T.R.N.C

NEAR EAST UNIVERSITY

INSTITUTE OF HEALTH SCIENCES

Pharmacogenomics Based Practice in North Cyprus: The Attitude, Knowledge and Adoption by the Pharmacists

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Master of Science in Pharmacology

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DEDICATION

I dedicate my dissertation work to my family and many friends and who support me every morning by words or even smile.

A special feeling of gratitude to my loving parents, who have always loved me unconditionally and whose good examples have taught me to work hard for the things that I aspire to achieve.

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Abstract:

This study aims to identify the current state of pharmacogenomics practice in Northern Cyprus to help identify barrier and solution to reap advantages from pharmacogenomics practices.

Knowledge, attitude as well as adoption of pharmacogenomics in clinical practice among the pharmacists in Northern Cyprus have not been reported. This cross-sectional study explores various facets of the pharmacists as related to pharmacogenomics to determine the need and preferred method to improve education among them.A questionnaire consisting of 25 questions in five parts was adopted and validated. It explores the respondents' characteristics, attitude, knowledge, adoption and education. One hundred forty survey instruments were distributed to community pharmacies in Northern Cyprus, Pharmacists in Northern Cyprus had positive pharmacogenomics orientations Interest in the education is very high, and most of them preferred to learn pharmacogenomics via lecture or seminar program**.**Pharmacogenomics is a field that promises many benefits, but to reap these benefits require its implementation in clinical setting. Pharmacists need to be equipped with adequate knowledge and positive attitude towards pharmacogenomics.

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LIST OF ABBREVIATIONS:

S. #	ABBREVATIONS	EXPLANATION
1	PG	Pharmacogenomics
2	ADR	Adverse Drug Reaction
3	FDA	Food and Drug Administration
4	CYP	Cytochrome P-450
5	VKORC	Vitamin K Epoxide Reductase Complex
6	HSR	Hyper Sensitivity Reaction
7	SNP	Single Nucleotide Polymorphism
8	EMA	European Medicine Agency
9	IRB	Institutional Review Board
10	AACP	American Association of Colleges of Pharmacy
11	ACCP	the American College of clinical Pharmacy
12	ASHP	American Society of Health System Pharmacist
13	6-MP	6-Mercaptopurine
14	TPMT	Thiopurine S-MethylTransferase
15	NEU	Near East University
16	TRNC	Turkish Republic of North Cyprus
17	CPE	Continues Professional Education
18	SPSS	Statistical Package for the Social Science

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I. Introduction:

Difference between individuals in the clinical response to drug therapy for both chronic and acute diseases is one of public health interests. This difference has been caused largely to non-genetic factors, like weight, age, disease conditions, and drug-drug interactions. Only 25% to 60% of the patients have a positive response to their medication, therefore the remaining fraction is not receiving an appropriate drug or is complaining from critical therapeutic problems, such as delays by switching between two drugs to achieve good prognosis (Adamu YA'U, 2015).

Pharmacogenomics (PG) is a branch of biotechnological science that combines the techniques of medicine, pharmacology, and genomics and is interested in creating drug therapies to compensate for genetic differences in patients, which cause different responses to a single therapeutic regimen (Spear BB et al., 2011).

If genetic factors are taken in consideration in an appropriate way before beginning the drug therapy regimen, the type of drug and its dosage can be optimized to the individual patient need. PG puts a considerable professionalism to the therapeutic approach, it is the relationship between dosage needed and genetic variation in enzymes of metabolizing drugs like Cytochrome P450, G-6-D-P, NAT2, VKORCI and TPMT or in drug transporters like P-glycoproteins that is established best (http://www.merriam-webster.com/ dictionary/pharmacogenomics).

PG is the study of fluctuation in pharmacokinetics and pharmacodynamics in connection to human genomic variation. PG has its foundations in biochemical genetics and the works of Archibald Garrot (1857–1936) who recommended the chemical individuality of humans as a basis for certain inborn errors of metabolism,for example,alkaptonuria (AdamuYau et al, 2015).

Physicians are progressively thought to integrate genomic medicine care (Scheuner MT et al., 2008). This incorporation has not been achieved as a result of poor attitudes, lack of knowledge and confidence, limited evidence of clinical utility and concerns about privacy and discrimination (Adamu YA'U, 2015).

An applicable example of the effect of PG is the genetic polymorphism of HLA-B*1502 which has been shown to decrease the total number of adverse drug reactions (ADRs). Genotyping of patients for HLA-B*1502 before carbamazepine is prescribe to patients decrease the risk of Steven Johnson Syndrome and Toxic Epidermal Necrolysis (Gage BF, 2008). Food and Drug Administration (FDA) further strengthen the roles of PG in optimum health care. FDA recommended pharmaceutical industries to modify the labeling for various drugs to incorporate the potential usefulness of genetic testing (Bannur Z, 2014).

II. Background

II.1 The difference between pharmacogenetics and pharmacogenomics:

The use of these two terms can lead to confusion, because both are used interconvertible to each other. The clinical observation document the inherited difference between individual regarding the drug effect in 1950's, which give rise to this new science field pharmacogenetics mentioned that it concentrate on the genetic determinants of a single gene that affects drug therapy, pharmacogenetics now boarder spectrum in academic curricula in pharmacy and medical schools and sheds light on pharmacogenomics by pharmaceutical industry (Julie A, 2002).

Although the two terms are synonymous in practical field, pharmacogenomics considered more preferable when we talk about clinical field because it deals with candidate genes, often more than one, and may include transcriptome and proteome information that affect drug metabolism, pharmacokinetics, and pharmacodynamics.

Pharmacogenomics also play a significant role in selecting appropriate therapy for individual with specific disease depends on certain genotype and it can predict the therapeutic outcome. In summary, pharmacogenomics is newer term and used all information turned out from pharmacogenetics (Majid Y, 2005).

II.2 The importance of pharmacogenomics in prescribing drugs:

It is clearly known that patients respond differently to the same medication, difference response result in different drug adverse reaction, effect and metabolism (Hughes, H.Bet al., 1954).

In addition to non-genetic factors that affect the drug efficacy like severity of disease, organ function, adherence to drug therapy and drug interaction, genetic factors may have potential role in affecting drug efficacy which affect in several way among individuals the drug metabolism, genetic polymorphisms of the receptors and drug elimination. The role of pharmacogenomics is not new, in 1950s was the first clinical observation sheds light on the individual differences in respond to drug and give rises to this field (Kalow, W, 1956).

