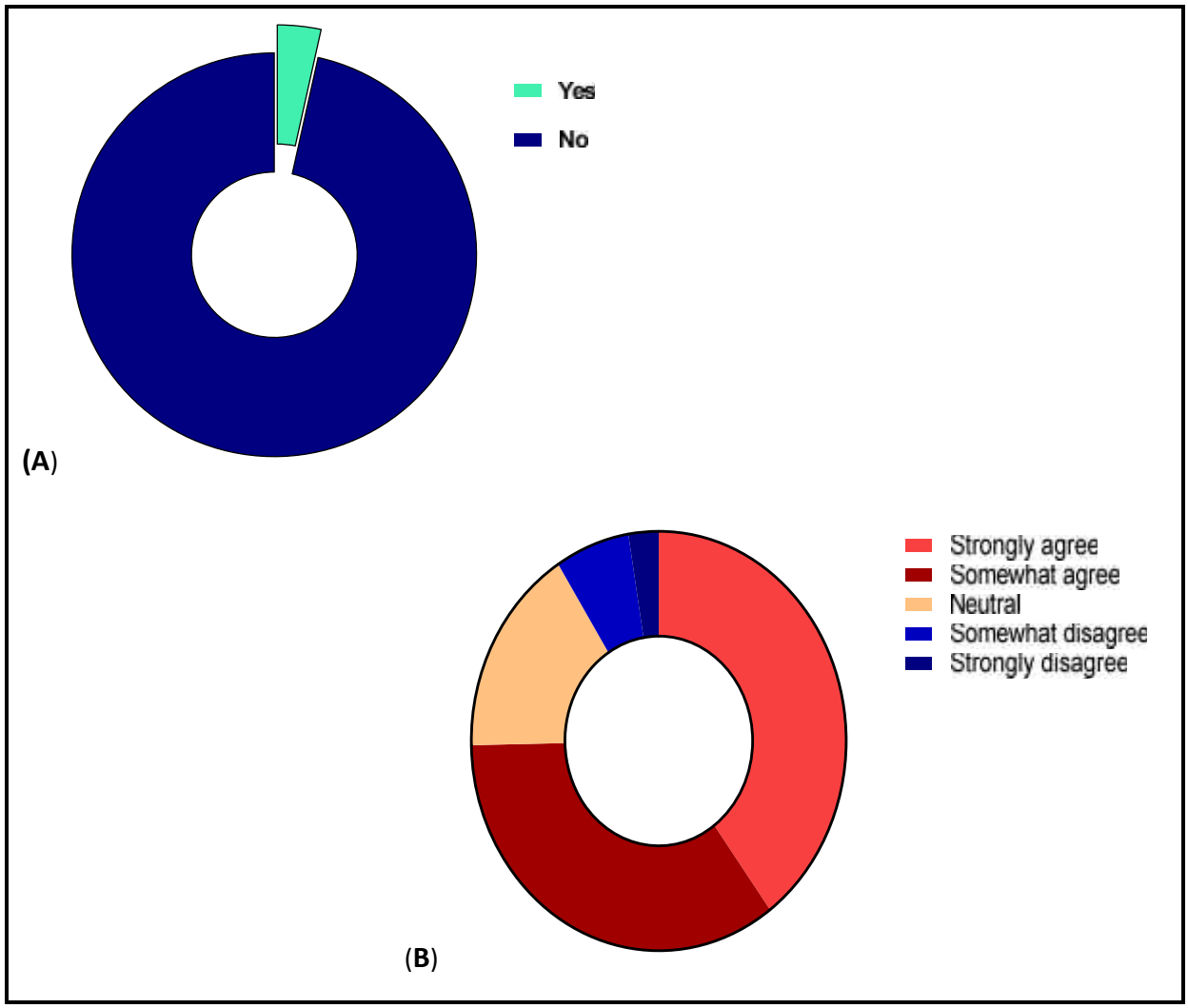

Figure 5.3: The extent of physicians' attitudes toward PGt comparing to their practice in PGt tests. The graph (A) shows the PGt actual practice in Palestine ▪Represents the percentage of physicians did not order PGx tests for their patients (96.5 %). ▪ Represents the percentage of physicians who order pharmacogenetic tests for their patients (3.5%). While graph (B**)** shows the high percentage of agree on the importance of PGtas seen in their answer on the 4 questions related to this section which range from strongly agree to strongly disagree.

Thisgapis most likely due tothe absence of restricted guidelines from theMinistry of Health, weak contribution in pharmaceutical drug companies in providing pharmacogenetic information in drug leaflet.Our results are similar to the results of U-PGx questionnaire which was conducted in seven implementation sites, there wasa general belief of usefulness of pharmacogenetic testing among participantsas65% did not ask for or recommend pharmacogenetic tests during the year preceded the study[97].

It was clear that the addressed physicians strongly believe in the role of the Ministry of Health, 74.4% of them consider that the Ministry of Health has a large responsibility

inforcing guidelines that control the dispensing of drugs accordingto genetic variations. Furthermore, 81.3% of the participants strongly agreed in the role of drug companies to enhancethe awarenessof doctorsabout genetic variations and its relation to different drug response, by adding clear pharmacogeneticsto drug leaflets. This response showed that the physicians tend to disclaim the responsibility in implementing PGt.Unfortunately, 8.7% of physicians disagree about the responsibility of MOH in PGt application with nearly percentage of those 6.9% also confused in the role of pharmaceutical companies in that.(Table5.2).This observation isconsistent with results from a survey assessing pharmacogenetics awareness among doctorscurrently practicing in Hamad Medical Corporation (HMC) hospitals in Qatar, where 92% of doctors agreed that genetic variations have an effect on patients' drug response, while only 40%of them appreciate their responsibility of applying pharmacogenetics in drug therapy and monitoring[85].

5.3 Pharmacogeneticseducation in Palestine

The majority of physicians 75.8% received education about PGt, either during or after university study(Figure5.4).

