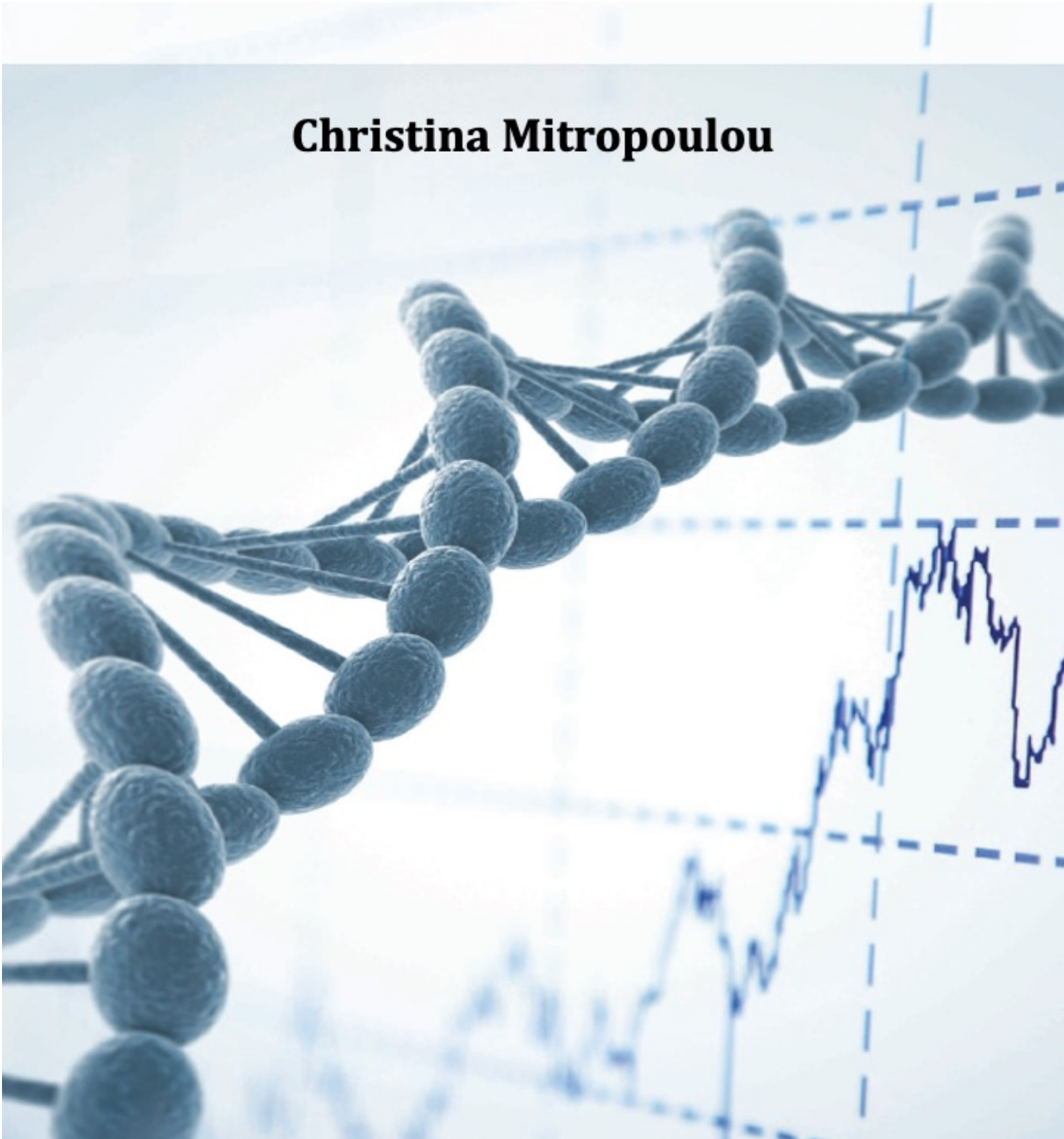
Economic evaluation of pharmacogenetics-guided interventions for cardiology

Christina Mitropoulou



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Economische evaluatie van farmacogenetica-geleide interventies in de cardiologie

Christina Mitropoulou

Colofon

Mitropoulou C

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Promotor

Prof. dr. R.H.N. van Schaik

Co-Promotor

Dr. A. Vozikis

Overige leden

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Prof. dr. T. van Gelder
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Abbreviations

ADP: adenosine diphosphate receptor blocker

ADRs: adverse drug reactions

AF: atrial fibrillation

AIS: acute ischemic stroke

BARC: Bleeding Academic Research Consortium

BD: bipolar disorder

BEP: break-even point

CBA: cost–benefit

CEA: cost-effectiveness analysis

CHADS2: cardiac failure, hypertension, age, diabetes, stroke2

CMA: cost-minimization analysis

COAs: coumarin oral anticoagulants

COI: cost-of-illness analysis:

CPIC: Clinical Pharmacogenetics Implementation Consortium

CUA: cost-utility analysis

DAPT: dual antiplatelet therapy (DAPT)

DTC: direct-to-consumer

EMA: European Medicines Agency

EGFR: epidermal growth factor receptor

ELSI: ethical, legal and social issues

FDA: Food and Drug Administration

FOA: foramen ovale apertum

GEM: genome economics model

GWAS: genome-wide association studies

HAART: highly active antiretroviral therapy

HIV-1: human immunodeficiency virus

ICER: incremental cost-effectiveness ratio

INR: international normalized ratio

LoF: loss-of-function (allele)

MAb: monoclonal antibody

MACCE: major adverse cardiovascular and cerebrovascular events

mCRC: metastatic colorectal cancer

MI: myocardial infarction

NICE: National Institute for Health and Care Excellence (UK)

PCI: percutaneous coronary intervention

PCR: polymerase chain reaction

PFS: progression-free survival

PGx: pharmacogenomics

PMI: precision medicine initiative (USA)

PSA: probabilistic sensitivity analysis

QALY: quality-adjusted life years

QWB: quality of welfare scale

SSRIs: serotonin reuptake inhibitors

ST: (acute) segment elevation

ST: stent thrombosis

STEMI: ST-segment elevation myocardial infarction

TIMI: thrombolysis in myocardial infarction

TPMT: thiopurinemethyltransferase

UI: uncertainty intervals

WTP: willingness-to-pay

Chapter 1

General introduction

1.1. The historic path to Pharmacogenetics

The central aim of Personalized Medicine is to exploit the individual's genomic information to support the clinical decision-making process (Manolio et al., 2013). Although the concept of Personalized Medicine is relatively new, its intellectual ancestors have been around for some considerable time. Thus, around 400 B.C., Hippocrates of Kos (460–370 B.C.) stated that "… it is more important to know what kind of person suffers from a disease than to know the disease a person suffers".

In 1956, Fredrich Vogel introduced the term "Pharmacogenetics" when describing the adverse effect of soldiers on primaquine, an antimalarial drug, appeared to be the result of a genetic defect in the G6PD enzyme. In 1962, Evans and coworkers described the genetic backround of peripheral neuropathy occuring when patients where treated with isoniazide, and linked this response to geentic variations in the *NAT2* gene. A major contribution in this field was the discovery by Richard Smith in 1977 about the genetic basis of the response to the antihypertensive drug debrisoquine. The enzyme involved, the cytochrome P450 2D6, is involved in the metabolism of approximately 20-25% of all drugs, and in fact appears to be absent in 5-10% of the population. In addition, 20-25% of the population has a low activity of this enzyme, whereas 2-4% has an increased activity, all due to different *CYP2D6* genomic variants. In 1985, Richard Weinshilboum reported the hereditary component of the thiopurine S-methyl transferase, which was subsequently linked to genetic variants in the *TPMT* (thiopurinemethyltransferase) gene.

The term used for this field is "Pharmacogenetics", that is the relation between hereditary factors and drug metabolizing capacity. Later, the term "Pharmacogenomics" was introduced, covering pharmacogenetics, but also including other genomic variants identified in the genome as well as mRNA expression profiles affecting drug metabolism.

Also in the early 2000, the term *Personalised Medicine* was introduced, while in 2015, the newest term "Precision Medicine" was introduced by former US President Barack H. Obama, who announced the US Precision Medicine Initiative (PMI).

While there are many definitions of the term, the concept of personalized medicine involves the combined knowledge of genetics to predict disease susceptibility, disease prognosis, or treatment response of a person to improve the person's health. Progress made in the development of personalized medicine in recent decades has coincided with health care systems placing greater emphasis on evidence-based clinical

practice, particularly as they are operating within an increasingly budget-scarce environment. It is often argued that personalizing treatment will inevitably improve clinical outcomes for patients and help achieve more effective use of health care resources. Hence, demand is increasing for demonstrable evidence of clinical utility and cost-effectiveness to support the use of personalized medicine in health care. (Shabaruddin et al., 2015).

Pharmacogenomics is a core component of Personalized Medicine and as such, it will be used as an example to highlight the application of economic evaluation in Personalized Medicine. Pharmacogenomics attempts to enrich our understanding of how medicines work in each individual based on genomic contributions to a medicine's safety and efficacy (reviewed in Squassina et al., 2010). The latter can lead to a more efficient and effective approach to drug discovery. Furthermore, pharmacogenomics may lead to a more diversified and targeted portfolio of diagnostics and therapies, which, when used together, would yield greater health benefits to society.

Pharmacogenetics is a term that refers to the study of the effect of genomic variations on drug response, in terms of both drug metabolism (pharmacokinetics) and drug action (pharmacodynamics). Additionally, genetic variants have been shown to explain what had previously been considered to be idiosyncratic adverse drug reactions (ADR). In other words, this discipline aims to identify the best medicine for a specific disease when the disease occurs in a patient population with a particular genotype. Considering the fact that there are genetic factors that account for 20-95% of the observed responses to drug therapies (Squassina et al., 2010), one could understand the impact of this new discipline in modern medicine. It is important to note that other factors such as age, food intake, drug-drug interactions, the simultaneous presence of other diseases (co-morbidity) influence an individual's drug response independent of, in conjunction with or in addition to genetic factors.

1.2. Aims of the thesis

The aim of the present thesis was to assess the health benefits of genome-guided treatment interventions, in comparison with the standard interventions used in the current medical practice. We focus on the economic analysis of pharmacogenomic-guided warfarin and clopidogrel treatment, particularly since in recent years cardiology

became the key medical specialty in which pharmacogenetics applications are emerging into practice. Furthermore, in this thesis, we investigated, through structural questionnaires, the views, opinions and attitudes of the various stakeholders and of the general public about genomic medicine and its impact to society. Lastly, we proposed an alternative methodological approach for cost-effectiveness analysis and developed a practical guidance for decision making by budget holders.

In **Chapter 2**, we provide some key examples of the applications of pharmacogenetics in modern medical practice, focusing on different medical specialties such as cardiology, oncology, psychiatric and infectious diseases and of these interventions that have been approved by all major regulatory bodies, such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Also, we emphasize the need to perform economic evaluation and its different types, summarize the main methodological aspects of economic evaluation and outline the few examples of economic evaluation in genomic medicine that have been performed so far. At first, we aimed to determine the level of awareness of healthcare professionals in Greece with respect to pharmacogenetics and personalized medicine using structured questionnaires addressed to a large number of pharmacists and physicians. These findings are presented in **Chapter 3**.

In **Chapter 4**, we sought to enrich our understanding over the policies and opinions of the key stakeholders involved in the translation of genomic findings in the clinic. To achieve our goals, we used the computerized version of the *PolicyMaker* political mapping tool to collect and organize important information about the pharmacogenetics and genomic medicine policy environment, to assess the policy's content, the major players, their power and policy positions, their interests and networks and coalitions that interconnect.

In **Chapter 5**, we present our findings from a prospective study to perform economic evaluation of genome-guided warfarin treatment in elderly Croatian patients suffering from atrial fibrillation, indicating that genome-guided warfarin treatment is cost-effective.

Similar to the previous chapter, in **Chapter 6**, we report our findings from a retrospective study to assess whether *CYP2C19*-guided genotyping was cost-effective for myocardial infarction patients receiving clopidogrel treatment in the Serbian population compared to the non-genotype-guided treatment. Our data show that clopidogrel

treatment coupled with *CYP2C19*-guided genotyping may represent a cost-saving approach for the management of myocardial infarction patients undergoing primary percutaneous coronary intervention in Serbia.

In **Chapter 7**, we propose the Genome Economics Model (GEM), which is a public health genomics-driven approach to adjust the classical healthcare decision making process with an alternative methodological approach of cost-effectiveness analysis. In particular, we combine the classical cost-effectiveness analysis with budget constraints, social preferences and patient ethics. This model provides the rationale to ensure the sustainability of funding for genome-guided interventions, their adoption and coverage by health insurance funds, and prioritization of the Genomic Medicine research, development and innovation, especially in those countries with budget restrictions, making it particularly appealing in developing countries and low-income healthcare settings in developed countries.

Lastly, in **Chapter 8**, we describe a new economic model, specifically for resource allocation for genomic medicine, based on performance ratio, with potential applications in diverse health care sectors. Similar to the previous model described in Chapter 7, this model also addresses the needs of developing countries and low-resource environments and takes into account the innovation and costs of the new technology/intervention and its relative effectiveness in comparison with social preferences.

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Chapter 2

Application of pharmacogenetics in clinical practice and its economic evaluation

2.1. Pharmacogenetics and treatment individualization

It has been known for decades that substantial inter-individual variability can occur in the clinical response to drug treatments for acute and chronic diseases. Approximately 50% of the patients respond satisfactorily to their medications, ranging from 25 to 60%, implying that the rest of the patient population is not receiving proper medication or is suffering from either marked therapeutic delays by switching from one medication to another until appreciable clinical benefit is attained, or worse serious adverse drug reactions (Spear et al., 2001). Furthermore, the side effects for the same therapeutic regime can be manifested in various degrees of severity, patterns and even time of onset. Adverse drug reactions (ADRs) represent a frequent event estimated to be between the fourth and sixth leading cause of death in the USA, with fatal ADRs occurring in 0.32% of patients (Davies et al., 2007). ADRs can be unpredictable, and a broader knowledge of predisposing biomarkers would greatly increase prevention capabilities.

It has been shown that the great heterogeneity in the phenotypic expression of the drug treatment response and ADRs might be determined by a complex interplay of multiple genetic variants and environmental factors (Squassina et al., 2010). This, in turn, increases the need for personalized prescriptions that should take advantage of the creation of a structured informational framework of phenotypic, environmental and genetic data, ultimately leading to the reduction of the high incidence of ADRs and therapeutic failure.

Pharmacogenetics has been defined as “the delivery of the right drug to the right patient at the right dose” (Piquette-Miller and Grant, 2007). Nowadays, pharmacogenomic-based techniques are used as diagnostic tools to select and/or dose currently available therapeutics. In addition, pharmacogenomic approaches are used to identify biomarkers and targets of currently prescribed medications as a source of new molecules suitable for drug-development process (Squassina et al., 2010). Ideally, pharmacogenomic tests would be proactively co-developed, together with new drug candidates (Giacomini et al., 2007). In this context, pharmacogenetics paves the path to personalized medicine, which consists of the implementation of genetic information to develop targeted therapies that, in turn, would allow the identification of those individuals unlikely to respond to a drug or likely to respond adversely to that same drug.

There are several medical specialties in which pharmacogenetics are currently being implemented, such that a number of pharmacogenomic tests have been approved by regulatory bodies, namely the United States Food and Drug Administration (FDA), and the European Medicines Agency (EMA). As a result, >150 drug labels nowadays include information for patients and clinicians on pharmacogenetics (https://www.fda.gov/Drugs/ScienceResearch/ucm572698.htm).

2.1.1. Pharmacogenetics for cardiovascular diseases

In recent years, the application of pharmacogenetics in the field of cardiology has grown quickly, particularly in relation to the clinical applications of two antithrombotic drugs, namely warfarin (and its analogs) and clopidogrel.