Pharmacogenomics potentially provide patient-specific data that guide to optimize the selection of drugs and doses regarding the individual, rather than starting with the safe and effective doses of the drug mentioned in the clinical trials (William E, 2003).

A patient's genotype needs to be determined only once for any given gene, because except for rare somatic mutations, it does not change over time. Genotyping methods are improving so quickly that it will soon be simple to test for thousands of single-nucleotide polymorphisms in one assay ((Julie A, 2002).

II.2.1 Pharmacogenomics and warfarin dose:

The appropriate dose of warfarin, an oral anticoagulant, is something difficult to initiate and differs from patient to another (Budnitz DS et al, 2007). More than one factor cause this variety; demographic variables, variations in two genes – cytochrome P450, family 2,

subfamily C, vitamin K epoxide reductase complex, subunit 1(VKORC1), polypeptide 9 (CYP2C9), and clinical factors (Anderson JL et al, 2007). In 2007, the Food and Drug Administration changed warfarin's label to add pharmacogenetic information without mentioned a specific strategy for using genetic information to predict the dose required in individual patients (Wu AH, 2007).

Developed a pharmacogenetics dose algorithm for warfarin that uses genotypes from two genes (*VKORC1* and *CYP2C9*) and clinical variables to predict the stable therapeutic dose. This pharmacogenetic algorithm guess the steady therapeutic dose of warfarin better than a fixed-dose approach and this algorithm is better than a clinical algorithm developed from the same large data set, too. Depending on this pharmacogenetic algorithm and a definition of the ideal estimated dose as a dose that differs by less than 20% from the stable dose, this algorithm produced significantly better dose estimates, with the best benefit seen in patients ultimately needs 21 mg or less of warfarin per week and in those needs 49 mg or more per week (Sconce EA et al., 2005). The pharmacogenetics algorithm thus provides a robust basis for a prospective clinical trial of the efficacy of genetically informed dose estimation for patients who needs warfarin (Rieder MJ et al., 2005).

II.3 Challenges face implementation of pharmacogenomics:

II.3.1 Economics:

In appropriate drug using may result in serious adverse reaction and increase the cost of hospitalization, applying pharmacogenomics intervention can lead to decrease the cost of the both and improve economic outcomes in treating disease. Many studies evaluate both pharmacoeconomic and pharmacogenomics of utilizing drugs, one of the most famous example on pharmacogenomics intervention is using abacivir in treating HIV positive patients . Abacivir, a nucleotide reverse transcriptase inhibitor, associated with lethal systemic hypersensitivity reaction (HSR) especially in first six weeks in a small proportion of patients (Stephanie Ross et al., 2012).

Studies showed that there is a strong relationship between HSR risk and HLA-B*5701 allele, and screening for HLA-B*5701 in HIV patients treated with abacivir before starting the therapy will decrease the risk of HSR (Bruce R, 2008).

Kauf et analysed the effective and cost-effectiveness of HLA-B*5701 screening by assessing the cost of prior genetic screening and the cost of using an alternative medication, tenofovir, within short-term and lifetime models (Kauf TL, 2010).

The study demonstrated that the cost of prospective screening depends on several factors; the cost of the test, the cost links between HSR treatment and screening performance for short model, while in life long model abacivir treatment with genetic guide is more effective and cost effective than tenofovir (Mallal S, 2008).

II.3.2 Ethical:

In addition to pharmacoeconomic challenge, ethical issues and privacy should be taken in consideration as a barrier of application of pharmacogenomics.

Unlike a serum bilirubin to measure liver function, or serum creatinine to test renal function, or the other biochemical tests, a patient's genotype for any given gene only needs to be determined once because it does not change over time.

Stored DNA samples or digitized sequence information will contain the individual's probabilistic 'future diary', which will sheds light on privacy than, for example determining the correct dose of azathioprine for patient with leukemia and consequences of the treatment.

Therefore, to reduce the risk of patient's privacy, strengthening the individual's control over his DNA should be strength, by modifying the informed consent to mention if the DNA sample will be stored or destroyed after the test covered by the consent has been done. The informed consent should be limited to the specific use of DNA as mentioned in

the research protocol, and the patients must have the right to withdraw the DNA samples from the research project, or the informed consent should mentioned that the sample may be stored and used for future analysis, and specific consent should be provided for each analysis (LT Vaszar, 2002).

The current consent process looksinsufficient and not enough in addressing the privacy of stored DNA material, as revealed by Weir and Horton, who have scored 23 informed consent for long-term storage of DNA samples from potential research participants.

In terms of privacy and confidentiality of personal identification Weir and Horton created scores from one (when sufficient statement was included of how confidentiality and privacy would be maintained) to four (when neither confidentiality nor privacy were mentioned in the consent document). The mean score for the 23 consent documents was 3.43 (standard deviation 0.79), and no consent documents received a score of one (Weir RF, 1995).

The privacy of non-consenting persons such as relatives and members of their ethnic (or otherwise defined) community may be threatened by an individual's genetic testing. Family members have a high risk of having the same single nucleotide Polymorphism SNP profile as the test subject and thus may share the same pharmacogenomics limitations. Family members do not have to provide formal consent, but common practice is to involve them in discussions as assenting adults. Recruiting families also challenges the traditional role of the physician as the patient advocate and the privileged physician–patient relationship, which is central to safeguarding the individual's privacy. These relationships are in danger if the family takes the patient's place in the 'covenant of trust' with the physician (Lennard L, 1989).

II.3.3 Clinical:

Common questions faced by regulators include the consistency of findings and results, the requirement for confirmation of pharmacogenetic data, the applicability of association studies to the clinical area, and the evaluation of the impact of pharmacogenetic testing in clinical practice. The main role of regulators with respect to available pharmacogenetics data is to interpret them with respect to their consistency and clinical applicability, to

match them to legal limitations, and to use them to protect and improve public health (Uhr M et al., 2008).

Regulatory involvement pushing the use of pharmacogenetics biomarkers in both drug development and clinical practice is evidenced by the public documents generated in the past five years by agencies worldwide. However, these documents provide only an initial framework for building policy. They are yet insufficient to address the moral, ethical, and economic implications of the application of genotypic information to the development of personalized therapeutics. Before pharmacogenetics can be routinely applied, multiple issues will need to be addressed by various stakeholders: privacy issues concerning the use of genotype information in multiple studies; informed consent and the need (if any) for genetic counseling; public access to genetic testing for prediction of therapeutic response; sample size and eligibility requirements for association study evaluation; public access to genetic testing for prediction of therapeutic response; and standardization of data across patient populations (FDA, 2011).