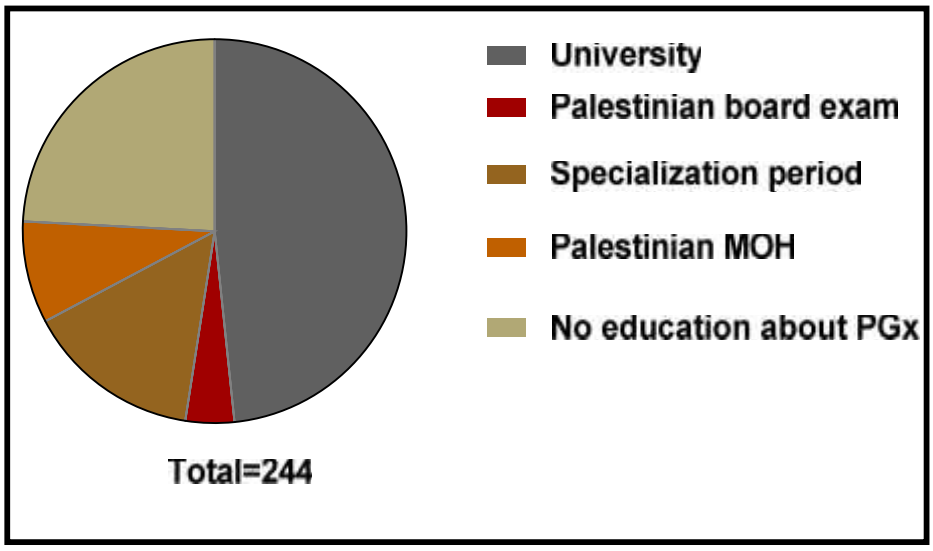

Figure 5.4: PGtformal education resources .(Multiple answers possible).

This graph shows the education resource about PGt among Palestinian physicians during their education period or during practice. Most physicians (48.4%) learned about PGt in universities, (4.1%) of them get information about PGtfrom Palestinian board exam, (14.8%)of physicians learned about PGtduring specialization period, (8.6%) of physicians learned from Palestinian Ministry of Health and Doctor Association and (24.2%) of them did not learn about PGt either during study period or after that.

The higher percentage got educated about it in universities either inside or outside Palestine. But this education was not reflected on the practical sides of applying pharmacogenetic testing in therapy management, because some physicians did not order pharmacogenetic testing, other physiciansstated that they ask for a genetic test instead of pharmacogenetic tests such as BRAC1, Philadelphia chromosome and Karyotyping. Also,when they were asked to provide some examples of drugs with known pharmacogenetics biomarkers, numerous participants indicated names of drugs that do not contain any pharmacogenetics informationsuch as ibuprofenand paracetamol. The social desirability bias is considered as a crucial factor behind physicians' answers related to their education about PGtfrom different sources. Another reason was that physicians did not want to show their lack of knowledge about this field so they preferred to answer whatever answer comes to their minds rather than stating their ignorance related to the field.

Older physicians who are>45 years, said that the number of PGtcourses or lectureswere taken in their study life was little. The results underscore the need to reviseavailable curricula in all medical field specialist from physicians to pharmacists and nurses to see if they have been receiving training in PGt or PGx as part of their core curricula or electives. That will help in providing comprehensive coverage of pharmacogenetics during study years.In addition, there is a need for more serious continuous training programs that can respond to the emerging challenges and modern topics in healthcare sector. Our results are similar to a study conducted on physicians in the United States, they received their formal training during a period when genetic tests had limited application, only 15% of them have got some education about pharmacogenetics during their graduate training[86].

Despite the fact that 82% of participants use extra learning sources, such as internet, conferences and journals, to learn about pharmacogenetics(Figure5.5).

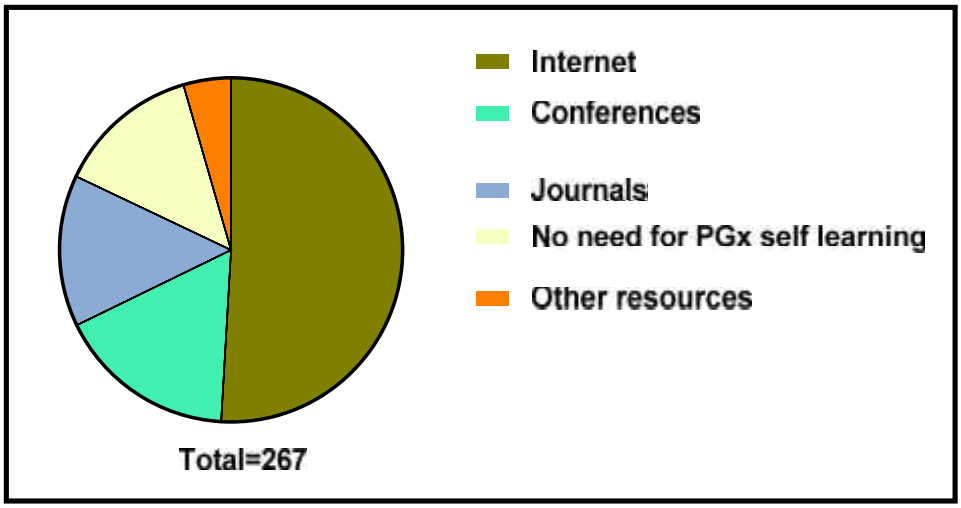

Figure 5.5: PGt self - learning resources. (Multiple answers possible).

The graph showed several self resources of information the physicians using it to learn about PGt. According to physicians answers about this question. (50.9%) of physicians used internet, (16.9%) of them get the information about PGtthrough attending conferences, (14.2%) of them read about PGt through journals , (13.5%) did not used any self learning resources because they see they don't need PGtin their job and low percentage of physicians (4.5%) used other resources such as medical books.