Coumarin oral anticoagulants (COAs), such as warfarin, acenocoumarol and phenprocoumon, are considered standard oral anticoagulant treatment for thromboembolic disorders for more than 60 years. However, COAs have a narrow therapeutic window and are associated with high risk of major bleedings, especially during the initial phase of treatment. There is substantial individual variation in response to COAs, necessitating frequent monitoring and dosage adjustment. As such, COAs are one of the leading causes of emergency hospitalizations worldwide (Pirmohamed, 2006).

Warfarin is the most commonly used anticoagulant in many countries worldwide, aiming to prevent and treat blood clots. Anticoagulation caused by warfarin is due to the inhibition of vitamin K epoxide reductase, an enzyme that activates vitamin K to produce anticoagulation factors II, VII, IX, and X. Warfarin is metabolized by the CYP2C9 enzyme. Cardiologists commonly prescribe it for patients with a history of atrial fibrillation, deep vein thrombosis, recurrent stroke, or pulmonary embolism, as well as in cases of heart valve replacements. A major challenge in treating patients with warfarin is that the optimal dose varies significantly from individual to individual. If the prescribed dose is too high, patients are in increased risk of serious bleeding while on the other hand, if the dose is too low, patients are at increased risk of having a thrombotic event that could result in a stroke or other vaso-occlusive events. The highest risk for these complications lies within the first 30 to 60 days after the beginning of warfarin treatment.

Individual characteristics and behavior, such as age, sex and diet, are some of the factors that account for the variation in warfarin dose across individuals although these factors account for at most 50% of the inter-individual variability (Flockhart et al., 2008). Importantly, genomic variants in the *CYP2C9* gene create variant alleles that have been found to reduce the activity of CYP2C9, thus decreasing warfarin's clearance. The variant *CYP2C9**2 allele decreases warfarin clearance by proximately 30% and *CYP2C9**3 allele by approximately 80%, when compared to the wild type *CYP2C9**1 allele. As a result, patients with a *CYP2C9* *1/*1 genotype require a daily mean maintenance warfarin dose of 5-7 mg, while *CYP2C9* *1/*3 heterozygote patients require lower doses (3-4 mg). *CYP2C9*1/*2* heterozygous patients should receive a lower daily warfarin dose (3-4 mg) if they also bear the *VKORC1* c.-1639 A allele in hetero- or homozygosity (Johnson et al., 2011). In various population groups, the variant alleles allele present with varying frequencies, with *CYP2C9**2 and *CYP2C9**3 being more common in European Americans, respectively, and less common in Asians and African Americans. In addition, genomic variants in the *VKORC1* gene, which encodes the production of vitamin K epoxide reductase, have also been shown to affect warfarin treatment. There are 5 *VKORC1* variant combinations (e.g., haplotypes) that are associated with altered *VKORC1* gene expression and as such with different warfarin dose requirements. The allelic frequencies of these *VKORC1* haplotypes also vary in different populations. The combination of the *CYP2C9* and *VKORC1* genomic variations appears to account for another 30-40% of inter-individual dose variation (Flockhart et al., 2008). Remaining unexplained variability could be due to other genetic variants, uncharacterized variants in other genomic loci as well as other personal or environmental factors yet to be identified. Currently available warfarin dosing calculators (e.g., warfarindosing.org) use a combination of clinical and genetic factors and have been demonstrated to be superior in predicting the stable warfarin dose when compared to clinical judgment alone (Johnson et al., 2011).

On average, one-third of the population carries one or both of the *CYP2C9* and *VKORC1* genomic biomarkers that are shown to be associated with slower warfarin metabolism, which in turn increases the likelihood of over-anticoagulation and the associated risk of serious bleeding. It is important to note that individuals who are 'wild type' require slightly higher warfarin doses than the recommended starting dose (6 mg/day compared to 5 mg/day). Currently, the appropriate dose is determined by

regularly monitoring the anticoagulation levels through blood tests and decreasing or increasing the warfarin dose if the international normalized ratio (INR) is too high or too low, respectively. As such, pharmacogenetics testing could potentially identify the patients that are likely to present with slower warfarin metabolism that could influence both the dose of warfarin as well as the recommended timing of INR studies. This may be a cost-effective way to reduce bleeding events from warfarin as demonstrated in an economic modeling analysis based on the results of a small prospective study (Meckley et al., 2010).

According to previously published reports, in 2004 and 2005, side effects from just three drugs were responsible for a third of all emergency hospitalizations by seniors (>65 years old) in the United States, who experienced adverse reactions to these medications. Warfarin was one of these drugs, accounting for 58,000 emergency hospitalizations per year. Also, the Adverse Event Reporting System of the United States Food and Drug Administration (FDA) provides evidence that warfarin is among the top 10 drugs with the greatest number of serious adverse drug reactions. Literature reports of major bleeding frequencies for warfarin vary from as low as 0% to as high as 16%. On the basis of these data, the FDA added a new black-box warning to the warfarin label in 2006. Also, in August 2007, the U.S. Food and Drug Administration updated the warfarin product label to add pharmacogenetics information and in January 2010, the FDA added specific instructions on how to use genotype to predict individualized doses: the new label provides a concise table of dosing recommendations, stratified by genotype. However, to date the FDA black box warning doesn't require that pharmacogenetics testing be done prior

to initiation of Warfarin. An evidence-based practice guideline for pharmacogenetically informed warfarin dosing has been published by the Clinical Pharmacogenetics Implementation Consortium (Caudle et al., 2014).

Another drug that is the standard for the care of acute coronary syndromes is clopidogrel. Non-responsiveness to clopidogrel is widely recognized and is related to recurrent ischemic events; approximately 25% of patients receiving clopidogrel experience a subtherapeutic antiplatelet response associated with increased risk of recurrent ischemic events (Gladding et al., 2008). Current experimental evidence suggests that the response to clopidogrel may be determined by the *CYP2C19* genotype (Geisler et al., 2008). In particular, *CYP2C19*2* allele, leading to impaired CYP2C19

function, is associated with a marked decrease in platelet responsiveness to clopidogrel (Hulot et al., 2006; Mega et al., 2009). In 2009, the FDA highlighted the impact of *CYP2C19* genotype on the clopidogrel's pharmacokinetics, pharmacodynamics and clinical response.

2.1.2. Pharmacogenetics for cancer therapeutics

Individualized therapies for various types of solid tumours are now a reality. Trastuzumab, a monoclonal antibody (MAb) blocking v-erb-b2 erythroblastic leukaemia viral oncogene homolog 2 (HER2, also ERBB2) receptors, is one of the commonest therapeutic modalities for breast cancer. Pharmacogenomic testing is an integral part of the treatment of breast cancer with trastuzumab. In this case, variable expression of the *HER2* receptor gene determines the likelihood a patient to respond to trastuzumab. HER2 is overexpressed in approximately one-fourth of breast cancer patients; its overexpression is correlated with poor prognosis, increased tumour formation and metastasis, as well as resistance to chemotherapeutic agents. HER2 testing predetermines patients who overexpress HER2 and who will likely respond to trastuzumab.

Erlotinib and gefitinib are tyrosine kinase inhibitors that have been on the market for several years and are designed to target the epidermal growth factor receptor (EGFR), which has been shown to play a role in predisposing to lung cancer. EGFR mutations are often employed as predictors of the progression-free survival with gefitinib in a comparison with carboplatin-paclitaxel (Mok et al., 2009). Another study has demonstrated the feasibility of genetic screening for *EGFR* gene variants in patients with advanced Non-Small-Cell Lung Cancer (NSCLC) for the selection of patients that are eligible for erlotinib therapy (Rosell et al., 2009). Taken together, these reports suggest that first-line tyrosine kinase inhibitors agents should be considered for carefully selected subgroups of patients affected by NSCLC.

Other MAbs that are used for (metastatic) colorectal cancer (mCRC) treatment are cetuximab and panitumumab, both directed against EGFR. Mutations in K-ras are thought to cause acquired activation of the Ras/Raf/MAPK pathway, independent of EGF binding. This in turn leads to a lack of activity of EGFR inhibitors (Lievre, Bachet et al., 2006). The

relationship between K-ras mutations and survival investigated in mCRC patients treated with cetuximab showed that the presence of a K-ras mutation was an independent predictor for shorter progression-free survival (PFS) and overall survival (Lievre, Bachet et al., 2008). A similar relationship between the presence of a K-ras mutation and lack of response was also demonstrated with single-agent panitumumab (Amado et al., 2008). In addition to K-ras, increases in *EGFR* gene copy number have been correlated with tumour response rate (Sartore-Bianchi et al., 2007).

Irinotecan is another drug that has been approved for the treatment of advanced colorectal cancer and with limiting adverse reactions, such as diarrhoea and severe neutropenia. The *UGT1A1*28* polymorphism, characterized by the presence of an additional TA repeat in the TATA sequence of the *UGT1A1* gene promoter, ($[TA]_7$, instead of $[TA]_6$; (Iyer et al., 2002)), is associated with reduced *UGT1A1* gene expression and decreased glucuronidation of the active metabolite SN-38, resulting in increased toxicity due to increased blood levels of the active metabolite. Patients homozygous for the *UGT1A1*28* allele are at higher risk of developing irinotecan-associated neutropenia and diarrhoea. The FDA recommended an addition to the irinotecan package insert to include *UGT1A1*28* genotype as a risk factor for severe neutropenia.

The antileukemics 6-mercaptopurine and 6-thioguanine, along with the immunesuppressant azathioprine, are being metabolized by the thiopurinemethyltransferase (TPMT) enzyme. Patients with inherited TPMT deficiency suffer severe (potentially fatal) hematopoietic toxicity when exposed to standard doses of thiopurine drugs. A pharmacogenomic test, classifying patients according to normal, intermediate and deficient levels of TPMT activity, enables physicians to predetermine patients' TPMT activity levels based on whether or not they have inherited the alleles associated with TPMT deficiency. Concordance between genotype and phenotype approaches 100%. Patients classified as having normal activity are treated with conventional doses, while lower doses [from 50% (intermediate metabolizers) to as low as 10% (poor metabolizers) of the normal dose] are administrated to avoid toxicity in deficient and intermediate patients, who are liable to suffer exaggerated, potentially life-threatening toxic responses to normal doses of azathioprine and thiopurine drugs (Relling et al., 1999). The *TPMT* genetic test has been well established as an invaluable tool for the effective clinical management of patients with acute lymphoblastic leukaemia

(ALL), allowing the treating physician to adjust the treatment dosing according to the patient's *TPMT* genotype.

2.1.3. Pharmacogenetics for infectious diseases

Pharmacogenetics for infectious diseases is an expanding area that is gradually assuming an important role in predicting adverse effects caused by treatments, particularly antiretroviral drug therapies (Picard and Bergeron, 2002). Nowadays, highly active antiretroviral therapy (HAART) enhanced the battery of HIV treatment modalities, which displays, though, certain adverse drug reactions, usually characterized by short and long-term toxicities, depending on the class of antiretroviral agent used. One of the most well-known examples of ADEs involves the drug Abacavir. Abacavir is a synthetic carbocyclic nucleoside analogue with inhibitory activity against human immunodeficiency virus (HIV-1). It, in combination with other antiretroviral agents, is indicated for the treatment of HIV-1 infection. Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir. Studies of patients who experienced an abacavir associated ADE identified an association between the ADE and a specific genetic variant in the HLA complex, HLA-B*57:01. Patients who carry the HLA-B*57:01 allele are at high risk for experiencing a hypersensitivity reaction to abacavir [Hughes et al., 2008; Mallal et al., 2008; Saag et al., 2008]. Approximately 0.5% of patients who are HLA-B*57:01 negative will develop hypersensitivity, while >70% who are HLA-B*57:01 positive will develop hypersensitivity. The FDA issued an alert in July of 2008 about this and information was added to the boxed warning [FDA, 2014]. Also, the *CYP2B6*:c.516G/T variant is a potential pharmacogenomic marker for adverse drug reactions in patients treated with efavirenz (Haas et al., 2004) while the *MDR*1:c.3435C/T genomic variation can be also predictive to antiretroviral therapy response (Brummeet al., 2003).

2.1.4. Pharmacogenetics for psychiatric diseases

The identification of key phenotypic measures of response to psychotropic medication is a major issue in psychiatry. As a consequence, pharmacogenetics and

personalized medicine is still far from being achieved in the field of psychiatry (Alda, 2013).

Promising results point to pharmacogenomic variation in elements of pharmacokinetic pathways (cytochrome P450 isoenzymes) at least as predictor of serum drug levels. Indeed, antidepressants and antipsychotics are mainly oxidized by CYP2D6, CYP1A1, CYP3A4, CYP2C9 and CYP2C19. A number of studies reported that *CYP2D6* gene polymorphisms predict side effects of the antipsychotic risperidone but do not predict response to it or to clozapine (reviewed in Tsermpini et al., 2013). In addition to predicting metabolic capacity, genotyping of the *CYP2D6* gene can also assist health professionals in the decisional process of identifying those patients who need to be monitored for serum levels or for the possible onset of ADRs. A number of findings have also shown that *CYP2D6* genetic variants correlate with serum levels of risperidone and the antidepressants venlafaxine, nortriptyline and paroxetine (Charlier et al., 2003; Scordo et al., 2005).

As far as atypical antipsychotics are concerned, pharmacogenomic studies have mostly focused on the serotonin system reporting association for the *HTR2A* and *HTR2C* serotonin receptor genes (Arranz and de Leon, 2007). Given the use of selective serotonin reuptake inhibitors (SSRIs) as current standard treatment for depression, the majority of pharmacogenomic studies have focused on serotonin system genes reporting significant association for the 5-HTTLPR polymorphism of the serotonin transporter (*SLC6A4*) gene [81-88] as well as for polymorphisms in *HTR2A* and *HTR1A* genes (reviewed in Squassina et al., 2010).

Finally, lithium chloride is a mood stabilizer with antisuicidal effects, and currently represents the mainstay of the management of acute-mania and maintenance treatment in bipolar disorder (BD) (Aral and Vecchio-Sadus, 2008;Yatham et al., 2013). However, due to the complexity of the response, pharmacogenomic studies on lithium response have so far produced little evidence (Severino et al., 2013), while genome-wide association studies (GWAS) of lithium treatment response identified few genetic determinants of lithium response using narrow criteria for the phenotypic characterization of treatment response (Perlis et al., 2009; Squassina et al., 2011; Hou et al., 2016).

2.2. The need for performing economic evaluation

A health care system aims to provide high-quality health services to their defined population on an equal basis and also to produce a large number of health services to meet the needs of the population (Drummond et al. 2005). The goal of the health care system is to find the best combination of available options in order to maximize the welfare of the society under conditions of limited resources.

Achieving these goals of the healthcare system is impeded by certain factors, which are, amongst others, the following:

(a) The demographic problem: Increase of life expectancy leads to fewer active workers to support the system relatively to the many more retirees in societies (**Fig. 2.1**).