The preclinical data that predict interindividual variations in the efficacy and side effects of the drugs in humans should encompass analyses either in the drug membrane transport and metabolism (pharmacokinetics) or in the targeted pathways (pharmacodynamics). Indeed, pharmacogenetic variations may be predicted from in vitro and in vivo data, usually available before first in human studies, therefore accelerating clinical drug development (Relling MV et al., 2010). Whereas pharmacogenetic traits influencing drug disposition are now relatively well identified, the genetic variability of drug targets remains to be explored. Many genetic polymorphisms affect drug response by modulating the functions of proteins that are drug direct response. These polymorphisms happen to occur in genes encoding for drug target protein function, for drug-target interaction, or for both (Swen JJ et al., 2011).

Throughout the workshop the focus was on methodological issues associated with pharmacogenomic biomarkers in relation to clinical development. A number of questions, partially raised in previous Reflection Papers from EMA, were considered of particular interest by the group. Which is the appropriate trial design or the right time for data analysis of pharmacogenetic/genomic studies in the drug developmentprocess? (Landon MR (2005).

Which is the role of the diagnostic performance of the pharmacogenetic/genomic biomarker?

What are the potential external influences on the evaluation of a pharmacogenetic/genomic marker?

Are there methodological issues to be considered?

What is the impact of adverse event frequency and severity? (Nies AT et al., 2008).

Another area that needs to be addressed is the involvement of Institutional Review Boards and Ethic Committees in pharmacogenetics research. These organizations will review and approve, disapprove or modify all the submitted research proposals concerning human subjects, submitted by the academic community or by the pharmaceutical industry (Niemi M, 2010). As research moves in the direction of genome analyses based on computational methods, it becomes increasingly important for participating members of IRBs and Ethic Committees to possess specific knowledge to properly evaluate the possible implications of a pharmacogenetic study. It might be that in the future, institutional independent review boards with such specialized knowledge are created that can be contracted to perform study analyses and provide guidance on study conduct (Schwarz UI, 2006).

II.4 Food and Drug Administration and drug labeling for pharmacogenomics:

At the beginning of the decade, the FDA began looking for opportunities to improve the quality of therapeutics using already marketed drugs by updating the labels to include PGx information. The Pediatric Oncology Subcommittee of the Oncology Drug Advisory Committee met in July 2003 to review data related to the use of 6-mercaptopurine (6-MP) in childhood acute lymphoblastic leukemia and the impact of thiopurine *S*-methyltransferase genotype on 6-MP-induced myelosuppression (www.fda.gov/Drugs/). The Committee agreed that the label of 6-MP (Purinethol®) should be updated and *TPMT* information was added to the Clinical Pharmacology, Warnings, Precautions, Adverse Reactions, and Dosage and Administration sections of the 6-MP label. Subsequently, other milestone PGx-related label updates were achieved for irinotecan (Camptosar®), linking *UGT1A1* mutations with increased susceptibility to neutropenia

(2005), warfarin (Coumadin®), linking *CYP2C9–VKORC1* combination genotypes with variable dose requirements (2007 and 2010), carbamazepine (Tegretol®), linking variants in the gene *HLA-B*1502* with increased risk of developing life-threatening skin reactions (2007), abacavir (Ziagen®), linking *HLA-B*5701* with higher risk of a hypersensitivity reaction (2008), panitumamab (Vectibix®) and cetuximab (Erbitux®), linking *KRAS* mutations with a lack of a treatment benefit in patients with metastatic colorectal cancer (2009) and clopidogrel (Plavix®), linking *CYP2C19* poor metabolizer status with a diminished antiplatelet response and higher cardiovascular event rates than *CYP2C19* extensive metabolizers (2009 and 2010). A representative listing of both new and previously approved drugs whose labels contain genomic information can be found in the online FDA Table of Genomic Biomarkers (www.PharmGKB.org).

Each label update has provided a unique opportunity to better understand the nuances of adding PGx to labels and the subsequent impact of label updates on adoption into clinical practice and diagnostic test reimbursement. The following represents some 'first in label updates' from the past 10 years along with some personal perspectives (www.aidsinfo.nih.gov/)

II.4.1 6-MP/TPMT

This was the first label to be updated in the last decade. There was a strong, mechanistically supported association between low TPMT enzyme activity (one in 300) and intermediate TPMT enzyme activity (11 in 100), increased concentrations of thioguanine derivatives at standard doses, and increased risk of myelosuppression. No specific doses of 6-MP were recommended in the label, although high- volume cancer centers (and later gastrointestinal practices) were developing dose-reduction schemas based on PGx and pharmacokinetic principles. TPMT testing does not obviate the need for monitoring complete blood count and platelet counts and looking for symptoms of myelosuppression. Clinical adoption of TPMT testing appears to be relatively low in cancer patients prescribed 6-MP (e.g., as compared with HER2 testing for trastuzumab) but there has been a more widespread uptake of TPMT testing in patients needing

immunosuppressive therapy, including those receiving other thiopurines (e.g., azathioprine) (Lesko LJ, 2002).

II.4.2 Irinotecan/UGT1A1*28

This was the first label update to recommend a specific dosing reduction based on PGx (at least one level dose reduction as defined in the package insert) in patients homozygous for *UGT1A1*28* because of an increased risk of neutropenia. There is a fairly well-understood causal link between dose, exposure levels of irinotecan's active metabolite, and its association with risk of neutropenia. There were no specific recommendations for prescreening patients before receiving irinotecan and clinical adoption appears to be progressing slowly (Lesko LJ, 2004).

II.4.3 Warfarin/CYP2C9–VKORC1

The first label update in 2007, which was based on a combination genotype, related to both the pharmacokinetics (*CYP2C9* gene variants) and pharmacodynamics (*VKORC1* gene variants) of the drug. It received a high amount of attention because of the widespread use of warfarin and the well-known risks of minor and major bleeding. The label did not dictate how physicians should change the dosage based on genotype. Clinical adoption appears to be relatively low at present; however, the 2007 warfarin label update was followed by a significant amount of new research to improve understanding of the role of genotype-guided dosing. This led to a 2010 update of the label in which specific ranges of initial doses were assigned to each genotype representing the expected steady-state maintenance doses (Lesko LJ, 2003).