Most of them failed to respond to basic questions about drugs' labels with PGtimplication or PGttests. Also, that did not improve their level of knowledge, which assures the absence of attention toward the pharmacogenetics field in conferences, both in practical and theoretical parts. So, it is important to include PGt training as part of a professionally acknowledged continuing education programs for physicians through the MOH in collaboration with the syndicate for keeping track of the training logistics and universities as training entities.

In general, the physicians showed positive attitudes with high percentage of them learned about PGt. But their answer regarding that may be affected by presence of the explanatory page in the beginning of questionnaire which contained a brief definition about PGt with three examples about drugs need pharmacogenetic testing. So that considered one of the limitations of our studybecause give uncertainty in educational level measurement.

5.4 Pharmacogenetics challenges in Palestine

Pharmacogenetics has the goal of improving therapeutic outcomes, increasing the efficacy of medications, and reducing adverse events.But integrating it into clinical practice faces a host

of challenges. However, integration pharmacogenetics into clinical practice requires recognition of these barriers and efforts to overcome them.Several factors are considered as a barriers facing the application of pharmacogenetics in Palestine,Figure 5.6 summarizes the main challenges facing the implementation of pharmacogenetics

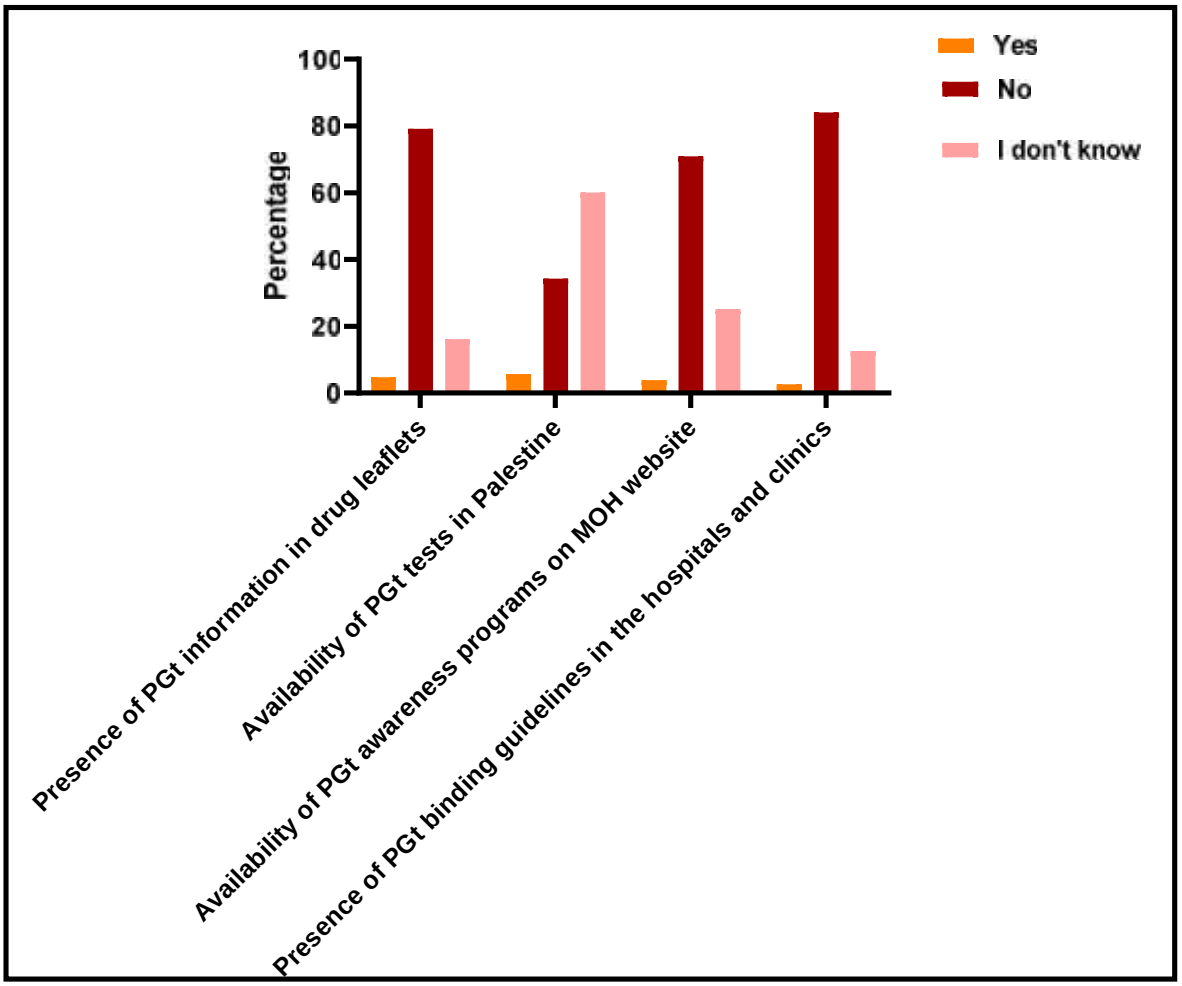

Figure 5.6: Availability of critical factors of PGt according to the physicians opinions.

The graph summarizes physicians' opinions about the presence of four essential factors for best practical application of PGx. The figure shows a consensus among physicians about the lack of PGt guidelines, awareness programs and PGt labels of locally sold drugs.