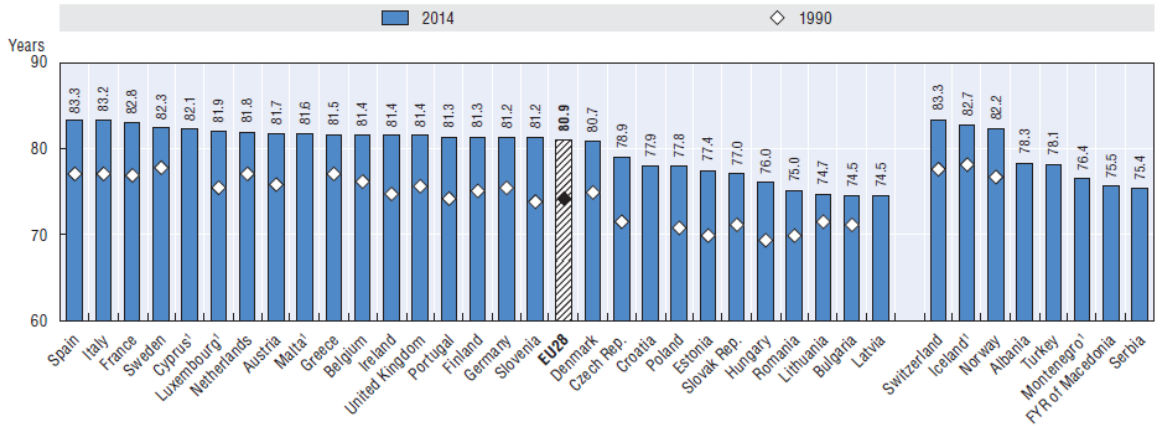

Figure 2.1. Life expectancy across EU countries increased by over 6 years between 1990 and 2014. Source: *Eurostat Database completed with data from OECD Health Statistics 2016*

(b) The modern unhealthy lifestyle, including carbohydrate-rich foods, sedentary lifestyle, use of alcohol, smoking, lack of exercise, poor diet, excessive consumption of drugs etc., which cause chronic diseases and complications that can only be treated at significant costs and with mediocre therapeutic results,

(c) The financial costs imposed by the technological advances in health services. Usually businesses bear very high R&D costs, which they wish to transfer to the end consumer or the public insurance funds, while also making some profit since they are for-profit enterprises,

(d) The extended average lifespan. Usually, older people suffer from multiple conditions and chronic diseases, with higher treatment costs,

(e) The public's expectations. It is the expressed conviction of a democratic state that the citizens' needs must be met with no particular consideration to the cost. Furthermore, the citizens' demands have increased, thanks to the improved educational systems and the cheap and widely available communication/information channels, such as the Internet, among others,

(f) Medical errors. These can be harmful or fatal for the patient and it is estimated that medical errors cost billions of Euros and thousands of lives each year (Van Den Bos et al, 2011)

Because all of these factors constitute a direct or indirect financial burden in modern health care systems, governments believe that the money spent for health care is excessive and that priorities must be set, or the ratio at which the state and the patient share these expenses must be amended. Also, in many countries, the share of GDP allocated to health has stabilized or decreased since 2009 (OECD Health Statistics 2016).

Economic evaluation attempts to rationalize the process of achieving the goals of the healthcare system. It must be underlined that an absolute restriction of health care expenditures is a difficult goal from a social point of view, whereas a reduction in the rate of expenditure growth is easier to achieve. Therefore, the aim of economic evaluation is not necessarily to restrict health care expenditures, but rather to rationally distribute the available resources in such a way to achieve the best possible level of health of the population, based on certain societal criteria. In certain cases, such criteria may lead to an increase in expenditures when this is financially viable or socially acceptable (Fragoulakis et al, 2015). If the ultimate goal were to reduce expenditures, then the state would simply cease to provide health care services to certain citizens, which would achieve immediate savings but would inflame the public sense of justice and would strain social cohesion. Such expenditure restrictions are socially justified and financially effective only if they include a substantial restructuring of the system to save resources without reducing benefits.

In conclusion, economic evaluation of health services is a systematic evaluation of the benefits and cost arising from the comparison of different health technologies. The

basic tasks of the economic evaluation are to identify, measure, value and compare the costs and consequences of the alternatives.

2.2.1. Types of economic evaluation

There are different types of economic evaluation, each one of which is used for a different purpose based on the goal that each time needs to be achieved. These types of economic evaluation are outlined below (Muenning, 2008; Phillips, 2005).

Cost–benefit analysis (CBA): A method of comparing the costs and the money-valued benefits of various alternative courses of actions. Systematic comparison of all these relevant costs and benefits of proposed alternative schemes with a view to determining which scheme or combination of schemes maximizes the difference between benefits and costs.

Cost-effectiveness analysis: Cost-effectiveness analysis (CEA) is used when benefits are difficult -from an ethical or technical point of view- to be valued monetarily which is the usual case in the health care sector (Canning, 2009). It is similar to cost-benefit analysis except that the benefit instead of being expressed in monetary terms is expressed in clinical result achieved (e.g., life years gained). For instance, these can be the number of lives saved or number of days free from the symptoms of the disease. There may be units that are specific to the procedures being compared, such as the speed of a healing wound or generic, such as Quality-Adjusted Life Years (QALY), thus enabling comparisons of cost-effectiveness to be made across many different technologies in different disciplines and patient groups (Ramsey et al, 2015). This type of analysis is most frequently used in the economic evaluation of the health care technologies and was also used in Chapters 4 and 5 of this thesis.

Cost-minimization analysis: Cost-minimization analysis (CMA) is the type of analysis used when two or more treatment alternatives achieve the same outcomes. However, it is difficult to justify if two alternatives offer the same level of effectiveness (Briggs & O'Brien, 2001).

Cost-of-illness analysis: Cost of illness (COI) analysis aims to assess the overall economic effects of illness and disease on individuals, the healthcare services, the economy and

society overall. A narrow interpretation of the cost imposed by illness focuses merely on the financial consequences of poor health, such as lost earnings from work, expenditure on healthcare services, medications, etc.

Cost-utility analysis: Another type of analysis we might use in the economic evaluation is the cost-utility analysis (CUA). The results of CUAs are typically expressed in terms of the cost per year gained or cost per QALY gained. This analysis represents the most widely form of economic evaluation.

2.2.2. The cost-effectiveness plane

If a standard health technology or intervention that is currently used by the healthcare system is compared against a new health technology with CEA (used in **Chapters 5 and 6** of this thesis), this will result in the following scenarios (Black, 1990):

1. The new technology is more expensive but is also more effective than the standard one, which constitutes the most common scenario (Quadrant I),
2. The new technology is considered to be "dominated by the standard technology", as it is more expensive and offers less effectiveness. In this case, the new technology is rejected (Quadrant II),
3. The new technology is less expensive than the standard one but also associated with less effectiveness (Quadrant III), and
4. The new technology provides more effectiveness and it is associated with lower costs. In this case, the new technology is considered to "dominate the standard one" and is accepted (Quadrant IV; **Fig. 2.2**).

The tool which is used for CEA is the incremental cost-effectiveness ratio (ICER). ICER is given by the difference in costs between two health care programs divided by the difference in outcomes between a new health care program and the existing approach to dealing with the same patient group. (Gafni et al, 2006)

The ICER provides a measure of average cost per additional unit of effectiveness. A common measure of effectiveness is the "quality-adjusted life-year" (QALY). Quality is often measured on a scale of 0 to 1, or of 0 to 100, where 0 is the "worst possible" and 100 is the "highest or best possible" state of health. A "quality-adjusted life-year" is a

period of one year weighted by the quality of life that the patient is experiencing when suffering from a disease or when improving as a result of a treatment, used in deciding whether a new program should be adopted.

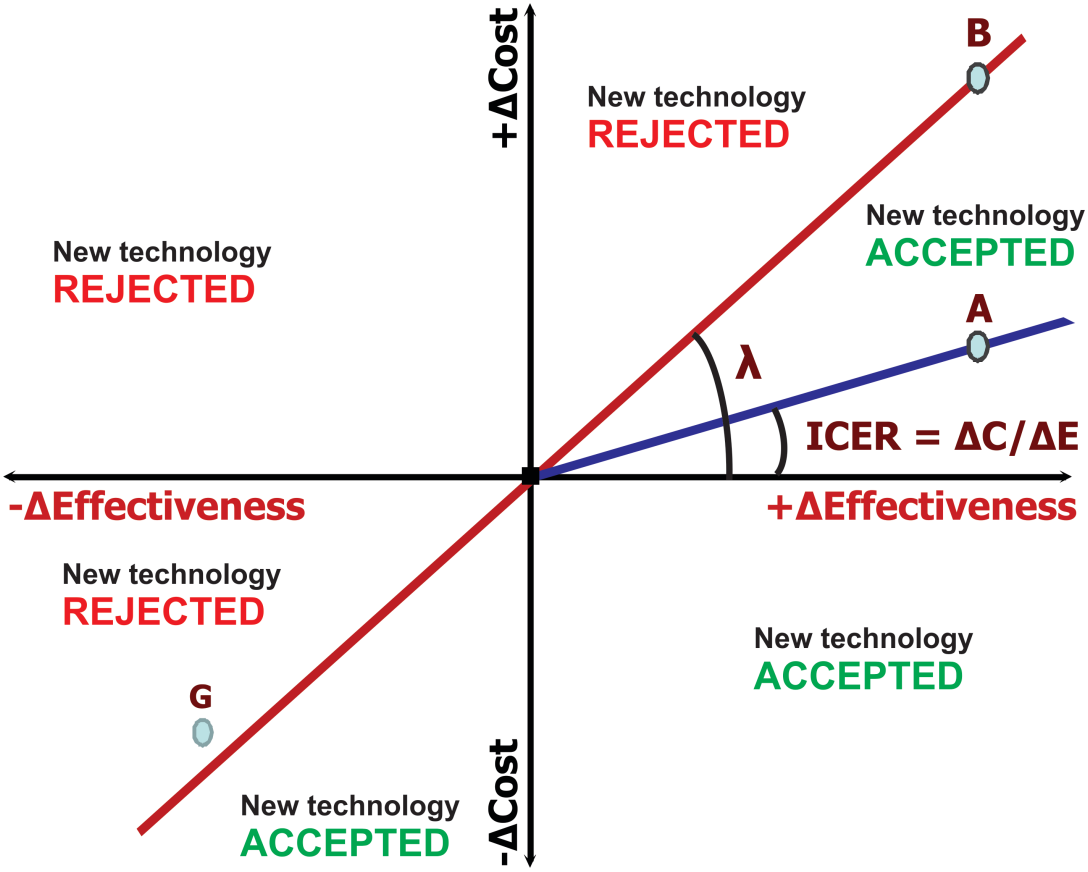

Figure 2.2 Depiction of the cost-effectiveness plane.

2.2.3. The size of the ICER and the relationship with Willingness To Pay

The ICER is intended primarily to provide information during the decision-making process in the case of more expensive and more effective treatments, which is the most common scenario. Nevertheless, the ICER calculation by itself does not allow conclusions to be drawn about the cost-effectiveness of the various options. Such conclusions require a quantitative criterion (measured in €/year or $/year), below which an option is considered effective and above which the option is rejected (Cantor, 1994; Willan et al, 2001).

The estimation of this indicator remains a subject of extensive debate with a lot of issues to be solved (Donaldson et al, 2002; Gafni et al 1998; Gafni et al, 2006; Smith et al 2005, Birch et al, 2006; Sendi et al, 2002; Waillo et al, 2009).Indeed, even large organisations such as the UK National Institute for Health and Care Excellence (NICE) have yet to announce a clear decision on its "correct" size (Towes, 2009; Dakin et al, 2014). In various other countries, however, willingness-to-pay (WTP) values have been proposed for the "purchase" of one year of life, in order to provide a transparent criterion for this difficult undertaking (Pauly, 1995). According to the World Health Organization, the desired value for the indicator is approximately three times the average per capita income of the country (Eichler et al., 2004). For the UK, a value between £40,000 and £60,000 is the maximum accepted value in most cases. A value between $50,000-$100,000 is considered cost-effective, a value below €20,000 is considered particularly attractive whereas values above €100,000 are considered particularly costly and are rejected (Devlin & Parkin, 2004). In economic theory another process to determine the value of λ is as follows: to rank all the available health care technologies from the lowest to the highest ICER and selected in descending order until the resources are exhausted (the league table approach; Birch & Gafni, 2006).

In practice, in those countries where CEA is used as a tool for resource allocation, budget impact analysis is usually performed. Budget impact analysis is the estimation of the budget impact after the adoption of a new technology in a health care system. Budget impact analysis often follows a cost effectiveness analysis. It is a forecast with their financial impact on the budget. In some cases, although a new technology is cost effective, it may not be acceptable based on the budget criteria. We have further looked into budget allocation and λ in **Chapters 7 and 8**.

2.2.4. Purpose of the analysis and cost determination

The study perspective is a key factor when determining the cost categories that will ultimately be involved in the analysis (Barber et al, 1998). The selected approach and the cost categories will not always be the same but will vary depending on the purpose of the analysis. For example, if the purpose of the analysis is how the resources will be distributed between various sectors of the economy such as education, health, defence,

etc, then a cost-benefit analysis must be performed in order to determine all the consequences of the relevant options. If, in other case, the analysis focuses on distributing resources between different sectors of health care (prevention, treatment, etc.) or between different interventions for the treatment of a specific condition, then the consequences to be measured will be more limited. The selection of analysis method is also affected by the person or institution (patient, hospital, insurance carrier, etc.) performing the analysis and by the availability of relevant data. In practice, economic evaluation is used for analyses for alternative interventions within a disease and less for interventions involving different sectors of the economy. For example, if the study concerns an insurance carrier, then the analysis is done from the perspective of the insurance fund and supplier charges are examined, whereas if the study focuses on all possible consequences then the perspective is social. The social perspective includes all possible consequences with no regard to who pays for them. If the analysis concerns an employer, then it would include the charges for insurance costs and loss of employee productivity. In this case, costs such as transfer to the hospital, feeding costs etc, which are covered by the employee, will not be included in the analysis while costs related to loss of productivity or temporary personnel would be included.

In general, all the cost categories are presented below:

Direct costs: the actual cost consumed for the intervention

- *Direct healthcare costs*: the cost caused by healthcare suppliers (the total expenditures for monitoring, treatment, diagnostic tests, medication, etc. which result from the treatment)
- *Direct non-healthcare costs*: expenditures arising for the patient as a result of the disease as well as the treatment-seeking process (home help costs, travel expenses, special diet expenses, etc.)

Indirect costs: Financial losses which are a result of the disease and do not include the costs for providing treatment. Indirect cost essentially refers to the loss of productivity because of the disease, either because of work absenteeism or because of reduced productivity. It usually includes lost productivity, free time, time expended by relatives providing assistance, etc.

Intangible costs: a term which describes hard-to-measure consequences of the disease and its treatment. It is due to the pain, discomfort, reduced quality of life or other social or moral consequences of the disease or the treatment.

It should be noted that the concept of intervention "cost" in economic evaluation refers to the "total resources" expended to treat the disease and is not limited to the cost of a specific technology e.g. the price of the drug. This cost may vary significantly depending on the institution's perspective and can increase considerably as we move to broader analyses of the consequences of the disease. Treatments in oncology, cardiology etc. follow a specific pattern of administration, are given in regimens together with many other drugs, and are associated with toxicity and side effects with various probabilities of occurring and very high management costs. In this case, a simple comparison of the price of two drugs is usually misleading because it does not take into account the effect their administration has on the overall burden to the system through utilisation of all the relevant resources, such as hospitalisation days, medication given to treat toxicities, etc.

2.2.5. Gathering information for effectiveness

For the economic evaluation, one needs to accurately and reliably estimate the effectiveness of each intervention. In many cases one can refer to various sources in order to estimate the effectiveness of a treatment, and each of these sources may have different advantages and disadvantages. The ranking of such sources reflects, in part, the reliability of the data collected, and therefore the quality of the analysis results.

The best-known source is the **clinical trial**, which belongs to a wider class of studies called "controlled experiments". Clinical trials are scientific experiments with people who suffer from a disease, that assess the difference in response between a new treatment and an alternative. The second source of data is **meta-analysis**. Meta-analysis is a statistical technique aimed at summarizing results obtained from clinical trials (Petiti, 1994). It constitutes original research and draws its information from the clinical trials included in the analysis. **Databases** are repositories of data and records accumulated in the daily operations of large organizations. Depending on the organization they may include data that encompasses much of the care provided to patients or insured persons. **Medical records** are records kept by treating physicians for

therapeutic or scientific purposes and may be electronic or physical. Also, **expert panels** are a qualitative method for determining effectiveness, based on the opinions of expert physicians from each field (Cialkowska et al., 2008).

2.2.6. Measuring quality of life

Cost–utility analysis uses various indices and tools to measure the quality of the patient's life, in order to adjust the result according to patient quality of life (Torrance, 1986). A common measure of measuring quality of life is the Visual analogue scale and the time trade off (TTO) method.