II.4.4Carbamazepine/HLA-B*1502

This was the first label update to include a strong association between a serious adverse event, Stevens–Johnson syndrome, and inherited variant in the gene based on relatively few cases (<125). The mechanism is unclear but consistent with other gene–drug pairs in which hypersensitivity is of concern. The gene variant is found almost exclusively in patients with Southeast Asian ancestry, potentially allowing for targeted genotyping. There is a boxed warning to prescreen patients with ancestry in genetically at-risk

populations. Little is known regarding the clinical adoption of testing for carbamazepine, which may differ globally based on regional racial composition (Zineh I, 2009).

II.4.5Clopidogrel/CYP2C19

This was the first label update based on synthesis from multiple epidemiological data sources, including academic cohort studies and subgroup analyses of cohorts from prospective, randomized clinical studies. Pharmacogenetic associations were mechanistically supported and strengthened by observational drug–drug (CYP2C19) interaction studies. FDA regulatory scientists worked with clopidogrel's sponsor to generate specific data to answer outstanding questions regarding the pharmacogenetics of the active metabolite. In 2010, the label of clopidogrel was updated with a boxed warning to caution that poor metabolizers may not receive the full protection from heart attacks, stroke and cardiovascular death.

From these examples that we have discussed it is clear that an update of a label with genetic information by the FDA does not guarantee the adoption of genetic testing into the practice of medicine. The latter is too complex to expect that it would be that easy. However, assessment of risk–benefit is, and will continue to be, a central issue for the FDA, and labels represent a necessary vehicle to provide medically appropriate information on PGx. Patients and their healthcare providers need to be able to make informed decisions on whether or not genetic information is useful in a given clinical context (Contopoulos-Ioannidis DG et al., 2008).

II.5 Pharmacogenomics in drug developing:

There have been remarkable advances in the utilization of genomic data to guide drug discovery and development, especially in oncology field . Table 1 highlights the drugs with genotype-specific indications. In many cases, development of these drugs was focused around specific mutations, based on the role of the mutation in the cancer of interest. While the majority of drugs mentioned in Table 1 are for the treatment of cancer, there are two exceptions. One is maraviroc, which is indicated for CCR5-tropic HIV infection. The other is the newly approved ivacaftor, indicated to treat cystic fibrosis patients with the CFTR G551D mutation (Ramsey BW., et al 2011). Not only have there

been various drugs created through a genetically guided approach, it is well accepted in the clinical setting to test for the relevant genetic mutation or downstream protein expression, prior to use of these therapies. A number of factors likely contribute to the widespread clinical adoption of genetic testing to guide use of agents in Table 1.

These factors include strong data pointing to poor efficacy in individuals lacking the genetic mutation, or absence of data in those lacking the mutation but lack of efficacy is presumed in the absence of the mutation. Additionally, there are strong statements in the product labels that the drug should only be used in patients with specific mutations, and in many cases a genetic test has been codeveloped with the drug. The very high cost for most of these drugs also produces sensitivity within the medical and payor communities to use them only in those patients with the potential for benefit based on genotype.

Review of Table 1 may also be instructive regarding the future potential for genetically targeted drug development. The only drug on this list that was approved at the time of completion of the HGP is trastuzumab, for HER2-positive breast cancer, the poster-child for targeted therapy. Like trastuzumab, all but two of the drugs in Table 1 target somatic mutations in cancer. Cancer drug development will continue to be highly focused on targeted mechanisms, further aided by genomics and systems biology approaches (Rubin EH, 2012).

Maraviroc targets a specific mutation in the HIV virus, not human genetic variation. Only ivacaftor targets a germline mutation, and this is in the gene that causes the monogenic disease, cystic fibrosis. Thus, while there been substantial advances in genetic-guided drug development in the last decade, it has been almost exclusively in cancer. It is unclear whether cancer and infectious diseases represent the low-hanging fruit for genetically informed drug discovery and development and examples in common complex diseases will follow, or if such approaches will not be widely successful for discovery and development of drugs for common complex diseases. The latter seems more likely (Asselbergs FW et al., 2012).

The common, complex diseases have environmental and multiple genetic influences, with each gene contributing in smaller ways, thus it is quite possible that the targeted approach, focused on specific mutations, that has been highly successful in cancer will not see the same success for chronic disease treatments. However, it is possible that genes identified through genome-wide association and other studies may still identify important protein targets. Several examples come from lipid regulation and drug development for

treatment of lipid disorders, including CETP and CETP inhibitors, and PCSK9 and PCSK9 inhibitors Cohen J et al., 2005).

Polymorphisms in CETP and PCSK9 are associated with high levels of high-density lipoprotein and low levels of low-density lipoprotein, respectively and inhibitors of CETP and PCSK9 show promise for their ability to raise high-density lipoprotein and lower levels of low-density lipoprotein, respectively (Nicholls SJ et al., 2011). Though these drugs do not target the specific polymorphisms, the genetic literature supported these proteins as drug targets and the early data strongly support that they have the anticipated effects on the respective lipid subclass. The next decade will provide clarity about whether genetic/genomic-guided approaches to drug discovery and development will largely remain within therapies for cancer and infectious diseases, or will also become a common, widespread approach to the development of drugs for chronic diseases (Do RQ et al., 2013).

Table I. Drugs approved by the US FDA with genetic indications.