The most important one is the absence of guidelines control PGt application in hospitals and clinics. The results showed that 84.8% of physicians admit the absence of laws forcing the application of pharmacogenetics in their working place. 2.6% of physicians said there are guidelines control pharmacogenetics field in their workplace and 12.6% didn't know about availability of guidelines or laws related this field. Also, according to physicians opinions, other crucial factor obstruct PGt application is the lack of awareness programs from the Ministry of Health to control pharmacogenetic testing. The pharmacogenetic awareness

programsprovided by MOH is also important for pharmacogenetics application. 3.9% of physicians see that MOH provides awareness program related to pharmacogenetics, 70.9 % of them answered no and25.2% did not know if any awareness and educated materials available by MOH.Also the presence of pharmacogenetics information in drug leaflet one of the important factors for PGtapplication . 4.8% of them think the pharmaceutical companies provide PGtinformation in their products, 79.1% said that drug companies did not put appropriate pharmacogenetics labeling and16.1% of them did not know about that.Another challenge facing PGt application is the presence of laboratories provide pharmacogenetic tests in Palestine. The results showed that 60% of physicians did not know whether pharmacogenetic testing is available in Palestine or not, whereas 5.7% answered yes and the rest 34.3%answered no.

In fact, regardingPGt, the ideal healthcare environment must ensure presence and tight cooperation between the following stakeholders under the supervision of the Ministry of Health: healthcare professionals, pharmaceutical industry, university researchers and medical laboratories. So,Ministry of Health should lead the initiative by enacting legislations to control the pharmacogenetics field and to force its application in hospitals and clinics.The presence of guidelines onpharmacogenetic testing for each drug will help doctors to understand more about this type of test in order to apply it in treatment management.Furthermore, there is a need to revise all related educational programs to strengthen the healthcare professional competences in this critical field. The presence of medical laboratories provides pharmacogenetic testing aid strongly in the of insertion PGt in clinical practice. Another important point is the pharmacogenetics research, which should be supported in order to achieve more advanceresults in this field.

Our study evaluated physicians' attitudes and knowledge from multiple clinical centers of West Bank in Palestine. Although the response rate was low, the study succeeded in gatheringresponse from physicians with various specialties and wide experience. Our study focused on physicians because they are thecornerstone in health care system, they responsible on diagnosis and prescribe medication for patients. That is considered one of the limitations of our study. However, other health care professionals should be surveyed, such as pharmacists, academic professors, genetic counselors and medical laboratory specialists, as thesegroups have also a role in pharmacogenetics application. These groups, either here in Palestine or elsewhere in the world, might be interested in learning and applying this fields knowledge in their practical life. For example, in a study conducted on practicing

pharmacistsin Quebec (Canada), it appeared that pharmacists are interested in integrating pharmacogenetics in their clinical practice but they need proper training[87].

5.5 Role of Ministry of Health regarding PGt

Ministry of Health is considered as important pillar forsupporting pharmacogenetics application. In order to investigate its role in this field, we examined the legislations, awareness programs and reportsrelated to PGtthat are available on the MOHwebsite. We searched for documents related to PGt in all the public administrations on the MOH website. But there were no guidelines to control pharmacogenetics or force its application in health care centers. Also, the pharmacogenetics information for drugs that need pharmacogenetic testing before prescription was absent from therapeutic protocols. Furthermore, awareness and educational materials about PGt are poor and not sufficient. One document was publishedin 2013 entitled "Palestinian National Formulary". This document is available on General Administration of Pharmacy website, it describes the therapeuticprotocols for certain diseases and drugs such asclopidogrel. The pharmacogenetics information for this drugs was added in the guidelines. In fact, the clinical implementation of pharmacogenetics needs proper guidelines from MOH describing when to prescribe a pharmacogenetic test and how to use thetests results in order to optimize medication therapy, this could bedone through periodical reports and awarenessprograms to all health care professionals especially the physicians. Additionally, we thinkthat one of the responsibilities of MOH is to force obligated legislations to control pharmacogenetics application in clinical practice.That will help in reducing unnecessary medical costs and adverse harmful outcomes.

5.6 Role of pharmaceutical companies regarding PGt

The pharmaceutical companies have a vital role in integrating pharmacogenetics in clinical practice. Leaflets of drugs that are commonly used such as carvedilol, clopidogrel andcarbamazepine which have pharmacogenetics biomarkers according to FDA, were collected from local pharmacies. These drugs areavailable in the Palestinian market either from local producersor frominternational drug companies with different brand names. A total of 100drugs leaflets of 49drugs from different brand name were obtained and reviewed for pharmacogenetics information (Table 5.7).

Table5.7: List of the dugs investigated in the study and the availability of pharmacogenetics information in its leaflet.

Drugs	Therapeutic area	Availability of PGt information					
Amitriptyline	Psychiatry	Teva	Jepharm	Genesis			
		×	×	×			
Azathioprine	Rheumatology	Aspen					
		×					
Bupropion	Psychiatry	Valeant					
		×					
Carbamazepine	Neurology	Desitin	Taro	Novartis			
		×	×	✓			
Carvedilol	Cardiology	Beit Jala	Dexcel	Teva			
		×	×	×			
Ceftriaxone	Infectious Diseases	Panpharma	Birzeit	Jepharm			
		×	×	×			
Celecoxib	Rheumatology	Beit Jala	Jepharm	Trima	Pfizer		
		×	×	×	×		
Chloroquine	Infectious Diseases	Sanofi					
		×					
Escitalopram	Psychiatry	H. Lundbeck	Pharmacare				
		×	×				
Clomipramine	Psychiatry	Novartis					
		×					
Clopidogrel	Cardiology	Sanofi	Jepharm	Pharmacare	Beit Jala	Beirzeit	Sama
		×	×	×	×	×	×
Clozapine	Psychiatry	Taro					
		×					
Codeine	Anesthesiology	Taro	CTS	Pharmacare	Jepharm		
		×	×	×	×		
Dexlansoprazole	Gastroenterology	Delpharm Novara					
		×					
Diazepam	Neurology	Birzeit	Teva	Beit Jala	Jepharm		
		×	×	×	×		
Duloxetine	Psychiatry	Eli lilly					
		×					
Esomeprazole	Gastroenterology	Pharmacare	AstraZeneca				
		×	×				
Fluoxetine	Psychiatry	Eli Lilly	Teva	Pharmacare	Birzeit		
		×	×	×	×		
Formoterol	Pulmonary	Novartis					
		×					
Glimepiride	Endocrinology	Birzeit	Beit Jala	Sanofi			
		×	×	×			