Some of these methods are used for specific diseases, whereas others seek to evaluate a patient's general state of health. Some are based on simple indices while others are more comprehensive but also more difficult to assess. The subjects in such studies are usually patients, but may also be health professionals, such as nurses or physicians, or the general population. Quality assessment may be done directly or indirectly through the use of certain characteristics of the treatment groups and the creation of empirical utility functions by professional investigators. Examples of such efforts are the EuroQol EQ-5D Health Utility Index, the Quality of Welfare Scale (QWB), the SF-36, etc. Because of the importance of the quality of life, and because this type of analysis will facilitate broad comparisons between different medical interventions by reducing them all to a common measure of value (the QALY), cost–utility analyses are becoming more and more common, and many organisations such as the UK National Institute of Health and Care Excellence (NICE) encourage their use.

2.2.7. Model types

By 'modelling' or 'models', we refer to a visual representation (usually presented graphically), which describes the course of a disease or a clinical activity or its treatment, with all possible intermediate options. Models usually need to be simple so that they can be understood, but they should also be sufficiently complex so that they incorporate certain basic features of reality. In practice, the creation of a model is a matter of experience and skill, but it should also result naturally from the type of question we wish

to investigate and should be validated by the clinical scientists with whom the analyst works.

The most basic form of a model is the decision tree (see **Chapter 5**). Such models include "decisions" which are represented as squares, "transition possibilities" represented as circles, "conclusions" represented as small triangles pointing to the left, and "alternative options" represented as branches (**Fig. 2.3**). Such analyses are used if it is more important to focus on the outcomes and not on the time that the outcome occurs. The next type of model is the Markov model. This model consists of specific "health states", "transition possibilities" from one state to another, and "cycles", i.e., the time scale in which patients are periodically evaluated. Markovian models are used when we need to determine the time that an event takes place, and usually have a long-term scope (e.g., in cardiology studies).

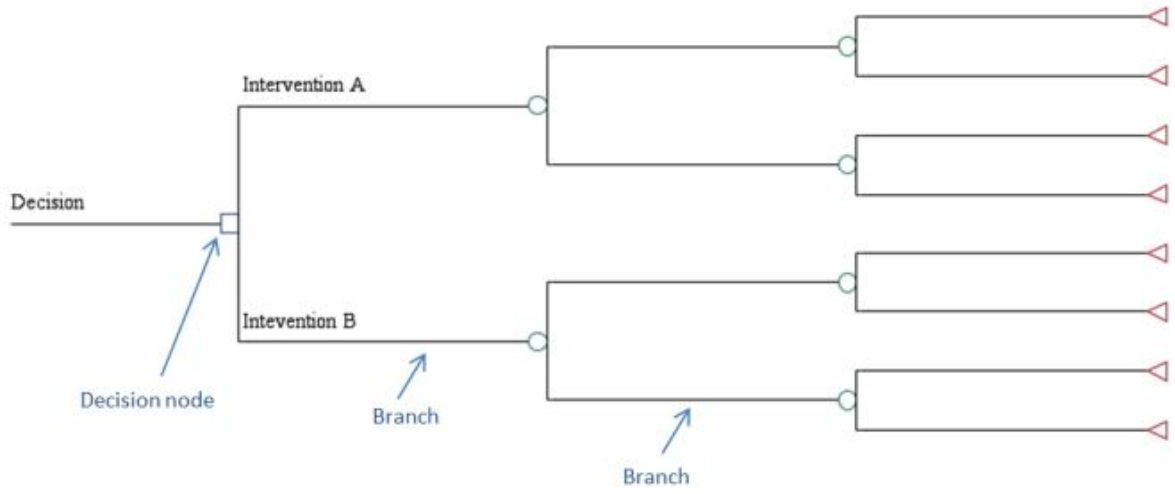

Figure 2.3. Depiction of a decision tree used in economic evaluation studies.

In those cases that we have a plethora of raw data, we may use the bootstrap method. It is a statistical method of estimating the distribution of an estimator or test statistic by 'resampling' the data. By duplicate the same many times over in a computer simulation, then one can simulate lots of samples from the artificial bootstrap population. Bootstrapping is particularly useful in estimating probability distribution of cost-effectiveness ratios, their confidence interval and variances (O'Hagan, 2003).

2.2.8. Sensitivity analysis

The term "sensitivity" essentially refers to the way in which our results change when we change our model's assumptions (Claxton et al, 2005). If sensitivity is high, the results vary greatly when we change certain assumptions; these assumptions must be very robustly established for our model to have any validity. Sensitivity analysis is a technique which estimates the effect that different values of an independent variable have on the end results (Jain et al. 2011). Sensitivity analysis is very important when examining the robustness and validity of our conclusions based on the significance of the initial parameters (Meltzer, 2001; Yoder, 2008). It needs to be performed mostly when the evaluator needs to determine the range of values in which the proposition of the economic model is valid, when we need to increase the model's reliability and in case the input data are elastic (for example, when estimates are used). The most common forms of sensitivity analysis are:

- One-way sensitivity analysis: Single analysis explores ICER variations when a single variable of the model – a different one each time – is altered.
- Multiple sensitivity analysis: Multiple analyses are performed in order to assess simultaneous changes in two or more variables, such as effectiveness and cost.
- Probabilistic sensitivity analysis (PSA): Probabilistic sensitivity analysis deals with the significant problem of statistical estimation of quantities and should always be included in any reliable economic analysis (see **Chapters 5 and 6**) (Briggs et al 1998; Fenwick et al. 2004; Barton et al. 2008; O'Hagan et al, 2000; Claxton et al, 2005; Willan, 2006).

2.3. Economic evaluation in the post-genomics era

As previously mentioned, it has long been known that patients respond differently to medications as a result of environmental and individual factors including genomic variation. Adverse Drug Reactions (ADRs) are a major contributor to morbidity, mortality and costs of care [Classen 1997; Classen 2010]. Considerable effort has been made to identify preventable causes of ADEs, such as age, gender, disease history, dietary preferences, lifestyle, *etc*, and create systems that reduce risks due to poor reliability of

delivery systems (such as computerized order entry). This effort, however, has not yet matched with activities to measure the effectiveness and the value of genome-guided treatment interventions.

In recent years, there is a growing demand to measure the value of pharmacogenetics testing so that policymakers are well-informed to decide about adopting and reimbursing pharmacogenetics testing. Presently, economic evaluation in genomic medicine and pharmacogenetics is still in its infancy. There are very limited economic evaluation studies of genome-guided treatment modalities that would allow decision makers to comparatively assess the value and clinical utility of such interventions.

Abacavir is very straightforward case for the application of economic analysis in this genome-guided treatment intervention. The first was performed in 2004 by Hughes and coworkers. The patient level data on abacavir ADE was obtained from a large HIV clinic and the analysis included costs cost of testing, cost of treating abacavir hypersensitivity, and the cost and selection of alternative antiretroviral regimens. The investigators used a probabilistic decision analytic model that compared testing to no testing and tested the model using Monte Carlo simulations. They concluded that based on the choice of comparators the testing strategy ranged from dominant (less expensive and more beneficial compared to no testing) to an incremental cost-effectiveness ratio (ICER) of ~€23,000. The study was done from the health system perspective as it did not include data to allow for a societal perspective. Several subsequent analyses have been performed all of which have determined testing prior to the use of abacavir as being cost-effective and potentially cost-saving under some assumptions.

A study by Schackman and coworkers [2008] used a simulated model of HIV disease based on the Prospective Randomized Evaluation of DNA Screening in a Clinical Trial study. The study modelled 3 different approaches: triple therapy including abacavir; genetic testing prior to triple therapy with tenofovir substituted for abacavir for patients that carry the HLA-B*57:01 allele; triple therapy with tenofovir substituted for abacavir for all patients. Abacavir and tenofovir were assumed to have equal efficacy and the cost of the tenofovir treatment was $4 more than the abacavir treatment. Outcomes were QALYs and lifetime medical costs.

The authors concluded that the genetic testing strategy was preferred and resulted in a cost-effectiveness ratio of $36,700/QALY compared with no testing (the tenofovir strategy was found to increase cost with no improvement in outcomes thus was dominated). The authors stressed that the model was robust provided that abacavir and tenofovir had equivalent efficacy and abacavir therapy was less expensive. This demonstrates that the result of an analysis is sensitive to changing conditions in the health care system thus may not remain 'true' in the face of these changing conditions.

From the above, it becomes evident that there is a need to evaluate additional pharmacogenomic studies, based on different types of economic evaluation. These efforts will aim to demonstrate that pharmacogenomic testing is ready for clinical implementation, based on the continuously increased evidence for their clinical utility and, at the same time, that pharmacogenomic testing costs can be reimbursed by healthcare systems, as pharmacogenomic testing costs continue to decline.

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Chapter 3

Critical appraisal of the views of healthcare professionals with respect to pharmacogenetics and personalized medicine in Greece

Mai Y, **Mitropoulou C,** Papadopoulou XE, Vozikis A, Cooper DN, van Schaik RH, Patrinos GP. (2014). ***Per Med***, **11(1)**: 15-26.

3.1. Abstract

In the post-genomic era, in many European countries, very little is known regarding the level of awareness of healthcare professionals with respect to pharmacogenomics and personalized medicine. Here, we report the findings of an in-depth study in a single country, involving 86 pharmacists and 208 physicians, to assess their level of awareness of pharmacogenomics and personalized medicine. Our findings indicate that around 60% of pharmacists consider their level of knowledge of personalized medicine to be very low, while over half of the pharmacists and physicians indicate that they would be unable to explain the results of pharmacogenomic tests to their customers or patients, respectively. This situation may be directly related to the low level of their undergraduate education in genetics and pharmacogenomics. These findings provide the basis for assessing the views of healthcare professionals in relation to personalized medicine in Greece and should help to facilitate the integration of genomics into the medical decision-making process.

Key Words: Public health genomics, healthcare professionals, physicians, pharmacists, genetics education, pharmacogenomics

3.2. Introduction

Personalized or genomic medicine exploits genomic information not only in the context of rationalizing drug prescription but also by influencing the overall medical decision-making process to the benefit of both the patient and the national healthcare system. Analysis of an individual's or a family's whole genomic sequence would, at least in principle, enable healthcare professionals to make disease risk assessments, determine an individual's pharmacogenomic profile and hence arrive at decisions regarding treatment modalities (Chen et al., 2010; Cooper et al., 2010). In recent years, personalized healthcare has gradually become a reality by combining whole-genome information with a patient's clinical profile (Guttmacher et al., 2010). As a consequence, not only can preventive medicine strategies be optimized but conventional therapeutic interventions can also be individualized. The latter constitutes a major challenge for customizing patient care (Ginsburg and Willard, 2009).

Unfortunately, the level of public awareness of genomics and its impact upon society is often rather low, and the same is true for the healthcare professionals who have been entrusted to be in the front-line of delivering these services to the general public. The lack of genetics/genomics awareness among healthcare professionals constitutes a major barrier to expediting the implementation of genomic medicine with its potential to adjust conventional treatment modalities according to a patient's genomic profile. Health care providers, including physicians and pharmacists, will play important roles in implementing pharmacogenomics in everyday practice. Education and training for these and other healthcare professionals regarding pharmacogenomics will help to ensure that pharmacogenomics technologies are appropriately and effectively used (Phillips and van Bebber, 2004), while it will enable healthcare professionals to interpret and apply pharmacogenomic information. This situation is exacerbated by a poorly developed and inadequately regulated genetic

testing landscape in many European countries, as indicated by the paucity of the literature on this topic both in European countries (Hietala et al., 1995; Balck et al., 2009; Makeena et al., 2010) and the United States of America (http://oba.od.nih.gov/SACGHS/sacghs_home.html). Thus, determining the level of awareness of the general public and healthcare professionals with respect to genomic medicine and its potential benefits to society, together with the challenges and pitfalls that need to be overcome, has become a major goal. For this reason, we have conducted nationwide surveys in Greece to critically ascertain patients' and healthcare professionals' views about pharmacogenomics and personalized medicine.

We have previously reported our results from several nationwide surveys to ascertain the landscape of the private genetic testing laboratories in Greece (Mai et al., 2011). We have also performed pilot surveys of the views of the general public and physicians in Greece, with the aim of understanding the challenges and pitfalls in relation to genomics and genetic testing and to identify ethical, legal and regulatory gaps and deficiencies (Sagia et al., 2011; Pavlidis et al., 2012). Here, we report our findings from a thorough survey of healthcare professionals, specifically physicians and pharmacists, to ascertain their views and opinions on various issues pertaining to genomics, personalized medicine and their impact on society. This study provides novel insights which we hope will be useful to other European countries that are aiming to more actively engage healthcare providers in all aspects of genomic medicine. This will in turn expedite the incorporation of personalized medicine into daily clinical practice.

3.3. Methods

3.3.1. Research design

We have used a cross-sectional survey design, which was conducted between July 2010 and September 2012. We have generated two independent questionnaires

(see ***Appendix 2***) from which the data on individual views of genetics, pharmacogenomics and personalized medicine were derived. Where necessary, clarifications to questions posed by the survey respondents were provided, both to pharmacists and physicians, to ensure that a valid response was given to each question.

In both questionnaires, non-random sampling was employed, and every effort was made to include several similar questions to allow comparative analysis of the results. One hundred and thirty seven pharmacists, selected from three cities mainly in Western Greece, were personally interviewed, using a questionnaire that was divided into four sections: (a) the first section (questions 1-5) requested demographic information such as gender, age and place and level of studies (BSc, MSc/PhD), (b) the second section (questions 6-7) aimed to assess their professional experience, (c) the third section (questions 8-15) aimed to assess the genomics knowledge of the respondents, and (d) the fourth section (questions 16-35) posed 20 questions on various aspects of genetics, such as awareness of and personal opinions about genomics, genetic tests and the use of pharmacogenomic testing from health care providers.

A similar questionnaire was also distributed to 208 physicians from all medical specialties who attended the national (Greek) medical conference in May 2011 and May 2012, to involve a broad range of physicians from all medical specialties and from all geographical regions within Greece. This questionnaire contained the following sections: (a) the first section (questions 1-5) requested demographic information such as age, gender, place and level of studies (MD, MSc/PhD) and specialty, (b) the second section (questions 6-8) aimed to assess their professional experience, and (c) the third section (questions 9-23) contained 15 questions regarding various aspects of genetics, such as awareness of and personal opinions about genomics, genetic tests and the use of pharmacogenomic testing from health care providers (**Table 3.1**). Ten questions were identical between the questionnaires for the sake of comparison (**Appendix 2**).

Table 3.1. Features of the various sections of the questionnaires addressed to physicians (Questionnaire A) and pharmacists (Questionnaire B). For each section, the corresponding questions (Q) are provided in brackets. The questions in each Section of both questionnaires are provided in the **Appendix 2**.

Questionnaire features	Physicians	Pharmacists
Demographic information	Section 1A (Q1A-Q5A)	Section 1B (Q1B-Q5B)
Professional experience	Section 2A (Q6A-Q8A)	Section 2B (Q6B-Q7B)
Genomics knowledge	-	Section 3B (Q8B-Q15B)
Self-reported views on various aspects of genomics	Section 3A (Q9A-23A)	Section 4B (Q16B-Q35B)

3.3.2. Measures

The questionnaires provided prospective data for this analysis. The dependent variables were derived from the questions in both questionnaires, scored using either the Likert-type scale (1-5) or a binary model (0=No, 1=Yes). Independent variables comprised the demographic characteristics of respondents, specifically their age, gender, level of study and place where they performed their studies, and their professional experience.

3.3.3. Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences, version 18.0 (SPSS Inc., Chicago, IL, USA) and the chi-square test**.** We also checked the data for completeness and frequency distributions. Mean values, standard deviations, and percentages were computed to describe the distribution of independent variables. Cross-tabulation tables (contingency tables) were created to display the relationship between two or more (nominal or ordinal) variables using the chi-square test. Probabilities of less than 0.05 were considered to be statistically significant, when testing null hypotheses.

3.4. Results

The overall sample sizes and characteristics of the surveyed pharmacist and physician groups are shown in **Table 3.2**. Every effort was made in the context of both the pharmacists' and the physicians' groups to be as representative as possible regarding age and gender.