Drug	Indication	Gene(s)
Cetuximab	EGFR+/KRAS− metastatic colorectal cancer	EGFR and KRAS
Crizotinib	ALK+ non-small-cell lung cancer	ALK
Denileukindiftitox	CD25+ T-cell lymphoma (CD25 component of IL2-R)	IL2R
Everolimus	HER2-negative breast cancer	ERBB2
Ivacaftor	Cystic fibrosis with G551D mutation in CFTR	CFTR
Lapatinib	HER2 positive (hormone receptor+) Metastatic breast cancer	ERBB2
Maraviroc	CCR5-tropic HIV infection	CCR5
Panitumumab	Metastatic colorectal cancer KRAS negative	KRAS
Pertuzumab	HER2+ metastatic breast cancer	ERBB2
Trastuzumab	HER2+ overexpressing breast cancer	ERBB2
Vemurafenib	Metastatic melanoma with BRAF V600E mutation	BRAF

II.6 The Significance of Pharmacogenomics in Pharmacy Education and Practice:

Pharmacists considered as health care provider and drug expert, days by days the responsibilities for pharmacists expanded to include contributing the best drug of choice for individuals also have a role in drug toxicities and adverse drug reaction warning, depending on this duties expand, pharmacists could be the only health care provider have an ability to educate healthcare providers and patients about applying the results of pharmacogenomics test The healthcare system to educate providers and patients about interpreting and applying the results of pharmacogenomics testing. Pharmacists' education and background also enable them to participate in pharmacogenomics conceptual development and practice integration. The field of pharmacogenomics undoubtedly will present a great opportunity for providing individualized drug therapy with minimal risk and/or optimal drug therapy

Accrediting institutions such as the American Association of Colleges of Pharmacy (AACP), the American Society of Health-System Pharmacists (ASHP), and the American College of Clinical Pharmacy (ACCP) have recommended the implementation of coordinated pharmacogenomics educational requirements and supported efforts that assess patient outcomes, improve drug dosing, and predict therapeutic response academic and health care leaders need to plan to incorporate pharmacogenomics into their curricula and familiarize themselves with advancements
in the field of pharmacogenomics to ensure best health care delivery related to the drug therapies of the future.

As information regarding the genotype of an individual becomes increasingly important to safe prescribing and dosage selection, pharmacists might be expected to have greater knowledge of their customers' genetic information than they are now required to have. The increased amount of genetic information in pharmacies raises privacy and confidentiality concerns, especially when pharmacists belong to large pharmacy chains or corporations with widely accessible centralized records. For physicians and pharmacists, the issue of completing continuing professional education and maintaining accurate records of it will become more important, not only for improving competency but also for preventing liability (Liu LW et al., 2010).

III. Methodology:

The aim of the study is to evaluate the attitude, level of knowledge and adoption of pharmacogenomics in pharmacists in community pharmacies in North Cyprus. In order to achieve the aim a prospective cross-sectional study between July and September 2016 was conducted using structured questionnaire to collect data. The questions were asked before in Malaysia (Bannur Z, 2014), and a pilot study was conducted in North Cyprus on 10 pharmacists and to determine the applicability of the questionnaire. Prior to study, verbal consent was obtained from all participants. Pretested, structured and self-administered; mostly close ended questions were used. According to the sections of the questionnaire, the data were summarized and organized by using descriptive statistics.

The questionnaire was translated from English into Turkish by an expert and health professional who is familiar with the terminology of the area covered by the survey, then it was sent to two independent Turkish native speaker expert in translation, they translated the questionnaire backward into English to keep the equivalence of the questionnaire in the target language.

The questionnaire after modification consists of 25 questions and divided into five sections;

Section 1: Respondent demographics

Information on respondents' gender, age, years of experience, location of the school attended, and position were obtained.

Section 2: Attitude

The respondents' attitude on financial coverage on pharmacogenomics testing and their concerns over the confidentiality and discrimination issues were assessed.A 5-point Likert scale of strongly disagree, disagree, neutral, agree and strongly agree were asked on eight questions.

Section 3: Knowledge

Understanding on pharmacogenomics and five factual questions on knowledge were asked. Their knowledge on pharmacogenomics demonstrate if further education is needed.

Section 4: Adoption

The respondents' practice regarding to the pharmacogenomics, the benefits they have obtained, as well as the level of evidence required for recommendation of pharmacogenomics test.

Section 5: Education

Finally, prior education, desire and enthusiasm for pharmacogenomics education were obtained and more than one answer is possible in this part (more than one answer is possible).

Data analysis:

The data collected were analyzed using the Statistical Package of Social Sciences (SPSS) program version 20.0. The methods used to analyze the data include an analysis of descriptive statistic variables such as percentages and frequency for the categorical variables. The continuous variables were expressed by means and standard deviations and analyzed using the Mann–Whitney U testand Kruskal–Wallis test. Level of significance is $p < 0.05$.

Ethical Consideration:

Near East Institutional Reviews Board (IRB) of Near East University Hospital approved the study and assigned this research as being just observational study and just initials were used during the study without recording patient's location or other related not clinical essential individual data.

IV. Results:

IV.1 Demographics of Respondents:

One hundred forty survey instruments were distributed to community pharmacies in Northern Cyprus. One hundred three (68.7%) pharmacists completed the survey instrument. Most of the respondents were females (60.2%) while males were (39.8%). Age distribution of respondents showed that (20.4%) of the pharmacists are above 30 years old and those within 1-5 years of working experience forms 65% of respondents. The majority of the respondents were graduated from Cyprus (51.5%) and from Turkey (32%). The respondents' demographics are shown in Table II.

IV.2 Attitude of the respondents:

The majority of the respondents agree that the pharmacogenomictesting will help to decrease the number of adverse drug reactions (40.8%), while those who agree that pharmacogenomictesting will help to decrease the cost of developing new drugs were (47.6%).In response to the third question (56.3%) agree that the pharmacogenomic testing will help finding the optimal dose for warfarin patients in less time, and (57.3%) of the pharmacists who respond to the survey agree that pharmacogenomic testing will help to decrease the number of adverse reactions experienced by patients on warfarin.

Nearly quarter of the respondents (21.4%) disagreed that unauthorized persons may gain access to the results of a patient's pharmacogenomic testing, while the majority of the respondents (35%) normally believed that the pharmacogenomic testing may result in discrimination by employers or/and insurance companies. Around third of the respondents (27.2%) disagreed that having genetic information incorporated into the determination of your patient's initial warfarin dose, and (31.1%) of the respondents strongly agreed that if they were the patient being started on warfarin, would be comfortable to have genetic information incorporated into the determination of your initial dose of warfarin. The respondents' attitude are shown in Table III.

IV.3 Knowledge of the respondents:

The majority of the respondent (98.1%) agreed that subtle differences in a person's geneticmight have a major impact on how the person responds to medications, while (1.9%) disagreed. In responding to the second question of this domain of the survey,

(84.5%) of the respondents agreed that genetic determinants of drugs response change over a person's lifetime. Most (72.8%) of the respondents agreed that genetic variants can account for as much as 95% of the fluctuation in drug disposition and effects, while (27.2%) disagreed, (62.1%) agreed that the package insert for warfarin includes a warning about altered metabolism in patients who have specific genetic variants, and the majority (55.3%) disagreed that the pharmacogenomic testing is currently available for most medications (table IV) .