Isosorbide Mononitrate	Cardiology	Dexcel					Jepharm				
		×					×				
Lansoprazole	Gastroenterology	Rafa									
		×									
Letrozole	Oncology	Teva									
		×									
Mafenide	Infectious Diseases	Beit Jala									
		×									
Meloxicam	Anesthesiology	Beit Jala					Pharmacare				
		×					×				
Metoclopramide	Gastroenterology	Rafa		Beit Jala			Birzeit				
		×		×			×				
Nitrofurantoin	Infectious Diseases	Beit Jala				Birzeit					
		×				×					
Omeprazole	Gastroenterology	Rafa	Birzeit	Beit Jala		Jepharm		Sama		Pharmacare	
		×	×	×		×		×		×	
Pantoprazole	Gastroenterology	Jepharm									
		×									
Paroxetine	Psychiatry	GlaxoSmithKline									
		×									
Ondansetron	Gastroenterology	Invamed					Novartis				
		×					×				
Phenytoin	Neurology	Pfizer									
		×									
Piroxicam	Rheumatology	Chiesi		Jepharm			Sama				
		×		×			×				
Propranolol	Cardiology	Dexcel					Birzeit				
		×					×				
Risperidone	Psychiatry	Janssen-Cilag		Pharmacare			Jepharm				
		×		×			×				
Rivaroxaban	Cardiology	Bayer									
		×									
Rosuvastatin	Endocrinology	AstraZeneca		Pharmacare			Birzeit				
		✓		×			×				
Sulfadiazine	Infectious Diseases	Teva					Jepharm				
		×					×				
Sulfasalazine	Gastroenterology	Pfizer									
		×									
Tamoxifen	Oncology	Teva									
		×									
Tamsulosin	Urology	Astellas Pharma		Inovamed			GlaxoSmithKline				
		×		×			×				
Thioridazine	Psychiatry	Taro									
		×									
Ticagrelor	Cardiology	AstraZeneca									
		×									

Tolterodine	Urology	Beit Jala	
		×	
Tramadol	Anesthesiology	Birzeit	Pharmcare
		×	×
Valproic Acid	Neurology	Sanofi	
		×	
Venlafaxine	Psychiatry	Dexcel	
		×	
Warfarin	Hematology	Taro	
		×	
Glipizide	Endocrinology	Perrigo	
		×	

The pharmacogeneticsinformation was present in just 2 drugs (2%).Astrazeneca drug company provides pharmacogenetics information for its product Crestor® (rosuvastatin) and Novartis drug company provides pharmacogenetics information for its productTegretol®(carbamazepine). The information in these two leaflets were in compliancewith the FDA recommendations.Table 5.8 shows the information related the two drugs contains pharmacogeneticsinformation in its leaflets.

Table 5.8: Drugs with pharmacogenetics information in its leaflets.

Name of drugs	Brand name	Manufacturers	Biomarker	Type of Biomarker	Labeling section
Carbamazepine	Tegretol®	Novartis	HLAB*1502	Target	Warning & precautions
Rosuvastatin	Crestor®	Astrazeneca	SLCO1B1	Transporter	Clinical pharmacology

Our results showed a lower percentage of drug leaflets that contains pharmacogenetics information when look to other similar studies such as the one conducted by Agarwal *et.al* in United Arab Emirates (UAE).In their study, Agarwal and colleaguesstudied 67 package inserts of 41 drugs and they found that 26out the 67 (38%) studiespackage inserts (PIs) provided direct genetic evidence and information on the type of polymorphism influencing drug efficacy and toxicitycomparable with FDA recommendations[101].Other study investigated the similarities and difference in availability of pharmacogenetics information in drugs labels from USA, United Kingdom(UK) and Japan. The number of (PIs) was 118 drugs

from US Food and Drug Administration (FDA) "Table of Pharmacogenomic Biomarkers in Drug Labels".The results of the study revealed that the number of Japanese PIs that provided information on genomic biomarkers was 44 compared to 118 for PIs in theUSA and 71 PIs in the UK.So USA is the country which is most likely to include pharmacogenetics information in PIs, followed by the UK and then Japan[102].

In general, drug package inserts represent the most fundamental tool for providing information on approved drugs to healthcare professionals and for promoting proper use of the drugs. The absence of pharmacogenetics information from several drugs leaflets reflects the defects in pharmaceutical sector.There is increasing interest among patients in medical information especially that information related to their diseases and its drugs. So, it is important to include this type of information in drugs leaflets with easy way for understand. The Palestinian drug companies should provide enough pharmacogenetics information in drug leaflet, which aid in increasing the level of awareness about PGtamong health care workers. Incorporating pharmacogenetics in clinical practice does not only rely on the experience and education of physicians, but also depends on a strong sustainable scalable and updatable formats guidelines and legislations facilitating the pharmacogenetics application.

CHAPTER 6 : CONCLUSION

The pharmacogenetics field have been developed rapidly in US and European union, with improvement in technologies to perform pharmacogenetic testing . Despite that, the developing countries are still facing regulatory, technological and scientific challengesto the translation of PGt information into personalized medicine. Some emerging economics are allocating funds for PGt research while the developing countries at risk of being excluded from the new genomic scientific and technological revolution. Indeed, inadequate basic services such as running water, electricity, and healthcare infrastructure in some countries would make personalized medicine in poor communities and nations seem too far out of reach. So the healthrelated funding in these countries go toward basic health needs and services. Unfortunately, the prevalence of chronic diseases in the developing world, including diabetes, obesity, cardiovascular disease, hypertensionhave increased significantly over the past 20 years. That lead to hospitalization and economic cost. So urgent improvement in pharmacogenetics research are required to decrease the consequences of chronic diseases. In general, the inclusion of developing countries in this pharmacogenetics revolution will require institutional leadership, with significant capital investment into infrastructure required for this biomedical field.