Table 3.2. Survey sample composition and demographic elements, as revealed by Section 1 of the questionnaires (see **Appendix 2**). [a]: Questionnaires were given only to adult respondents with a minimum age of 18-years. [b]: Only 1 respondent indicated that they had studied in Italy. The remainder did not provide this information. [c]: Five respondents indicated that they had performed their post-graduate studies abroad, namely Italy, Germany and Sweden (1 respondent each), whereas 2 did not indicate the country in which they performed their post-graduate studies. It should be noted that the sample size in both surveys includes only those healthcare professionals who responded to the questionnaires.

	Physicians [n (%)]	**Pharmacists [n (%)]**
Sample size	208 (100)	86 (100)
Age (years)		
<35 [a]	72 (34.6)	31 (36.1)
35-60	126 (60.6)	50 (58.1)
>60	10 (4.8)	5 (5.8)
Gender		
Male	120 (57.7)	48 (55.8)
Female	88 (42.2)	38 (44.2)
Place of study		
Greece	136 (65.4)	55 (63.9)
Abroad	72 (34.6)	31 (36.1) [b]
Graduate studies		
Yes	80 (38.5)	12 (13.9) [c]
No	128 (61.5)	74 (86.1)

.

The most common medical specialties of those physicians who responded to our survey were pathologists (50%), general practitioners (28%), surgeons (28%), cardiologists (9%), oncologists (8%) and psychiatrists (8%). A full list of these specialties is provided in **Appendix 2**. Regarding the professional experience of the

pharmacists who responded to our survey, almost 3/5 (59.3%) of the pharmacists had practiced pharmacy for more than 10 years (10-19 years=16.3%, 20-29 years=32.6%, Over 30 years=10.5%), while almost 2/5 (40.7%) of the pharmacists who responded to our survey had professional experience of less than 10 years (Up to 4 years=20.9%, 5-9 years=19.8%). The vast majority of pharmacists who responded to our survey (84/86; 97.7%) were employed in, or actually owned, a private pharmacy.

The opinions of the physicians and pharmacists were assessed with respect to the following three issues: (a) level of awareness of genetics and pharmacogenomics, (b) involvement with genomics, genetic testing and pharmacogenomics, and (c) professional opinions regarding ethical, legal, societal and regulatory issues pertaining to genetics and pharmacogenomics. The pharmacists were also interviewed to assess their basic knowledge of genetics, since their formal genetics education is often very limited.

3.4.1. Awareness of genetics and pharmacogenomics

We first attempted to assess the level of awareness of healthcare professionals with respect to genetics and pharmacogenomics. Some 58% (almost 3/5) of the pharmacists considered that they knew very little or nothing about genetics (Q16B), while the proportion was even higher (66.3%) in relation to pharmacogenomics and personalized medicine (Q17B, **Fig. 3.1A**). A mere 4.6% felt that their knowledge level of genetics, pharmacogenomics and personalized medicine was high or very high (**Figs. 3.1A, B**). Almost half (45%) of physicians volunteered that their knowledge level of pharmacogenomics and personalized medicine (Q12A) was poor or very poor, while around 1/4 (24%) of respondents felt that their knowledge level of pharmacogenomics and personalized medicine was high or very high (**Fig. 3.1C**). A similar response pattern was also observed in physicians and pharmacists with regard to self-assessment of the undergraduate level of their education in genetics and pharmacogenomics (Q20A and Q20B, respectively; **Fig. 3.1D**).

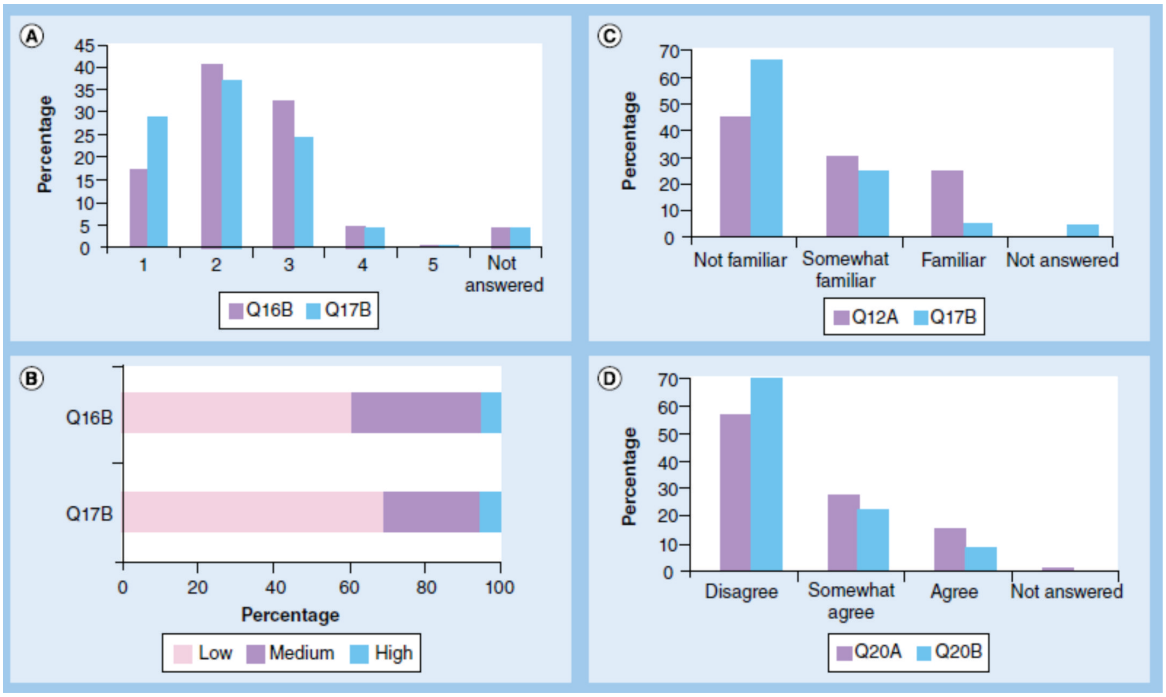

Figure 3.1. Assessing the genetics knowledge of the respondent groups. A and B. Graphical representation indicating the pharmacists' level of knowledge of genetics (Q16B) and pharmacogenomics and personalized medicine (Q17B). Numbers 1-5 [A, (Y-axis=Percentage)] and the Low-Medium-High scale corresponds to the Likert scale (see also Supplementary Information). **C.** Comparative analysis of the self-assessed level of knowledge of physicians' (Q12A) and pharmacists' (Q17B) of pharmacogenomics and personalized medicine. Y-axis=Percentage. **D**. Comparative analysis of undergraduate level of education of genetics and pharmacogenomics, based on the self-assessment of physicians (Q20A) and pharmacists (Q20B). Y-axis=Percentage.

Finally, approximately 3/4 (78%) of the physicians and 3/5 (58%) of pharmacists stated that they would be interested in attending educational events in relation to genetics and pharmacogenomics (**Appendix 2**), indicating their willingness, at least in principle, to improve their knowledge of this rapidly emerging new field in medicine.

Genetic and pharmacogenomic tests are gradually becoming integrated into the modern medical decision-making process. Indeed, worldwide, there are an increasing number of genetic tests that are being made available from genetic laboratories (Metzker, 2010), but also directly to the consumer via the internet, or (even more recently) over the counter in pharmacies (Patrinos et al., 2013).

We asked the pharmacist's group whether they provide genetic analysis kits (e.g. buccal swabs or saliva collection kits) over the counter. The responses given indicated that only 7% of the pharmacists provide such genetic analysis kits over the counter, while almost 9 out of 10 pharmacies do not (Q22B; **Fig. 3.2A**). A significantly larger proportion of pharmacists (45%) were aware that genetic analysis kits are considered to be medical devices and as such they require regulatory clearance to be sold over the counter in pharmacies (Q23B). However, a smaller proportion, namely 1/3 (31%), were aware that certain drug labels specify that it is recommended to undertake a pharmacogenomic test prior to obtaining the drug in question so as to avoid an adverse drug reaction (Q26B; **Fig. 3.2A**).

It is broadly accepted that pharmacogenomics contributes towards a reduction not only in healthcare costs by minimizing adverse drug reactions, but also in the overall cost of developing new drugs by stratifying patient subgroups in clinical trials. Therefore, we posed these questions to pharmacists in order to ascertain whether they are familiar with these issues. We found that around 3/5 (60%) of the respondents believed that pharmacogenomics can help to reduce the occurrence, overall frequency and severity of adverse drug reactions (Q31B), while almost 2/3 (65%) believed that pharmacogenomics can help to reduce healthcare costs by rationalizing drug use (Q33B; **Fig. 3.2B**). However, only one third of the responding pharmacists believed that pharmacogenomics would play a role in reducing the cost of developing new drugs (Q32B; **Fig. 3.2B**).

3.4.2. Involvement with genetics, genetic testing and pharmacogenomics

Subsequently, we addressed the level of involvement of physicians and pharmacists with genomics, genetic testing services and pharmacogenomics. Firstly, we asked physicians and pharmacists about the extent to which pharmacogenomics and pharmacogenomic testing impacted upon their daily practice.

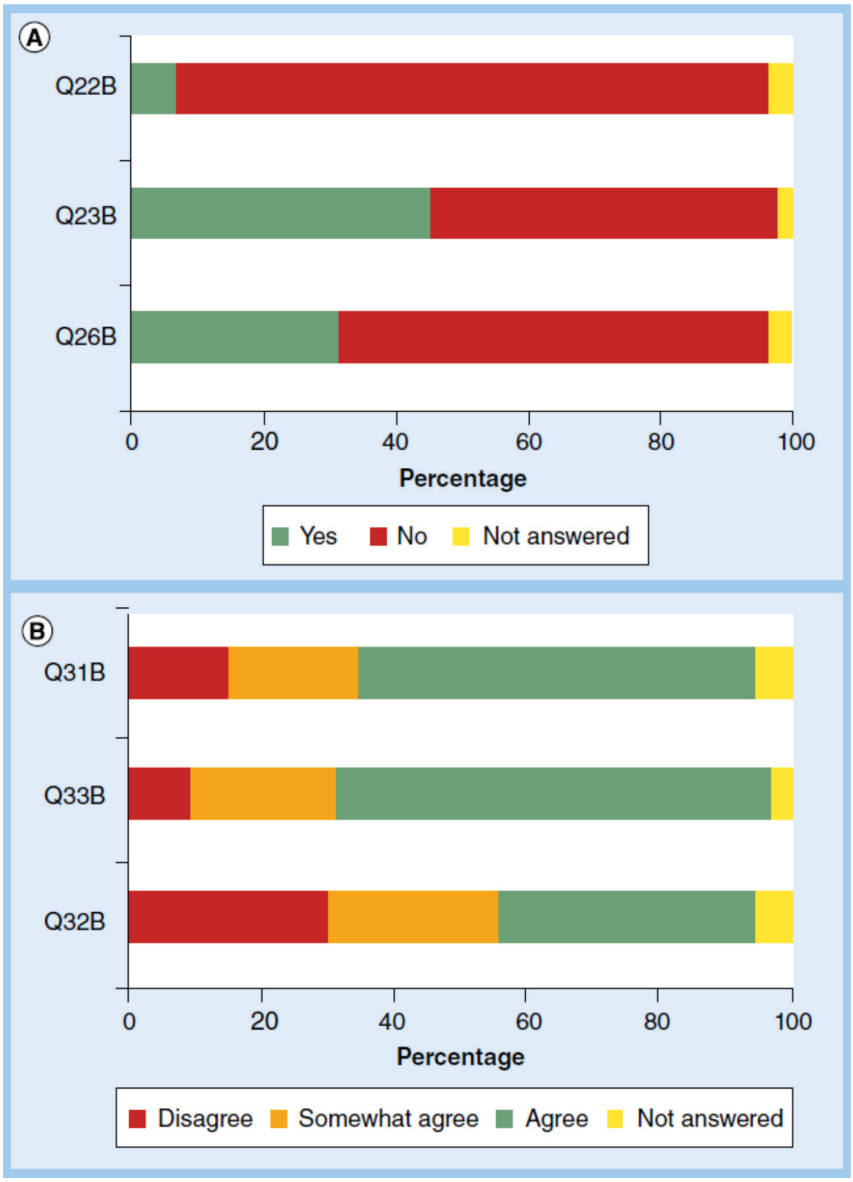

Figure 3.2. Evaluating pharmacists' opinions and attitudes with respect to pharmacogenomics. **A**. Graphical display of the pharmacists' attitudes to providing genetic analysis kits over the counter (Q22A), their awareness that the genetic analysis kits are considered a medical device (Q23B) and the recommendation for a pharmacogenomic test in certain drug labels (Q26B). **B**. Pharmacists' opinions regarding the contribution of pharmacogenomics towards reducing the occurrence and the overall frequency and severity of adverse drug reactions (Q31B), healthcare costs (Q33B) and costs of developing new drugs (Q32B).

From their responses, we surmise that physicians are more frequently involved with genetics and pharmacogenomics in their routine practice than pharmacists. However, more than half of the respondents stated that their level of involvement was

low, with almost half (53%) of physicians and almost 3/4 (73%) of pharmacists only rarely becoming involved with pharmacogenomics (**Fig. 3.3A**).

When we enquired whether physicians had advised their patients to undergo genetic and/or pharmacogenomic testing, more than half (*i.e.*, 53%) stated that they have advised their patients to do so. By contrast, a mere 15% of the pharmacists stated that they had advised their clients to undergo genetic and/or pharmacogenomic testing (**Fig. 3.3B**). The same pattern was also observed when physicians and pharmacists were asked whether their patients had sought their advice in relation to undertaking genetic and/or pharmacogenomic testing (42% vs. 9%, respectively; **Fig. 3.3B**). At the same time, more than 3/4 (79%) of the pharmacists indicated that they could not provide sufficient information to their clients or explain the results of pharmacogenomic tests to them (Q27B); this proportion was much lower in the physicians group (58%; Q16A: **Fig. 3.3C**).

3.4.3. Professional opinions on ethical, legal, societal and regulatory issues pertaining to genetics and pharmacogenomics

Genetic analysis must always comply with various ethical, legal, societal and regulatory guidelines. As such, we sought the opinions of our groups of healthcare professionals on this important topic.

A large proportion of healthcare professionals (69% of physicians and 77% of pharmacists) believe that in Greece there is currently neither a well-regulated environment nor the appropriate legal framework covering genetic and pharmacogenomic testing to protect the general public and ensure privacy, informed consent, control of the costs of genetic analysis, monitoring of the accreditation of genetic laboratories, etc; **Fig. 3.4A**). In particular, 72% of the pharmacists thought that there was the potential for pharmacogenomic information to be inappropriately or even malevolently exploited by employers and insurance companies in order to discriminate against certain patients or population subgroups (not shown).