IV.4 Adoption:

Most of the respondents (87.4%) believe that patients' genetic profile influences drug therapy and (79.6%) of the respondents will order or recommend pharmacogenomic test in the future, (62.1%) feel adequately informed about availability of genetic testing and its application in drug therapy and (87.4%) rely on FDA labels in ordering or recommending pharmacogenomic test (table V).

IV.5 Education:

The most frequently sources of information were pharmacists (79.6%), then physicians and genetic test lab (31.1%), and those who received undergraduate education were (35.9%) and postgraduate education were (26.2%) while most respondents prefer continue education (50.5%) as an education method. For those who interest in pharmacogenomic education they prefer seminar or lecture (45.6%), and ward round (34%), followed by all day conference (30.1%) and the least one was CPE (15.5%), (Table VI).

There is a significant difference between 26-30 and > 30 years regarding the comparison in total attitude score ($P = 0.008$) and total knowledge score ($P = 0.004$), also a significant difference found between two group (1-5) and (6-10) years of experience ($P = 0.02$) (Table VII).

Table II. Demographic data of Respondents

Characteristics	(n=103)	Percentage Respondents %
Sex:		
Male	41	39.8
Female	62	60.2
Age:		
21 -25	42	40.8
26-30	40	38.8
31 and above	21	20.4
Years of Experience:		
1 to 5	67	65
6 to 10	22	21.4
11 to15	6	5.8
16 to 20	4	3.9
21 and above	4	3.9
School location		
Cyprus	53	51.5
Turkey	33	32
Other	17	16.5

Table III. Attitude of respondents on pharmacogenomics

	Strongly Disagree	Disagree	Normal	Agree	Strongly agree
In your opinion, how likely is it that pharmacogenomic testing will help to decrease the number of adverse drug reactions?	0 (0 %)	1 (1%)	40 (38.3%)	42 (40.8%)	20 (194%)
In your opinion, how likely is it that pharmacogenomic testing will help to decrease the cost of developing new drugs?	2 (1.9%)	8 (7.8%)	18 (17.5%)	49 (47.6%)	26 (25.2%)
In your opinion, how likely is it that pharmacogenomic testing will help to decrease the time it takes to find the optimal dose for warfarin patients?	0 (0%)	14 (13.6%)	9 (8.7%)	58 (65.3%)	22 (21.4%)
In your opinion, how likely is it that pharmacogenomic testing will help to decrease the number of adverse reactions experienced by patients on warfarin?	0 (0%)	12 (11.7%)	8 (7.8%)	79 (57.2%)	24 (23.3%)
How concerned are you that unauthorized persons may gain access to the results of a patient's pharmacogenomic testing?	10 (9.7%)	22 (21.4%)	29 (28.2%)	18 (17.5%)	24 (23.3%)
How concerned are you that the pharmacogenomic testing may result in discrimination by employers and/or insurance companies?	0 (0 %)	24 (23.3%)	36 (35%)	34 (33%)	9 (8.7 %)
How comfortable would you be having genetic information incorporated into the determination of your patient's initial warfarin dose?	15 (14.6 %)	28 (27.2%)	10 (9.7%)	24 (23.3%)	26 (25.2%)
If you were the patient being started on warfarin, how comfortable would you be having genetic information incorporated into the determination of your initial dose of warfarin?	15 (14.6%)	29 (28.2%)	8 (7.8%)	19 (18.4%)	32 (31.1%)

Table IV. Knowledge of respondents on pharmacogenomics

	Agree	Disagree
Subtle differences in a person's genome can have a major impact on how the person responds to medications.	101 (98.1%)	2 (1.9%)
Genetic determinants of drugs response change over a person's lifetime.	87 (84.5%)	16 (15.5%)
Genetic variants can account for as much as 95% of the variability in drug disposition and effects.	75 (72.8%)	28 (27.2%)
The package insert for warfarin includes a warning about altered metabolism in individuals who have specific genetic variants.	64 (62.1%)	39 (37.9%)
Pharmacogenomic testing is currently available for most medications.	46 (44.7%)	57 (55.3%)

Table V. Predictors of pharmacogenomic adoption

	Yes	No
Believe that patients' genetic profile influences drug therapy	90 (87.4%)	13 (12.6%)
Feel adequately informed about availability of genetic testing and its application in drug therapy	64 (62.1%)	39 (37.9%)
Ordered or recommended pharmacogenomic test	79 (76.7%)	24 (23.3%)
Anticipate ordering or recommending pharmacogenomic test in the future	82 (79.6%)	21 (20.4%)
Rely on FDA labels	90 (87.4%)	13 (12.6%)

Table VI. Sources of pharmacogenomics information by profession

	N	%
Drug labels	21	20.4
Internet	27	26.2
Genetic test lab	32	31.1
Pharmacists	82	79.6
Physician	32	31.1
Preferred education mode		
	N	**%**
Prior pharmacogenomic education	5	4.9
Undergraduate pharmacogenomic education	37	35.9
Postgraduate pharmacogenomic education	27	26.2
Continuing education	52	50.5
Seminar or workshop	26	25.2
Ward round	21	20.4
Education offering of interest		
	N	**%**
Ward round	35	34
Seminar or lecture	47	45.6
CPE	16	15.5
Web based CPE	18	17.5
Half day conference	25	24.3
All day Conference	31	30.1