The health care system in Palestine is facing a lot of obstacles hindering the best clinical outcomes. Some of these problems includethe increased hospitalization cases and mortalities related to adverse drug problems.In addition,"one size fits all" is the most abundant approach used by most physicians in treating their patients, although, high percentages of elderly patients have chronic diseases which requires multiple drug therapy. All these and other obstacles affect the quality of medical services provided to the patients. Currently, the medical therapy is moving toward more personalized medication in order to improve drug efficacy and minimize the harmful drug effects for each individual. Hence, the adoption of pharmacogenetics in clinical practice will help physicians making moreenlightened decisions in drug selection, dosing and monitoring depending on pharmacogenetic tests' results. Which will improvepatient adherence to therapy, and decreases the risk for an ADRs. Additionally, that will lend a helping hand todecrease health care costs and provide more efficient health care services.

The study showed the weaknessin application of PGt in clinical practice.However, interpretation of pharmacogenetic testing custom-made software are needed for each. We need for bioinformaticians with pharmacy background and higher computer skills.On the other hand, the physicians have positive attitudes toward PGt and they agree on the importance of it in clinical practice but they did not order this type of tests for their patients. The inadequate education among physicians about PGt lead to misconception between pharmacogenetics and genetic for some of them. They also see that MOH and pharmaceutical companies bears large responsibility for pharmacogenetics application. However, the lack of guidelines and awareness programs fromthe Ministry of Health and drug companies is considered as an impediment toward the implementation of PGt. So, in order to get advancement in health care system both in its medical services and organizational structure a strong contribution and collaborationbetween all stakeholders is highly neededto construct the foundations for pharmacogenetics initiative and best practice in Palestine.

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Appendices

Appendix 1.Questionnaire

Biotechnology Master Program

بسم الله الرحمن الرحيم

كلية الدراسات العليا

برنامج ماجستير التكنولوجيا الحيوية المشترك بين جامعتيّ بوليتكنك فلسطين وبيت لحم

استبيان حول موضوع الصيدلة الجينية وتطبيقها في فلسطين

هذا الاستبيان موجه للأطباء العامين وأطباء الاختصاص الذين يعملون حاليا في مستشفيات وعيادات الضفة الغربية في فلسطين والذي يهدف لقياس مدى وعي الأطباء لمفهوم علم الصيدلة الجيني وأهمية استخدامه في اختيار العلاج المناسب للمريض بالإضافة إلى معرفة التحديات التي تواجه تطبيق الصيدلة الجينية في النظام الصحي في فلسطين في سبيل التغلب عليها.

لذا يرجى التكرم بتعبئة هذا الاستبيان بكل موضوعية شاكرة لكم حسن تعاونكم

إعداد الطالبة **المشرف الأكاديمي**

بيسان أبو سنينة **د. يعقوب الأشهب**

PHARMACOGENETICQUESTIONNAIRE FORSPECIALIST, RESIDENT AND GENERAL DOCTORS IN WEST BANK OF PALESTINE

- ✓ علم الصيدلة الجيني (Pharmacogenetic): حقل جديد من العلوم يجمع بين علم الصيدلة وعلم الجينات، مخصص لدراسة تأثير الاختلاف الجيني للأفراد على استجابتهم للأدوية لتطوير علاجات أكثر فاعلية وأمان.
- ✓ أكثر من ٢٠٠ دواء تضع منظمة الغذاء والدواء الأمريكية(FDA) معلومات الصيدلة الجينية لكل دواء في نشرته ويلزم قانونيا عمل فحص صيدلة جيني قبل وصفه للمريض .

- ✓ على سبيل المثال: دواء (ClopidogrelPLAVIX®)

يلزم عمل فحص الصيدلة الجيني لمعرفة إذا كان لدى المريض ضعف فعالية الإنزيم المسؤول عن عملية الأيض للدواء (CYP 2C19)، نتيجة تغيرات جينية معينة في الجين المسؤول

(Carbamezabine) TEGRETOL®
يلزم عمل فحص الصيدلة الجيني لأن الدواء يؤدي إلى حدوث أعراض جانبية جلدية قاتلة مثل متلازمة (Stevens-Johnson) نتيجة تغيرات جينية معينة في (HLA-B) جين عند بعض الأفراد .

(Fluorouracil Carac®)
حدوث الأعراض الجانبية القاتلة عند المريض ترتبط بوجود عدة طفرات وتغيرات جينية في الجين المسؤول عن إنزيم (Dipyrimidine Dehydrogenase) المهم في عملية التخلص من الدواء لذلك يلزم عمل فحص صيدلة جيني قبل إعطاءه.

PARTICIPANT'S INFORMATION:

Gender: ○♀○♂	**الجنس**
Age: ○ 25- 34 ○35-44○45-54○55-64○>=65	**العمر**
Job Position: ○ Specialist ○ Resident ○General	الموقع الوظيفي **الحالي**
Specialty :	**التخصص**
Workplace:.....	**مكان العمل**
Experience : ○ 1-5○ 6-10 ○ 10-20 ○>20	**سنوات الخبرة**
What is the name of the university you graduated from? **.....**	**ما اسم الجامعة التي** تخرجت منها؟
When did you start your specialization? **.....**	**متى بدأت برنامج الاختصاص؟**
Where did you specialize? **.....**	**ما اسم المكان الذي قمت بعمل برنامج** الاختصاص فيه؟

SECTION ONE:

Please choose the most appropriate response to the following statements:

1. Do you think it is important to test your patient for certain genetic variations in order to avoid adverse drug reaction?

هل تعتقد أنه من المهم اختبار مريضك من أجل تحديد بعض **الاختلافات** الوراثية المرتبطة بالدواء **لتجنب المخاطر و** الآثار السلبية؟

.