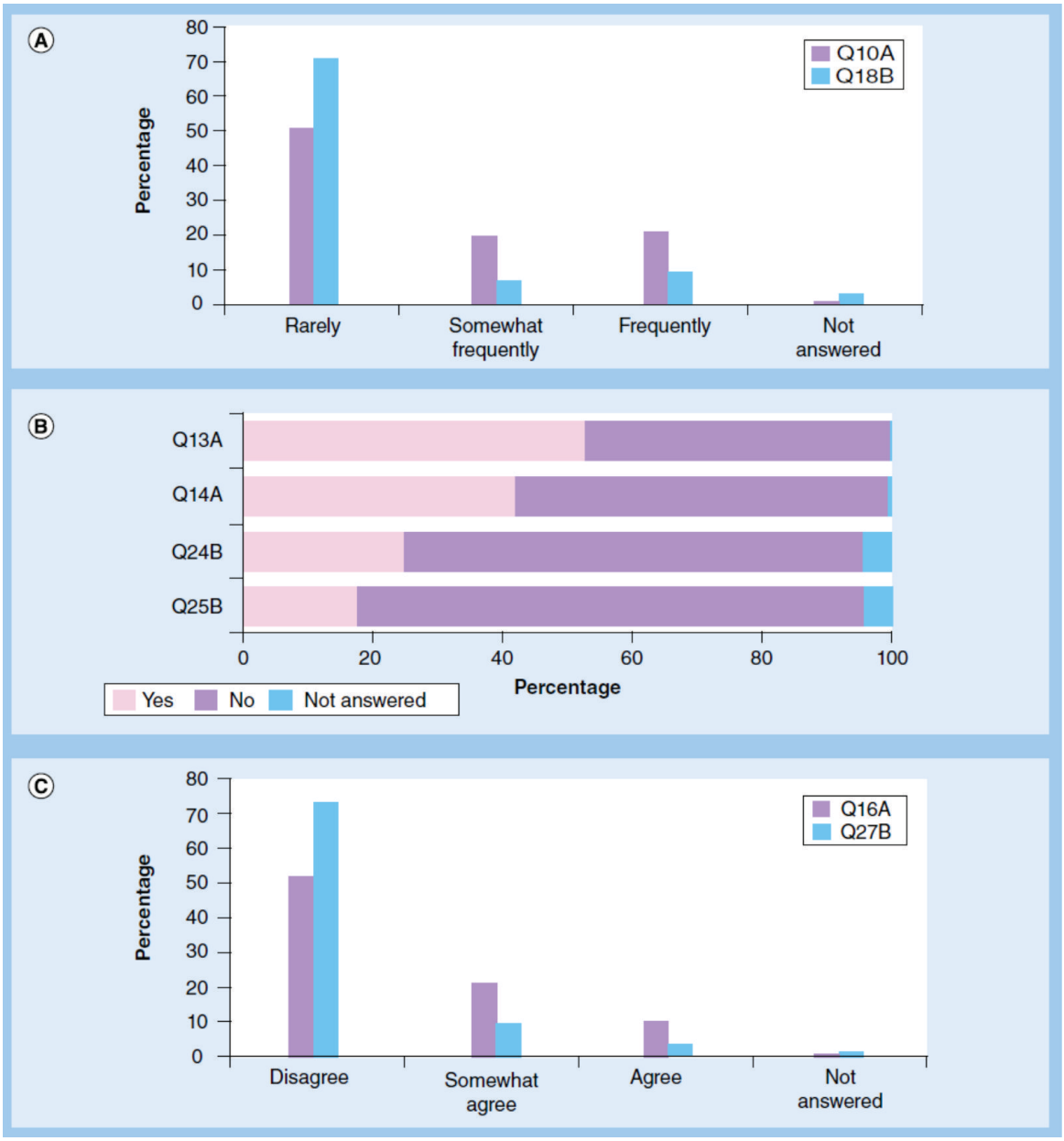

Figure 3.3. Involvement with genetics, genetic testing and pharmacogenomics. A. Level of involvement of physicians and pharmacists with pharmacogenomics in their daily practice. Y-axis=Percentage. **B**. Graphical display indicating whether physicians (Q13A) and pharmacists (Q24B) have advised their patients and clients, respectively, to undergo genetic and/or pharmacogenomic testing and reciprocally, whether physicians' and pharmacists' clients (Q14A and Q25B, respectively) had requested them to undertake genetic and/or pharmacogenomic testing. **C**. Self-assessment as to whether physicians and pharmacists can provide sufficient information or explain the results of pharmacogenomic tests (Q16A and Q27B, respectively). Y-axis=Percentage.

An even bigger proportion, namely 86% of physicians and 66% of pharmacists, disagreed with the idea of direct-to-consumer genetic testing (**Fig. 3.4B**), while almost

2/3 of physicians and pharmacists (62% and 66% respectively) believed that the pharmacogenomic testing costs should be covered by insurance companies (**Fig. 3.4C**). Overall, the majority of healthcare professionals (50% of physicians and 70% of pharmacists) agreed that the results of pharmacogenomic testing would have a positive impact on patient medical care by rationalizing their drug prescription and dosage, their frequency of medical appointments and overall diagnoses (**Fig. 3.4D**).

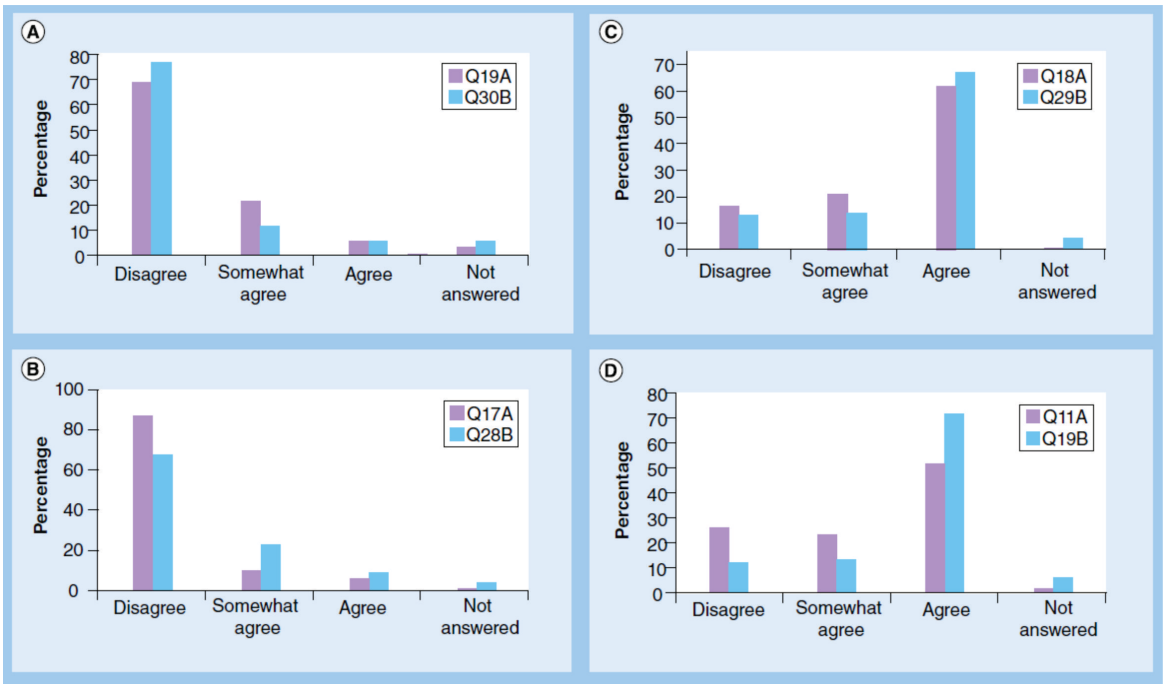

Figure 3.4. Professional opinion on ethical, legal, societal and regulatory issues pertaining to personalized medicine. A. Opinions of physicians and pharmacists (Q19A and Q30B, respectively) as to whether an appropriate legal framework to cover genetic and pharmacogenomic testing exists in Greece. **B**. Opinions of physicians (Q17A) and pharmacists (Q28B) of direct-to-consumer genetic testing. **C**. Opinions of physicians (Q18A) and pharmacists (Q29B) regarding the reimbursement of expenses of pharmacogenomic testing by insurance companies. **D**. Opinions of physicians (Q11A) and pharmacists (Q19B) in relation to whether the results of pharmacogenomic testing would positively affect patients' medical care. Y-axis=Percentage.

3.4.4. Assessing genetics knowledge among pharmacists

Finally, we wished to assess how well-educated pharmacists are in relation to genetics and pharmacogenomics. Our data revealed that the younger pharmacists and

those with a graduate degree (MSc and/or PhD) are better informed about genetics as compared to the older generation of pharmacists and those who have not studied at postgraduate level. Thus, more than 3/4 (77%) of the younger pharmacists (<35 yrs old) correctly stated that genomic DNA is 99.9% identical between different individuals as compared to 44% of the older pharmacists (>35 yrs old; Q8B; $p<0.001$). In addition, 8 out of 10 pharmacists realised that the statement "... adenine only pairs with cytosine and thymine only pairs with guanine" (Q10B) was wrong, while 6 out of 10 pharmacists noticed that the statement "Humans have 48 chromosomes" (Q9B) was wrong. In both cases, pharmacists with a post-graduate education tended to give more correct answers ($p<0.001$). All of the younger pharmacists (<35 yr old) correctly stated that DNA changes are capable of influencing drug response compared to just 82% of the older pharmacists (Q13B; $p=0.015$), while 97% of the younger pharmacists opined that DNA changes could result in adverse drug reactions as compared to almost 2/3 (62%) of the older pharmacists (Q14B; $p<0.001$). Further, 71% of younger pharmacists were of the opinion that pharmacogenomic analysis is not appropriate for all drugs, although this proportion was lower for older pharmacists (Q15B; $p=0.042$). When we assessed the influence of post-graduate education on genomics knowledge, we found that graduate pharmacists (MSc and/or PhD) have a better genetics education as compared to those who have not followed post-graduate studies (not shown). These data are summarized in **Figure 3.5**.

3.5. Discussion

In recent years, it has become clear that pharmacogenomics has the potential to ensure optimal treatment and medication use in a growing number of diseases. The advent of high-throughput genotyping and whole-genome sequencing analysis has revolutionized medical practice bringing the concept of personalized genomic medicine ever closer to reality and resulting in a gradual increase in the number of

genetic tests becoming available, a number which is likely to increase steadily in the coming years (Metzker, 2010).

Given the potential of genomic medicine to grow exponentially, it is imperative that comprehensive analyses are performed in various countries to assess the level of awareness of healthcare professionals in relation to genomics and personalized medicine so that the delivery of genomic services may be expedited in their respective healthcare systems. Genetics education and communication will also play an important role in increasing the level of awareness of the general public with respect to genomic medicine so that they come to appreciate the benefits that this new discipline can offer (Reydon et al., 2012).

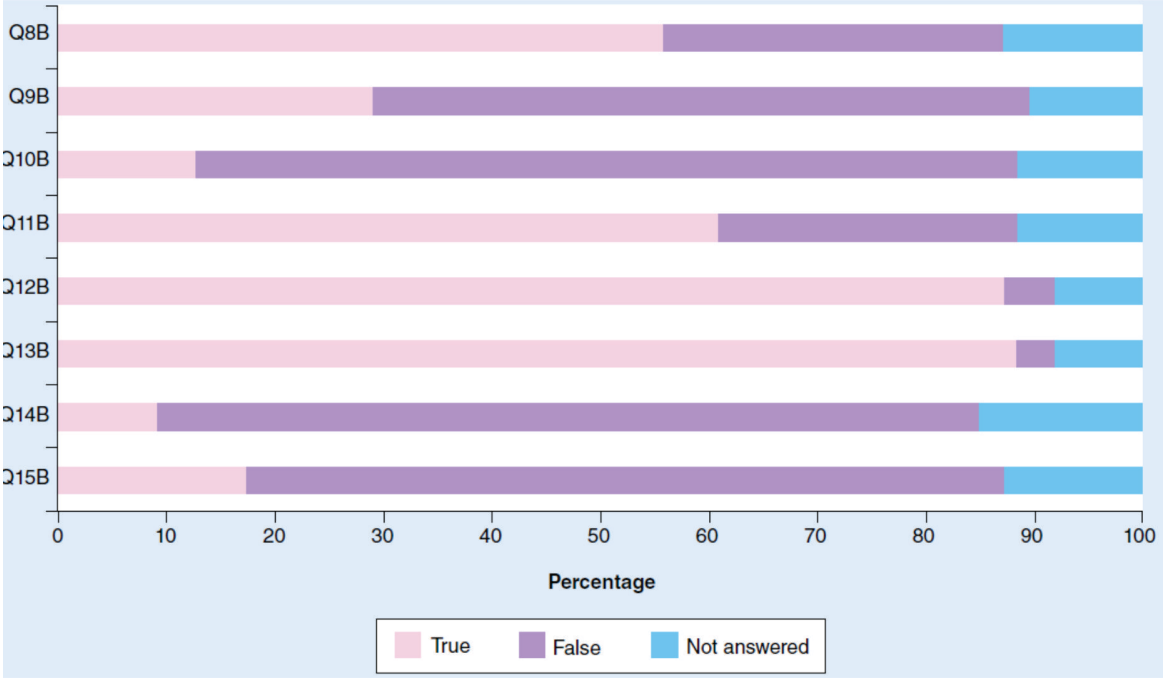

Figure 3.5. Assessing genetics knowledge in pharmacists. Graphical display of the correct answers of pharmacists in relation to various questions pertaining to their knowledge of basic genetics (Q8B-Q11B) and pharmacogenomics (Q12B-Q15B).

There are currently only a handful of studies in the literature that have attempted to quantify the differences between individual countries regarding the level of awareness and education of healthcare professionals in relation to

pharmacogenomics and genomic medicine. In contrast to the United States (Singer et al., 2008), significant differences have been documented between European countries, and also between European Union member states (Hietala et al., 1995; Balck et al., 2009; Makeena et al., 2010; Pavlidis et al., 2012), and in-depth analysis, based upon comprehensive surveys, is still lacking. We have previously attempted to explore the views of both the general public and physicians over genetic testing services in Greece (mai et al., 2011; Pavlidis et al., 2012) and to correlate this information with the private genetic testing laboratories in Greece (Sagia et al., 2011). Interestingly, for the first time in Europe, these surveys paid special attention to attitudes to pharmacogenomic testing.

This study has attempted to shed new light into the views of healthcare professionals with respect to genomic medicine and pharmacogenomics in particular. This study differs significantly from that recently conducted in Greece (Mai et al., 2011) in the following respects: (a) this study comparatively evaluated the views of physicians and pharmacists in relation to key aspects of genomic medicine, (b) both questionnaires were designed (using the Likert scale) in such a way as to allow better analysis of the responses of the target groups, (c) this study attempted to correlate genomic knowledge with professional and training experience, and (d) this study highlighted the willingness of both target groups to participate in continuous educational events in relation to pharmacogenomics.

As with our previous study, we opted to carry out face-to-face interviews rather than acquire information by means of impersonal electronic surveys since it allowed us to provide clarification to the respondents when required to do so. Pharmacists were approached in their practice, whereas physicians were selected while attending two major annual national medical conferences in Athens. However, in comparison to our previous study, we significantly expanded the questionnaires since we sought a more detailed evaluation of the views of our target groups.

3.5.1. Perception of genomic medicine and pharmacogenomics

Integration of genomic information into the daily medical decision-making process depends upon several parameters. Increased awareness of various aspects of genomic medicine greatly facilitates the entire process. Our results indicate that approximately 60% of the pharmacists who responded to our survey considered their level of genetics knowledge to be low, a proportion comparable to the pharmacists who admitted very limited or no knowledge of pharmacogenomics and its relationship with personalized medicine (**Fig. 3.1**). Only 4.6% of pharmacists felt that their genetics and pharmacogenomics knowledge was high. This situation contrasts with that for the physicians as a group; the proportion of the physicians who admitted that their level of knowledge of pharmacogenomics and personalized medicine was poor or very poor was significantly lower (45%), while 1/4 (24%) of the physicians felt that their level of knowledge of genetics, pharmacogenomics and personalized medicine was high or very high (**Fig. 3.1C**; $p<0.05$). Our findings are in accordance with the picture outlined in a sample of the UK community pharmacists interviewed, who also had a relatively limited knowledge of pharmacogenomics (Kimberly, 2012), as well as a similar survey in the United States (McCullough et al., 2011), further outlining the need for expanding pharmacogenomics education in higher education (Higgs et al., 2008; Lee et al., 2012).

This difference can most easily be explained by the fact that genetics and molecular biology courses are included for a longer period of time in the medical schools in Greece as compared to the schools of pharmacy. It is unfortunate that in the latter schools, the undergraduate curricula only address these topics quite superficially. When physicians and pharmacists were asked to self-assess the level of their undergraduate education with respect to genetics and pharmacogenomics, similar responses were given (**Fig. 3.1D**).