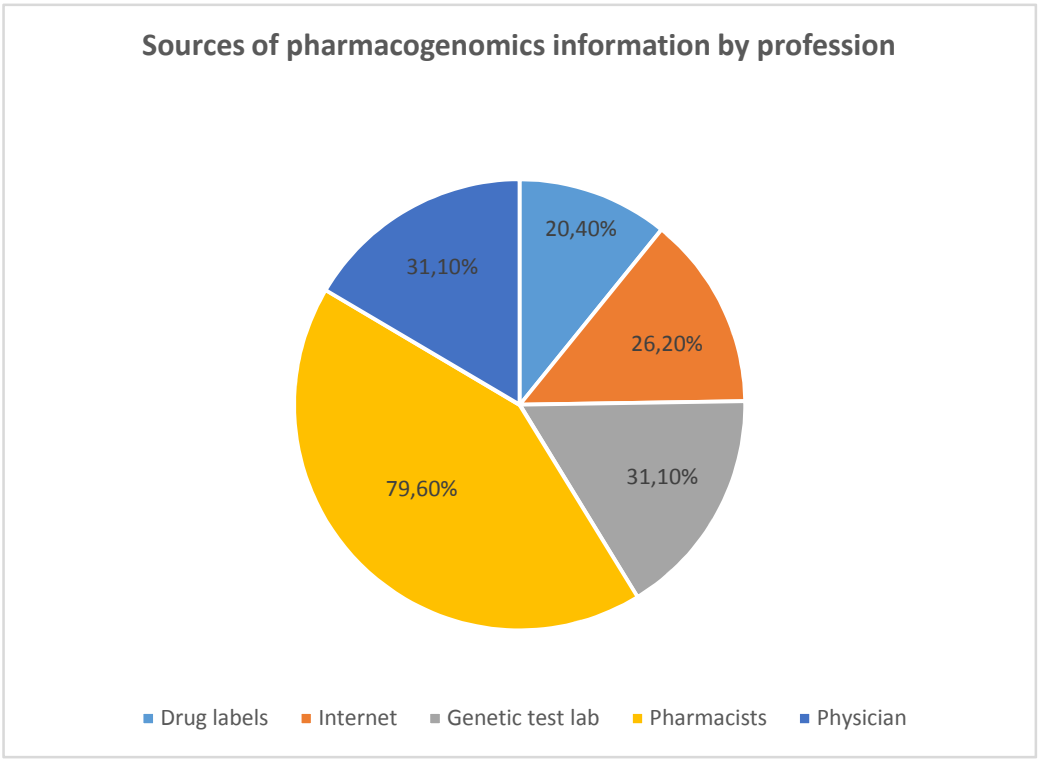

Figure 1. Sources of pharmacogenomics information by profession

Table VII. Association of the total attitude and knowledge scores with respondent demographics

	Total Attitude score			Total Knowledge score		
	Mean	**SD**	**P**	**Mean**	**SD**	P
Gender						
Male	29.1	5.4	0.222	6.4	0.83	0.675
Female	27.7	5.2		6.3	1.1	
Age						
21-25	28.4	5.1		6.4	1.1	
26-30	29.7#	5.4	0.008	6.6	0.74#	0.004
> 30	25.3	4.5		5.8	1.1	
Experience						
1-5	29.9*	5.3	0.02	6.4	0.93	0.9
6-10	25.8	4.3		6.3	1.1	
> 10	26.2	4.9		6.3	1.2	
School location						
Cyprus	29.3	5.4	0.19	6.4	0.97	0.6
Turkey	26.8	6.02		6.3	1.08	
Other	27.9	2.1		6.1	1.1	

 # P < 0.05 significant differences when compared to > 30 age group.

*** P < 0.05 significant differences when compared to 6-10 experience group.**

V. Discussion:

This study assess pharmacists' attitudes, knowledge and practice disclosures their limited knowledge concerning PG and pharmacogenetic testing. Pharmacists are furnished with professional drug knowledge and have been considered as valuable source of drug information, therefore, are well placed to play an important role in the application of pharmacogenomics (PG) in to clinical practice. This might prevent drugs related adverse events and improve patient consequences, despite the moral, privacy concerns and possible consequences of lifelong genetic-data.

Drug experts have long been considered as the drug experts amongst the healthcare providers. It has gone beyond hesitation that PG is progressing into additional essential means to ensure optimum pharmacotherapy in a developing zone of clinical practice (Roederer MW et al, 2012). Therefore, it is important that pharmacists are equipped to appropriately use pharmacogenetic information towards personalized drug therapy for suitable patients currently and beyond. The pharmacist assists many roles in the enactment of PG in the healthcare setting (Murphy JE et al, 2010).

Nearly quarter of the respondents (21.4%) disagreed that unauthorized persons may gain access to the results of a patient's pharmacogenomic testing, which is similar to the study done by Bannur Z et al, 2012 in Malaysia where lower percentage of the respondents (15.7%) believed that unauthorized persons may gain access to the pharmacogenetics test results and therefore, had less fear of privacy intrusion; compared to other studies of which the healthcare professionals, researchers and leaders of drug companies and regulatory agencies had more concerns on privacy intrusion while the majority of the respondents (35%) normally believed that the pharmacogenomic testing may bring about discrimination by employers or insurance companies which is comparable to another study where 38.7% of the respondents were concerned about the discrimination by employers and insurance companies due to their genetic profile (Hoop Jg et al, 2010).

Two different studies revealed that females had a significantly higher concern for discrimination ($p = 0.031$), in accordance with the findings in another study that revealed females were generally more afraid of the perceived risks.(Hedgecoe AM, 2006), but in contrast in our study no statistical significant difference were found between male and female for discrimination.

Around third of the respondents (27.2%) disagreed that having genetic information merged into the determination of your patient initial dose of warfarin, and (31.1%) of the respondents strongly agreed that if they were the patient being started on warfarin, would be comfortable to have genetic information assimilated into the determination of the initial warfarin dose.

A study by (Dodson C, 2011) show that 78.5% of respondents felt that adverse drug reactions would be decreased, while 81.5% felt that adverse drug reaction for warfarin would be reduced while in contrast in our study 40.8% agreed that the pharmacogenomictesting will help to decrease the number of adverse drug reactions while (57.3%) of the pharmacists who respond to the survey agree that pharmacogenomic testing will help to decrease the number of adverse reactions experienced by patients on warfarin. Those who agree that pharmacogenomictesting will help to decrease the price of developing new drugs were (47.6%) while 56.3% pharmacogenomic testing will help finding the optimal dose for warfarin patients in less time which is not comparable to the result obtained from study by Roederer MW, 2011 whereOnly a minority of the healthcare professionals felt that it would save time (23%) and cost (14.1%).

Some barriers to application of PG in to practice were described in this assessment, which contain among others; moral, discrimination, incomplete knowledge on PG, price, insurance exposure, secrecy, absence of clinical strategies, lack of clinical suggestions, authorization by regulatory bodies (Bannur Z et al, 2014). This is an agreement to similar review done on medical-doctor.Another observation is that, only one researcher used random sampling for retaining the applicants, and this might seriously affects the results due to probable biases from the investigators. Additionally, only three articles that reported the statistical authentication of the instruments used, therefore the rationality and dependability of the remaining researches are remained questionable as well as their outcomes. Additionally, more than half of the studies assessed have response rate of fewer than 60% for pharmacists which may confines the generalizability of the results.