○Strongly agree ○Somewhat agree ○Neutral ○Somewhat disagree ○Strongly disagree

2. Do you think it is important to test your patient for certain genetic variations to determine the most effective therapeutic dose of drugs?

هل تعتقد أن تحديد الاختلافات الوراثية لدى مريضك مهمة من أجل تحديد الجرعة المناسبة لبعض الأدوية؟

O Strongly agree OSomewhat agree ONeutral OSomewhat disagree OStrongly disagree

3. Do you think the Ministry of Health should force obligated guidelines for drugs that show its effects depending on the genetic variations?

هل تعتقد أن من واجب وزارة الصحة إصدار تعليمات ملزمة للأطباء خاصة بالأدوية التي لديها تأثير مختلف بناءً على الاختلافات الوراثية

O Strongly agree OSomewhat agree ONeutral OSomewhat disagree OStrongly disagree

4. Do you think the drug companies should add clear labeling pharmacogenetic information in drug leaflet?

هل تعتقد بأنه يجب على شركات الأدوية إضافة المعلومات المتعلقة بالاختلافات الجينية لكل دواء في النشرات الدوائية؟

O Strongly agree OSomewhat agree ONeutral OSomewhat disagree OStrongly disagree

SECTION TWO:

5. Where did you learn about pharmacogenetic؟أين تعلمت عن موضوع علم الصيدلة الجيني

(You can select more than one option).

oUniversityoPalestinian Bord Exam

oSpecialization periodoPalestinian Ministry of Health and Doctor Association

o I didn't learn about pharmacogenetic

6. What are the sources of information you are currently using to learnabout pharmacogenetics? (You can select more than one option).

ما هي مصادر المعلومات التي تستخدمها حالياً للقراءة والتعلم عن علم الصيدلة الجيني؟

oInternet. oConferencesoJournals.

oI do not need pharmacogenetic in my specialty o Other sources:.....

.

SECTION THREE:

7. In your opinions, do pharmaceutical companies provide proper pharmacogenetics labeling for their drugs?

برأيك،هل تعتقد بأن شركات الأدوية تضع ما يكفي من المعلومات اللازمة حول الاختلافات الجينية في نشرات الدواء؟

oYes o No o I don't Know

8. IF YES:Please name one drug that has an appropriate pharmacogenetic labeling.

إذا كانت إجابك نعم: من فضلك أكتب اسم دواء تحتوي نشرته على المعلومات الجينية الصحيحة؟

.....

9. Is pharmacogenetic testing available in Palestine?

هل تتوفر فحوصات الصيدلة الجينية في فلسطين؟

oYes o No o I don't Know

10. IF YES: Please name one Pharmacogenetictest?

إذا كانت إجابك نعم: اذكر اسم فحص صيدلة جيني .....

11. Do you thinkthePalestinian Ministry of Health provides periodical awareness programs that explain the importance of inter- individual genetic variation in drug therapy decisions?

هل تعتقد أن وزارة الصحة الفلسطينية تصدر برامج توعيةوتعليمات حول أهمية الاختلافات الجينية بين الأفراد؟

oYes o No o I don't Know

12. Are there any clear and binding guidelines to control clinical practice of pharmacogenetic in the hospital/ clinic you are working in?

هل يوجد تعليمات واضحة وملزمة لتطبيق موضوع الصيدلة الجيني في المستشفى/ العيادة **التي تعمل بها؟**

oYes o No o I don't Know

SECTION FOUR:

13. Do you ask for pharmacogenetic test for your patients?

o Yeso No **هل تطلب عمل فحص صيدلة جيني للمرضى لديك ؟**

14. IF YES: How often do you ask fora pharmacogenetictestin annual base?

إذا كانتإجابتك نعم: كم عدد المرات التي تطلب فيها هذا الفحص سنوياً؟ ...../ Year.

15.Could you please write the name of pharmacogenetic test you have previously requested?

هل بإمكانك كتابة اسم فحص الصيدلة الجيني الذي طلبته مسبقاً؟ .....

16. For which type of diseases you needed this test?

لأي نوع من الأمراض طلبت عمل هذا الفحص؟ .....

17. For which type of drugs you asked for apharmacogenetictest?

لأي نوع من الأدوية طلبت عمل فحص الصيدلة الجيني؟ .....

18.When pharmacogenetic test is required for the patient?

(You can select more than one option) متىيلزمعملفحصصيدلةجينيللمريض؟

○ Before drug prescription.

○If medication does not give the desired efficacy.

○If patients have adverse effects from the prescribed drug.

○ Poly-pharmacy patients.

○ Other: .....

Other Notes/ Suggestion ملاحظات أخرى

.....

.....

توقيع/ختم- الطبيب/ة .....

رقم الهاتف .....

Appendix 2:Frequencies and percentages for all questions in the survey

Section one

Questions	Strongly agree	Somewhat agree	Neutral	Somewhat disagree	Strongly disagree
Do you think it is important to test your patient for certain genetic variations in order to avoid adverse drug reaction?	**70 (30.4%)**	**94(40.9%)**	**41 (17.8%)**	**21 (9.1%)**	**4 (1.7%)**
Do you think it is important to test your patient for certain genetic variations todetermine the most effective therapeutic dose of drugs?	**72 (31.3%)**	**93 (40.4%)**	**43 (18.7%)**	**17 (7.4%)**	**5 (2.2%)**
Do you think the Ministry of Health should force obligated guidelines for drugs that show its effects depending on the genetic variations?	**94 (40.9%)**	**77 (33.5%)**	**39 (17%)**	**11 (4.8%)**	**9 (3.9%)**
Do you think the drug companies should add clear labeling pharmacogenetics information in drug leaflet?	**131 (57%)**	**56 (24.3%)**	**27 (11.7%)**	**10 (4.3%)**	**6 (2.6%)**