The educational level of the physicians and pharmacists with respect to genetics and pharmacogenomics could also be defined in relation to their level of

involvement with genetic and pharmacogenomic testing services. Our results show that although physicians are more frequently involved with genetics and pharmacogenomics in their routine practice as compared to pharmacists, more than half of them indicated that the level of their involvement with pharmacogenomics was low (53% of physicians vs. 73% of pharmacists). Moreover, significantly more physicians (53%) have advised their patients to undergo genetic and/or pharmacogenomic testing, compared to 15% of pharmacists (**Fig. 3.3B**). To this end, we should also bear in mind that physicians may recommend more genetic testing for genetic disorders as opposed to personalized medicine and pharmacogenomics. A comparable trend was also observed when physicians and pharmacists were asked whether their patients had enquired about undertaking genetic and/or pharmacogenomic testing (42% vs. 9%, respectively; **Fig. 3.3B**). These data are comparable with our previous survey [48%; Mai et al., 2011].

Interestingly, a large proportion of pharmacists (79%) felt that that they were unable to provide adequate information or explain the results of pharmacogenomic tests to customers, while only 5% stated that they could satisfactorily explain the results of pharmacogenomic tests, a response which is directly proportional to their genetics education level. This result concurs not only with a recent study performed in a Canadian pharmacist respondent group, only 7.7% of whom felt that they were able to advise patients and interpreting their pharmacogenomic test results [de Denus et al., 2013), but also with similar surveys in the United States (McCullough et al., 2011; Stanek et al., 2012; Haga et al., 2012). As previously indicated, the proportion of physicians stating that they were unable to explain genetic and pharmacogenomic test results was much lower than the pharmacists while reciprocally the proportion of physicians who stated that they were in a position to adequately interpret genetic test results was significantly higher than the pharmacists (58% and 15%; $p<0.01$). A national survey by American Medical Association and Medco in a sample of 10,303 physicians, also showed that only 10% believe they are adequately educated and trained to exploit pharmacogenomic tests (Stanek et al., 2012).

In recent years, kits for sample collection for downstream genetic tests have become widely available over the counter in pharmacies. Our group of pharmacists indicated that only 7% of them sell such kits over the counter, whereas almost 9 out of 10 pharmacies do not. Such collection kits are considered medical devices and as such, special clearance is required from regulatory agencies to sell them. Interestingly, less than half (45%) of the pharmacists who responded to our survey were aware that the genetic analysis kits are considered medical devices. Surprisingly, 8% and 22% of pharmacists agreed or somewhat agreed with the idea of direct-to-consumer genetic and pharmacogenomic testing, compared to 5% and 9% of physicians, respectively. Although the results from the physicians' group were in full agreement with our previous surveys (Mai et al., 2011; Pavlidis et al., 2012), the smaller proportion of the pharmacists who were opposed to direct-to-consumer (DTC) genetic and pharmacogenomic testing is of special interest, warranting further investigation, and could be partly explained by the limited information available to this professional group regarding the risks of DTC genetic testing. The issue of DTC genetic testing is a controversial one and there are considerable differences in the regulatory framework between the US and Europe (Kricka et al., 2011). Moreover, considering the absolute need for a doctor to mediate between the patient and the diagnostics company offering the pharmacogenomic test, extra caution should be exercised with DTC pharmacogenomic testing (Howard and Borry, 2011). This is a symptom of the lack of a well-regulated environment to govern genetic testing with the aim of protecting the general public and ensuring privacy, consented analysis, control of genetic analysis costs, monitoring genetic laboratories accreditation, a point made by both respondent groups (**Fig. 3.4**).

It is broadly accepted that pharmacogenomics has the potential to improve quality of life at the same time as reducing healthcare costs by minimizing adverse drug reactions at both a personal and national level. Around 2/3 (60%) of the responding pharmacists believed that pharmacogenomics can potentially help to reduce the incidence and severity of adverse drug reactions, while almost 2/3 (65%) believed that pharmacogenomics can contribute towards reducing healthcare costs

by rationalizing drug use. Surprisingly, only 31% of the respondent pharmacists were aware that certain drug labels indicate that a pharmacogenomic test should be undertaken prior to obtaining or being prescribed the drug in order to avoid adverse drug reactions.

Overall, the majority of healthcare professionals (50% in the physicians' group and 70% in the pharmacists' group) agree that the results of pharmacogenomic testing will positively affect medical care for the patients by rationalizing their drug type and dose, their frequency of medical appointments and overall diagnoses.

3.5.2. Knowledge and education of pharmacists in relation to pharmacogenomics

In several countries, pharmacists are considered to be experts in medication and as such, they are expected to be able to use pharmacogenomic information appropriately in order to individualize treatment regimens. Pharmacists can be particularly useful in the implementation of pharmacogenomics, mainly by assisting clinicians to ensure that all available pharmacogenomic information is taken into consideration during the medical decision-making process, or by acting as educators to patients and healthcare professionals in the context of raising awareness of pharmacogenomics. Pharmacists can play an important role in the application of pharmacogenomics into clinical practice to improve the quality and safety of health care. However, the process for the application of pharmacogenomics data into pharmacy clinical practice must be defined and a viable business model in this emerging field must be developed (American Pharmacists Association, 2011).

As such, pharmacogenomics should play an integral role in modern undergraduate curricula in schools of medicine and pharmacy. Our findings suggest that younger pharmacists and those with graduate degrees, despite having less professional experience, are likely to have a better understanding of genetics and pharmacogenomics (**Fig. 3.5**). This could be because genetics and molecular biology have only recently been added to the undergraduate pharmacy curriculum. These

findings concur with those of a recent survey of 284 pharmacists practicing in the province of Québec (Canada), indicating that more than 95% of respondents are willing to recommend pharmacogenomic testing, and the vast majority of respondents (97%) suggesting that they would be happy to undertake further pharmacogenomics education (de Denus et al., 2013). This latter proportion was much higher than in our own survey (58% for pharmacists and 78% for physicians, respectively).

It should be noted that, in our own study, 51 of the pharmacists who were initially approached refused to participate in the survey (37%); 14 of these were unaware of the term *pharmacogenomics*. It is also noteworthy that 6 of the pharmacists stated that this survey was insulting, maintaining that pharmacists should not participate in this type of survey, while 12 pharmacists gave other excuses for not participating. Taken together, these findings indicate that although most pharmacists have a positive view of pharmacogenomics and are willing to increase their knowledge of pharmacogenomics with a view to gradually integrating it into their practices, proper pharmacogenomics education will be required to optimize the integration of pharmacogenomics into patient care.

3.6. Future perspective

In this study, we provide results from two in-depth surveys to assess the level of awareness of healthcare professionals, namely pharmacists and physicians on pharmacogenomics and personalized medicine in Greece. Our results complement our previous studies (Mai et al., 2011; Sagia et al., 2011; Pavlidis et al., 2012) and provide new insights that should facilitate integration of pharmacogenomics into patient care in Greece. In order to gain further insights and to compare the level of awareness of healthcare professionals over pharmacogenomics and personalized medicine throughout Europe, this study could be eventually replicated in several other European countries, both developing and developed, to identify possible gaps in

pharmacogenomics education. To this end, it is to be hoped that the level of awareness and education over pharmacogenomics will become harmonized throughout Europe, which would, in turn, facilitate the integration of personalized medicine into front-line patient care.

3.7. Acknowledgements

We are indebted to the participants of our surveys without whose cooperation, this study would not have been possible. This work was endorsed by the Genomic Medicine Alliance and partly funded by the Golden Helix Foundation and by a European Commission grant (FP7-305444) to GPP.

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Chapter 4

Stakeholder analysis in pharmacogenomics and genomic medicine in Greece

Mitropoulou C, Mai Y, van Schaik RH, Vozikis A, Patrinos GP. ***Public Health Genomics.*** 2014;17(5-6):280-286.

4.1. Abstract

The pace of discoveries and advances in genomic research to individualize healthcare decision-making process is not reflected in the pace of their translation and incorporation into day to day clinical medicine. One of the main obstacles is the poor understanding of the policies and key stakeholders involved in this translation process. We used the computerized version of the *PolicyMaker* political mapping tool to collect and organize important information about the pharmacogenomics and genomic medicine policy environment, serving as a database for assessments of the policy's content, the major players, their power and policy positions, their interests and networks and coalitions that connect them. Our findings indicate that the genomic medicine policy environment in Greece seems to be rather positive, as the vast majority of the stakeholders express their medium to high support in the initially set goals of genomic medicine policy environment. The Ministry of Health and public healthcare insurance funds seems to oppose, most likely due to financial constraints. These findings would contribute in adopting those policy measures that will expedite the adoption of genomics into conventional medical interventions.

Keywords: pharmacogenomics, genomic medicine strategic planning, policymaking, stakeholders, software

4.2. Introduction

Genomic medicine aims to optimize the overall medical decision-making process and to rationalize drug prescription to the benefit of both the patient and the national healthcare system, by means of exploiting an individual's unique genomic profile. This enables healthcare professionals to make tailor-made disease and treatment risk assessments based on a patient's unique pharmacogenomic profile (Guttmacher et al., 2010), hence individualizing conventional therapeutic interventions (Cooper et al., 2010).

The Genomic Medicine environment is complex, with a plethora of key players and stakeholders with varying levels of genetics awareness and education. Previous studies have attempted to shed light into the level of genetics awareness of the general public and have investigated the genetics education level of healthcare professionals, as well as their views on ethical, legal and social issues (ELSI) pertaining to genomics towards adopting certain policies and perform the necessary steps that would facilitate integration of genomics into healthcare. These studies, conducted in various countries in Europe and the United States [Hietala et al., 1995; Balck et al., 2009; Makeeva et al., 2010; Mai et al., 2011; Mai et al., 2014), have shown that the level of general public awareness of genomic medicine and its impact to society is often rather low, which constitutes a major barrier to expediting the implementation of genomic medicine. In addition, the lack of proper mapping of the opinions of various stakeholders leads to an inadequately regulated environment in the field.

We have previously reported the results from several nationwide surveys to obtain the views of the general public and healthcare professionals (e.g. physicians, pharmacists; Mai et al., 2011; Mai et al., 2014) and to ascertain the landscape of the private genetic testing laboratories in Greece (Sagia et al., 2011), with the aim of understanding the challenges and pitfalls in relation to pharmacogenomics and genomic medicine and to identify ethical, legal and regulatory deficiencies that need to be rectified.

Here, we pursued a stepwise approach aiming to understand and analyze the pharmacogenomics and genomic medicine policy environment in Greece and

to identify the role of the key stakeholders in the field. In addition, we attempted to identify the main opportunities and obstacles for policy implementation in the pharmacogenomics and genomic medicine environment and to prioritize the various stakeholders' interests, in an effort to better plan the undertaking of various measures in genomics healthcare.

4.3. Methods

4.3.1. Study design

The key stakeholders were identified by expert consultation in the field of pharmacogenomics and genomic medicine policy, by extensive literature review and our own previous experience and published reports (Sagia et al., 2011; Mai et al., 2011; Mai et al., 2014). A list of the main key stakeholders in the field of pharmacogenomics and genomic medicine policymaking environment in Greece was obtained, namely: (a) academic and research organizations, (b) the National Greek bioethics council, (c) private and public genetic laboratories, (d) religious organizations and the church, (e) consumers and citizens, (f) genetics and genomics professional associations, (g) the Greek Ministry of Health, (h) payers (including both the public health insurance fund and the private health insurance industry), (i) pharmaceutical and biotechnology companies, (j) pharmacies, (k) physicians (Geneticists and other medical specialties), (l) the Press and the Media, (m) public and private providers, and (n) the Greek National Medicines Organization.

All the above stakeholders were interviewed either by structured interviews and/or by questionnaires, consisting of 3 different questions (**Appendix 2**) according to the *PolicyMaker* method for collecting and organizing important policy information (Reich, 1996; Reich and Cooper, 1996; Glassman et al., 1999). For every stakeholder, its current territorial level (national or regional), sector (governmental, non-governmental, political, media, commercial, private, social), position (high support, medium support, non-mobilized, medium opposition, high opposition) and power (low, medium, high) was obtained. Also, for selected groups of stakeholders, namely citizens, consumers, physicians, and

pharmacists. their views and roles were also identified either through their publicly expressed opinions in the media, conferences and professional bodies or from our previous studies (Sagia et al., 2011; Mai et al., 2011; Mai et al., 2014).

Figure 4.1. The 3-tier stepwise approach used for our analysis. The methodology used that guides the researcher through the three analytical steps for assessing the pharmacogenomics and genomic medicine policy environment

4.3.2. Data analysis

We have employed the *PolicyMaker's* computerized version of political mapping, which enhances the flexibility of this method for application to diverse policy environments (Reich, 1996; Reich and Cooper, 1996). *PolicyMaker* serves as a database for assessments of the policy's content, the major players, the power and the policy positions of key players, the interests of different players, and the networks and coalitions that connect the players. As such, this research method aims to help policymakers managing the processes of reform and promote strategic programming as well as strategic thinking (Mintzberg, 1994). Our analysis of the pharmacogenomics and genomic medicine environment in Greece was performed in a 3-tier approach, outlined in **Figure 4.1**. All the participants

signed the informed consent section and their anonymity and the confidentiality of the questionnaire content was ensured.

Table 4.1. Key stakeholders, their respective sector, position and power to intervene in pharmacogenomics and genomics medicine. [a]: In the field of genomic medicine and/or pharmacogenomics, including pharmaceutical and biotechnology companies

Stakeholder	Abbreviations	Sector	Position	Power
Academic and research organizations	AcadResOrg	Local non-governmental	High support	Medium
Greek bioethics council	BioethicsCouns	Local non-governmental	Medium support	High
Private genetic laboratories	PrivGenLab	Private	High support	Low
Religious organizations and church	ReligOrg&Church	Religious	Medium opposition	Low
Consumers and citizens	Cons&Citiz	Social	Medium support	Medium
Pharmaceutical and biotechnology companies	Pharma&Biotech	Private	High support	High
Genetics and genomics professional associations	G&GProfAssoc	Local non-governmental	High support	Medium
Ministry of Health	MoH	Governmental	Medium opposition	High
Payers (Private Health Insurance Industry)	PrivInsInd	Private	High support	Medium
Payers (Public Health Insurance Funds)	PubInsFund	Governmental	Medium opposition	High
Other private companies [a]	OthPrivComp	Private	High support	High
Pharmacies	Pharmacy	Private	High support	Medium
Physicians (Geneticists)	Phys (Genet)	Private	Medium support	Medium
Physicians (Others)	Phys (Others)	Private	Low support	High
Press and Media	(Press)	Media	Non-mobilized	Medium
Private providers	PrivProvider	Private	High support	Medium
Public providers	PubProvider	Governmental	High support	Medium
Greek National Medicines Organization	NatlMedOrg	Governmental	Non-mobilized	High

4.4. Results and Discussion

We have analyzed questionnaires from representatives of all key players and stakeholders in the pharmacogenomics and genomic medicine policymaking in Greece, as outlined above (**Table 4.1**), while the views of a total of 1717 members of the general public, 704 physicians of various medical specialties, 87 healthcare professionals (other than physicians) and 86 pharmacists were also included in our analysis. Based on these findings, we have generated the Current Position Map (**Fig. 4.2**), in which each stakeholder was grouped according to the extent of its support or opposition to pharmacogenomics and genomic medicine in Greece. Also, based on the same dataset, we have constructed a more comprehensive graphical presentation of the key stakeholders' initial position, including their various interests (deducted from Question 3 of the questionnaire; see **Appendix 2**) and their clustering is shown in the Coalition Map (**Fig. 4.3**).

Our data show that in general, half of the key stakeholders are highly supportive of pharmacogenomics and genomic medicine in Greece, among which were pharmaceutical and biotechnology companies, as well as molecular diagnostics laboratories. These also have strong influence and are driving forces to support clinical implementation of pharmacogenomics from a technology-driven point of view.

On the other hand, there is a medium opposition from the Ministry of Health and the public health insurance funds, based on not yet fully proven cost effectiveness of a pharmacogenomics approach, both of which have high power to intervene against the implementation of pharmacogenomics and genomic medicine into mainstream clinical practice.