V.1 Strength and limitation:

Obtaining 103 responses out of 140 distributed questionnaires could be considered as good response rate for this study, this number forming more than 40% of total licensed pharmacists in Northern Cyprus can be also considered as a reflective sample size.

A second strength of this study is that the surveyed pharmacists included those of all major cities in North Cyprus: Lefkosa, Magusa and Kyrenia.

An expert translated the questionnaire from English into Turkish and health professional who is familiar with the terminology of the area covered by the survey, then it was sent to two independent Turkish native speaker expert in translation, they translated the questionnaire backward into English to maintain equivalence of the test questionnaire in the target language.

Pharmacists who participate in the survey generally were positive toward pharmacogenomic tests, But also pharmacists who were not willing to participate may have had different views, especially those of older ages since majority of responders were young or middle aged.

Pharmacists receiving their degree in the decades prior may have different perspectives and lived experiences concerning applicability of pharmaceutical care services in Northern Cyprus.

There was no wide range of variations on pharmacist respond maybe due to close ageing and experiences also a question should be asked whether the positive attitudes and practice claims match with the reality of pharmacy practice in Northern Cyprus, which could be further studied with better objective tools.

Another limitation of the study that the survey administered only to community pharmacists in NC and other health care provider (physicians and nurses) should be included to see the gap between health care providers in pharmacogenomic.

VI. Conclusion:

Pharmacists in Northern Cyprus had positive pharmacogenomics orientations. This should encourage pharmacist bodies educators and regulatory agencies to design initiatives to increase the frequency and quality of practicing pharmacogenomics test in community pharmacy.

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Appendix I: Questionnaire in English

Demographic data of Respondents					
Sex		Male		Female	
Age	21-25		26-30		31 and above
Years of experience	1-5	6-10	11-15	16-20	21 and above
Location of school	Cyprus	Turkey			Other countries

Attitude and knowledge of respondents on pharmacogenomics					
	Strongly Disagree	**Disagree**	**Normal**	**Agree**	**Strongly agree**
In your opinion, how likely is it that pharmacogenomic testing will help to decrease the number of adverse drug reactions?					
In your opinion, how likely is it that pharmacogenomic testing will help to decrease the cost of developing new drugs?					
In your opinion, how likely is it that pharmacogenomic testing will help to decrease the time it takes to find the optimal dose for warfarin patients?					
In your opinion, how likely is it that pharmacogenomic testing will help to decrease the number of adverse reactions experienced by patients on warfarin?					
How concerned are you that unauthorized persons may gain access to the results of a patient's pharmacogenomic testing?					
How concerned are you that the pharmacogenomic testing may result in discrimination by employers and/or insurance companies?					
How comfortable would you be having genetic information incorporated into the determination of your patient's initial warfarin dose?					
If you were the patient being started on warfarin, how comfortable would you be having genetic information incorporated into the determination of your initial dose of warfarin?					

Knowledge		
	Agree	**Disagree**
Subtle differences in a person's genome can have a major impact on how the person responds to medications.		
Genetic determinants of drugs response change over a person's lifetime.		
Genetic variants can account for as much as 95% of the variability in drug disposition and effects.		
The package insert for warfarin includes a warning about altered metabolism in individuals who have specific genetic variants.		
Pharmacogenomic testing is currently available for most medications.		

Predictors of pharmacogenomic adoption and interest in education and preferred education mode					
				Yes	**No**
Believe that patients' genetic profile influences drug therapy					
Feel adequately informed about availability of genetic testing and its application in drug therapy					
Ordered or recommended pharmacogenomic test					
Anticipate ordering or recommending pharmacogenomic test in the future					
Rely on FDA labels					
Interest in pharmacogenomic education					
Internet		Drug labels	Genetic test lab	Pharmacists	Physicians
Preferred education mode					
Prior pharmacogenomic education	Undergraduate pharmacogenomic education	Postgraduate pharmacogenomic education	Continuing education	Seminar or workshop	Ward round
Education offering of interest					
Ward round	Seminar or lecture	CPE	Web-based CPE	Half-day conference	All-day conference

Appendix II: Questionnaire in Turkish

KatılımcılarınDemografikVerileri			
Cinsiyet	Erkek		
	21-25	26-30	
1-5	6-10	11-15	16
Kıbrıs'taDevletÜniversitesi	Türkiye'deÖzelÜniversite/Devletüni.		

KatılımcılarınFarmakogenomikBilgileriveTutumları			
	Kesinlikle Katılmıyorum	**Katılmıyorum**	**N**
rsilaçetkileşimleriniazaltmadakiolasılığınedir?			
çlarıngeliştirilmesineharcananbütçeyiazaltmadaetkilimidir?			
farin kullananhastalarda optimal dozutahliletmesüresiniazaltmaetkilimidir?			
n kullananhastalardakiyanetkileriazaltmabakımındanetkilimidir?			
etkisiolmayankişilerinsonuçlaraulaşabileceğikonusundaherhangibirendişenizvarmı?			
e/yasigortaşirketleritarafındanayrımcılıkyapılmasınasebepolabileceğikonusundakiendişeniznedir?			
elirlenmesiiçin genetic bilgilerineulaşmaksizirahatsızeder mi?			
langıçdozutayiniiçin genetic bilgilerinizinöğrenilmesindenrahatsızolurmuydunuz?			

Bilgi
rklılıkların, bireylerinilaçlaraverdiğitepkiüzerindeciddietkilerivardır.
elirleyicifaktörlerkişininyaşamsüresiboyuncadeğişiklikgösterebilir.
ndekifarklılıkların %95inde roloynayabilir.
olizmasıbozulmuşhastalariçin warfarin kutularındauyarıcıbilgilerbulunmaktadır.
niktestlermevcuttur.

Farmakogenomikbenimsemeveeğitimdekiilgininbelirleyicilerivetercihedileneğitimsistemi	
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Farmakogenomikeğitimeilgi				
Internet	İlaçetiketleri	Genetik test laboratuvarı	Eczacı	

Tercihedileneğitim

ikeğitimdenönce	Lisanssırasındafarmakogenomikeğitim	Lisansüstüfarmakogenomikeğitim	Sürekliğitim	Seminerveya workshop
İlgialanınayönelikeğitim				
kturları	Seminerveyaders	CPE	İnternet temelliCPE	Yarımgünlükkonferans