Section two

Where did you learn about pharmacogenetics?	
University	**118 (48.4%)**
Palestinian Bord Exam	**10 (4.1%)**
Specialization period	**36 (14.8%)**
Palestinian Ministry of Health and Doctor Association	**21 (8.6%)**
I didn't learn about pharmacogenetic	**59 (24.2%)**

What are the sources of information you are currently using to learnabout pharmacogenetics?	
Internet	**136 (50.9%)**
Conferences	**45 (16.9%)**
Journals	**38 (14.2%)**
I do not need pharmacogenetics in my specialty	**36 (13.5%)**
Other sources	**12 (4.5%)**

Section three

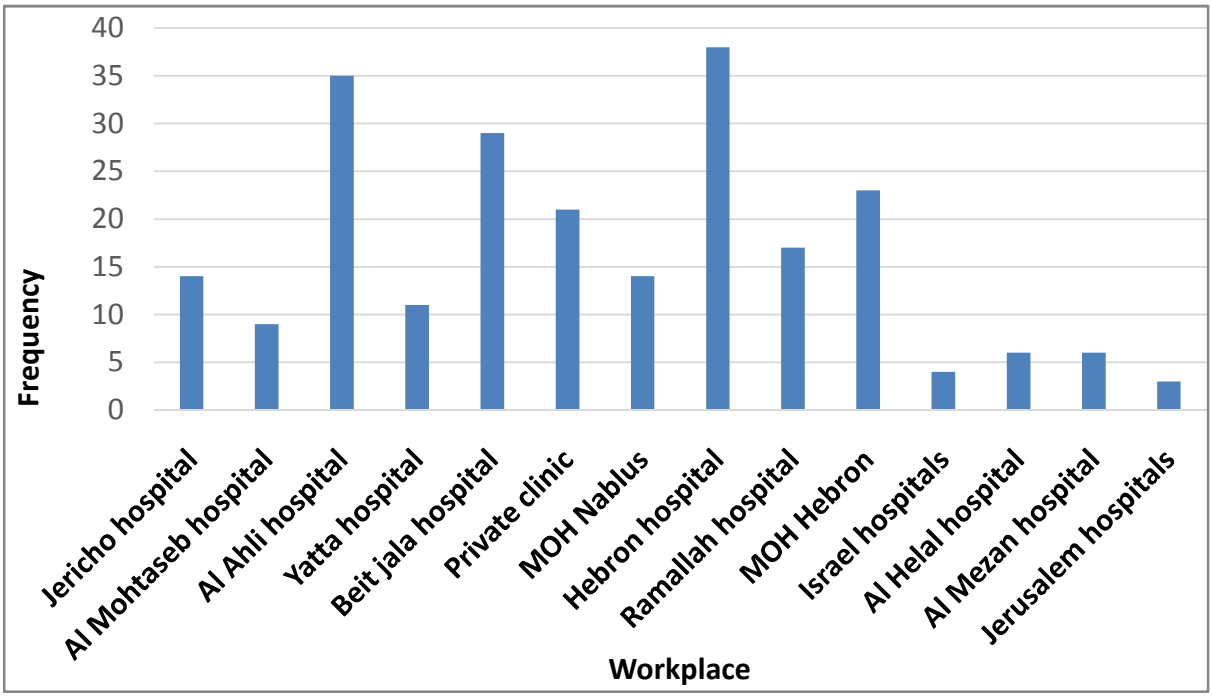
Questions	Yes	No	I don't know
In your opinions, do pharmaceutical companies provide proper pharmacogenetic labeling for their drugs?	**11 (4.8%)**	**182 (79.1%)**	**37 (16.1%)**
Is pharmacogenetic testing available in Palestine?	**13 (5.7%)**	**79 (34.3%)**	**138 (60%**
Do you think the PalestinianMinistry of Health provides periodical awareness programs that explain the importance of inter- individual genetic variation in drug therapy decisions?	**9 (3.9%)**	**163 (70.9%)**	**58 (25.2%)**
Are there any clear and binding guidelines to control clinical practice of pharmacogenetic in the hospital/ clinic you are working in?	**6 (2.6%)**	**195 (84.8%)**	**29 (12.6%)**

Section four

Question	Yes	No
Do you ask for apharmacogenetic test for your patients?	**8 (3.5%)**	**222 (96.5%)**

When Pharmacogenetic test is required for the patient?	
Before drug prescription	**98 (30.2%)**
If medication does not give the desired efficacy	**84 (25.8%)**
If patients have adverse effects from the prescribed drug	**99 (30.5%)**
Poly-pharmacy patients	**29 (8.9%)**
Other	**15 (4.6)**

Workplace



Specialty

Specialty	Frequency	Percent
Anesthiologist	3	1.3
Dermatologist	2	1.6
Emergency Medicine	3	1.3
ENT	9	3.9
Family Medicine	4	1.7
General Surgery	8	3.5
Gynecologist	15	6.5
Internal Medicine	22	9.6
Neurologist	2	0.9
Neurosurgery	3	1.3
Oncologist	6	2.6
Orthopedic	18	7.8
Pathologist	2	0.9
Pediatric	18	7.8
Primary ICU	3	1.3
Radiologist	1	0.4
Urologist	6	2.6
Total	**125**	**54.3**

Specialization Place

Country	Frequency	Percent
Belarus	1	0.4
Egypt	5	2.2
Germany	1	0.4
Greece	1	0.4
India	1	0.4
Occupied lands 48	16	7.0
Italy	2	0.9
Jordan	12	5.2
Lebanon	1	0.4
Palestine	46	20
Qatar	2	0.9
Romania	4	1.7
Russia	16	7
Serbia	1	0.4
Syria	2	0.9
Ukraine	12	5.2
United Kingdom	1	0.4
Yugoslavia	1	0.4
Total	**125**	**54.3**

Graduation University