The strong financial interest and responsibility of both stakeholders (**Table 4.3**) could in part explain this finding. Public health insurance funds may lack the information on how reimbursement of genetic testing could decrease the overall healthcare expenditure, instead of increasing, particularly since over 75% of the physicians think that the costs of genetic testing services should be reimbursed by insurance companies (Mai et al., 2011).

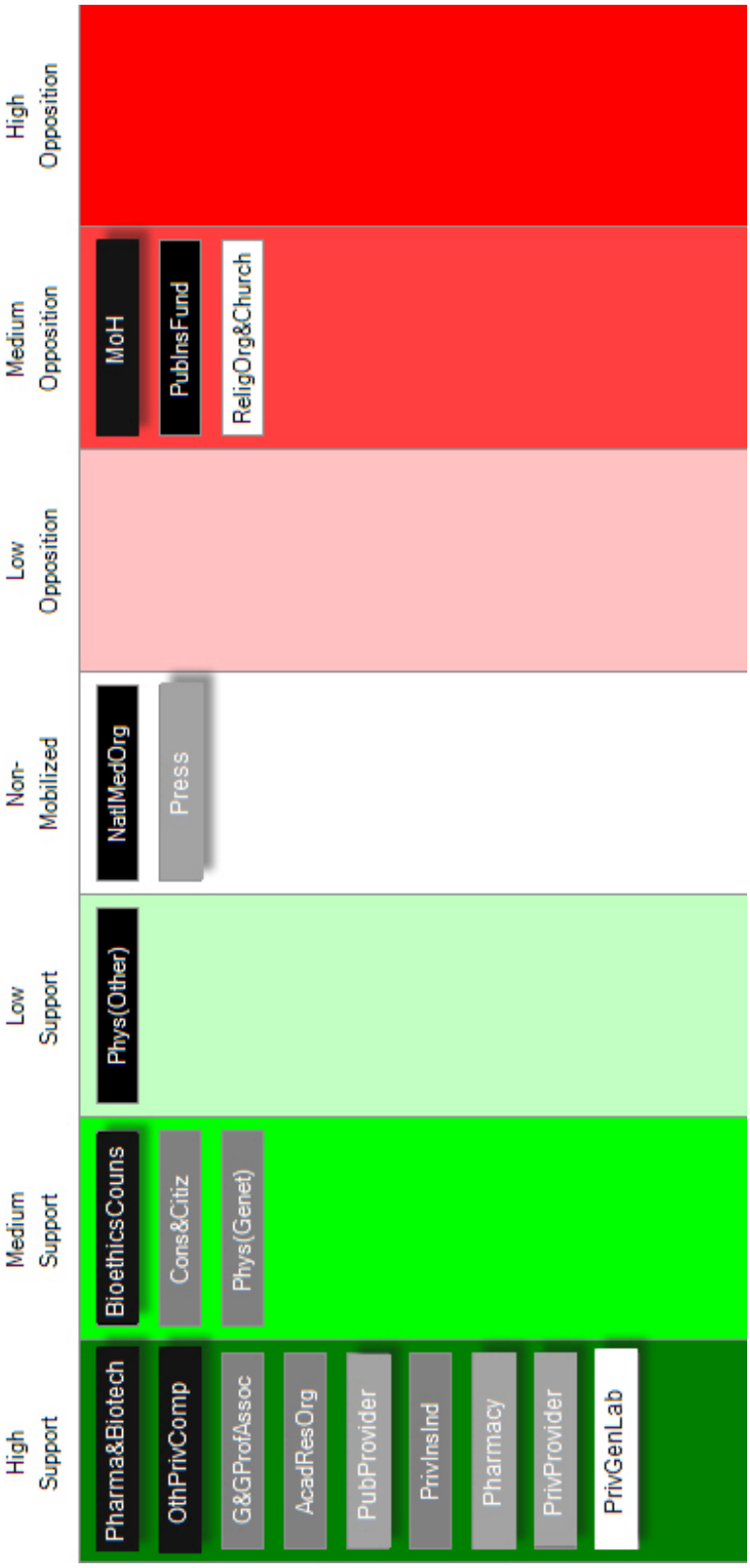

Figure 4.2. Current Position Map. The stakeholders' current position on pharmacogenomics and genomic medicine (see also **Table 4.2**). Black boxes depict "High Power" of the stakeholders to intervene, grey boxes "Medium Power" and white boxes "Low Power", respectively. For abbreviations, please refer to **Table 4.1**.

This would constitute a major challenge for an economy for which the GDP contracted by 20% in 4 years, unemployment rate increased by 15 percentage points to almost 24% (European Commission, 2013) and for a healthcare system struggling to rationalize licensing, pricing and reimbursement systems for healthcare services, medicines and medical devices.

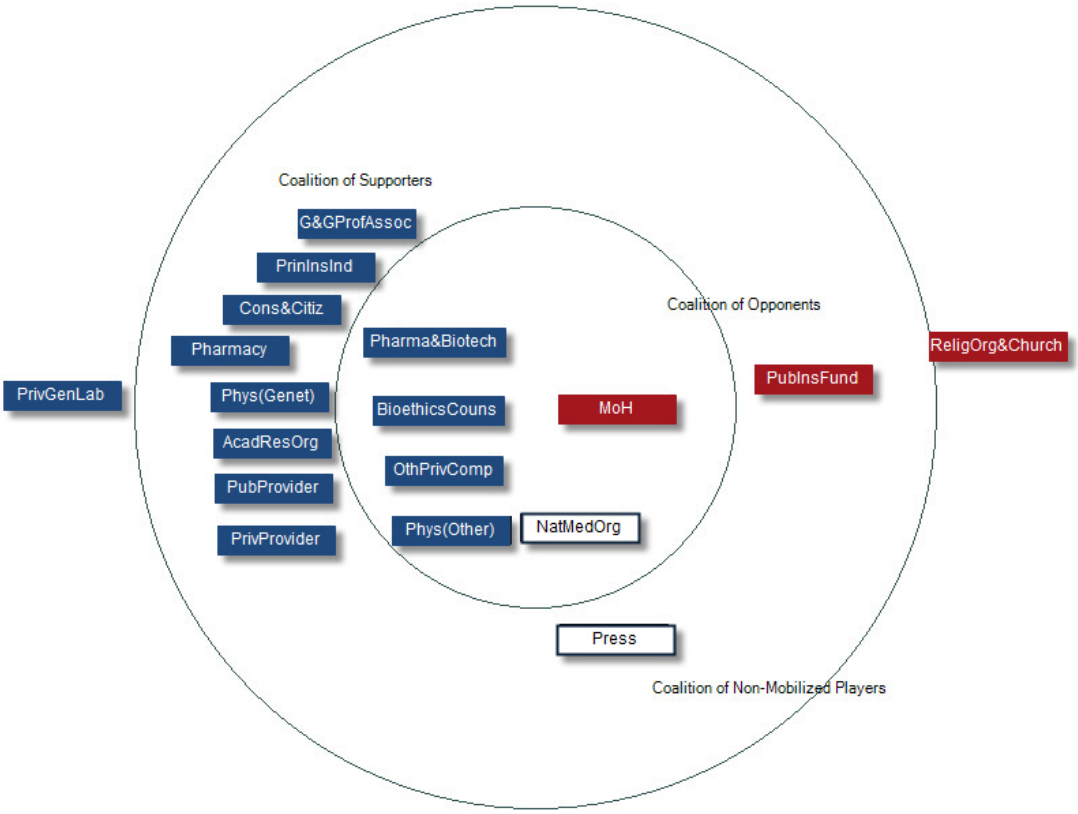

Figure 4.3. Coalition Map. A more comprehensive graphical presentation of the key stakeholders' current position, but also of the homogeneity of their interests and their grouping. For abbreviations, please refer to **Table 1**.

The current lack of proper legislation to oversee the operation of private genetic testing laboratories (Sagia et al., 2011; Kechagia et al., 2014) could also explain the medium opposition of these stakeholders. This, notwithstanding, contradicts the positions of both the National Medicines Organization (non-mobilized) and the National Bioethics Council (highly supportive), particularly since issuing an opinion regarding direct-to-consumer genetic testing services (www.bioethics.gr/images/pdf/GNOMES/OPINION%20DTC%20genetic%20tests-Final-GR.pdf; report in Greek).

Table 4.2. Stakeholders' interests and the respective priority level. [a]: In the field of genomic medicine, including pharmaceutical and biotechnology companies

Stakeholder	Interest	Priority
Academic and research organizations: 1	Scientific	High
Academic and research organizations: 2	Financial	Medium
Greek bioethics council: 1	Humanitarian	High
Private genetic laboratories: 1	Financial	High
Private genetic laboratories: 2	Professional	High
Religious organizations and church: 1	Religious	Medium
Consumers and citizens: 1	Self-interest	High
Consumers and citizens: 2	Financial	Medium
Other private companies [a]: 1	Financial	High
Other private companies [a]: 2	Professional	High
Other private companies [a]: 3	Scientific	High
Genetics and genomics professional associations: 1	Professional	High
Genetics and genomics professional associations: 2	Scientific	High
Ministry of Health: Control health care costs	Financial	High
Payers (Private Health Insurance Industry): 1	Financial	High
Payers (Public Health Insurance Funds): 1	Financial	High
Pharmaceutical and biotechnology companies: 1	Financial	High
Pharmacies: 1	Financial	High
Pharmacies: 2	Professional	Medium
Physicians (Geneticists): 1	Professional	High
Physicians (Geneticists): 2	Scientific	High
Physicians (Geneticists): 3	Financial	High
Physicians (others): 1	Professional	Medium
Physicians (others): 2	Scientific	Medium
Physicians (others): 3	Financial	Medium
Press and Media: 1	Ideological	Medium
Press and Media: 2	Political	High
Private providers: 1	Financial	High
Public providers: 1	Financial	High
Greek National Medicines Organization: 1	Scientific	High

Quite surprisingly, the position of the private health insurance companies is highly supportive, that is at the opposite direction compared to that of the public health insurance funds, a fact that warrants further investigation and possibly exploitation in order to convince the latter funds to also adopt a supportive attitude towards this emerging trend of genomic medicine. Lastly, the Church displays a medium opposition, although the power to intervene is lower than the other stakeholders.

Table 4.3. Opportunities and obstacles to implement Genomic Medicine in Greece

Opportunities	Obstacles
• The ability of treating diseases at a personal level • Very rapid development of the biotechnology industry • Personalized, effective treatment with fewer side effects • Lower costs for drug therapies and treatment • Implementation of next-generation sequencing technology • Development and (diagnostic) application of array-on-demand technology in combination with next-generation sequencing • Development of diagnostic applications of next-generation sequencing to unravel the cause of unknown genetic diseases and for non-invasive prenatal diagnosis (NIPD) • Maintenance of the general multidisciplinary approach, while avoiding further diversification • Continue strengthening national and international interactions in the bio-banking area	• The ignorance or incomplete knowledge of patients-citizens • Lack of sufficient funding • Personal data protection assurance • Denial of insurance based on the genetic profile • Cost of tests not covered from the insurance companies. • Incomplete information for physicians to select appropriate therapy based on the genetic profile. • Health care reform is likely to elicit opposition from many powerful and well-organized interest groups • Lack of a stable healthcare environment • Lack of a consistent National strategy on Genetics-Genomics

We found that citizens, geneticists, other physicians as well as the pharmacies are highly supportive. These findings are in line with our previous

observations, indicating that the general population is in general positive towards genomic medicine and individualization of drug treatment, despite the fact that they professed that their level of genetics awareness is fairly low [6]. However, the general public may get confused as to which tests can be truly beneficial for them (Patrinos et al., 2013; Kampourakis et al., 2014).

The Media and the Press currently hold a neutral position on genomic medicine, which if changed to a medium to high support and present objective opinions and facts by academics, qualified professionals, and regulatory bodies, it would significantly facilitate and expedite adoption of pharmacogenomics and genomic medicine and also alter the position of governmental organizations that currently hold an opposition stance towards genomic medicine.

Subsequently, we have identified several opportunities and obstacles in the pharmacogenomics and genomic medicine policymaking in Greece, based on the current position and power of the key stakeholders to intervene. These opportunities and obstacles are outlined in **Table 4.3**, underlining the fact that the majority of the stakeholders seem to unveil their financial interest at a high priority. Most of the professional key players also express their scientific and professional interest, while the consumers highly prioritize their self-interest to access to, high quality and affordable health services. Finally, the strategic goals of the pharmacogenomics and genomic medicine policymaking was defined, based on the first and second questions of the questionnaire, and outlined in **Appendix 2**, along with the proposed implementation mechanism.

4.5. Concluding remarks

We provide here results from a stakeholder analysis to analyze the policy environment and identifying the role, the interests and the position of the key stakeholders related to pharmacogenomics and personalized medicine. Our findings underline that the majority of the key stakeholders are favorably viewing the implementation of genomic medicine, despite the fact that the Ministry of Health and the public health insurance funds stand at this moment against this new trend in medical practice. It is anticipated that once some tangible benefits from the implementation of pharmacogenomics become available, the overall

position of these key stakeholders are likely to change to a more favorable one, accompanied by the likely change of the overall economic climate in Greece and the demonstration of genomic medicine and pharmacogenomics as yet another cost-containment measure. These findings will be valuable to adopt the necessary steps and measures not only to maintain the overall positive attitude of most stakeholders towards genomic medicine but most importantly to shift the remaining stakeholders from a neutral-to-negative opinion into a more supportive position.

Our future goal is to replicate this study not only in Greece in the coming few years in order to acquire further insight into the future views of these stakeholders in but also in other countries to compare the views and attitudes of the same stakeholders in order to harmonize policies towards the establishment of the genomic medicine landscape into future medical practice.

4.6. Acknowledgements

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Chapter 5

Economic evaluation of pharmacogenomic-guided warfarin treatment for elderly Croatian atrial fibrillation patients with ischemic stroke

Mitropoulou C, Fragoulakis V, Bozina N, Vozikis A, Supe S, Bozina T, Poljakovic Z, van Schaik RH, Patrinos GP. ***Pharmacogenomics***. 2015;16:137-148.

5.1. Abstract

Economic evaluation in genomic medicine is an emerging discipline to assess the cost-effectiveness of genome-guided treatment. Here, we developed a pharmaco-economic model to assess whether pharmacogenomic-guided warfarin treatment of elderly patients with atrial fibrillation in Croatia is cost-effective compated with non-pharmacogenomic therapy. The time horizon of the model was set at one year. Our primary analysis indicates that 97.07% (95%CI: 94.08%-99.34%) of patients belonging to the pharmacogenomics-guided group have not any major complications, compared to the control group (89.12%; 95%CI: 84.00%-93.87%, $p<0.05$). The total cost per patient was estimated at €538.7 (95%CI: €526.3-€551.2) for the pharmacogenomics-guided group vs €219.7 (95%CI: €137.9-€304.2) for the control group. In terms of QALYs gained, total QALYs was estimated at 0.954 (95%CI: 0.943-0.964) and 0.944 (95%CI: 0.931-0.956) for the pharmacogenomics-guided and the control groups, respectively. The true difference in QALYs was estimated at 0.01 (95%CI: 0.005-0.015) in favour of the pharmacogenomics-guided group. The incremental cost-effectiveness ratio of the pharmacogenomics-guided vs the control groups was estimated at €31,225/QALY. Overall, our data indicate that pharmacogenomics-guided warfarin treatment may represent a cost-effective therapy option for the management of elderly patients with atrial fibrillation in Croatia.

Key words: pharmacogenomics, economic evaluation, warfarin, atrial fibrillation

5.2. Introduction

Atrial fibrillation (AF) is the commonest cardiac arrhythmia of the general population. The prevalence of AF increases with age from <0.5% at those of 40-50 years to 5-15% at those at 80 years of age, while, due to demographic trends, its frequency is expected to rise in the future (Go et al., 2001; Lloyd-Jones et al., 2004; Heeringa et al., 2006; DeWilde et al., 2006; Rietbrock et al., 2008; Naccareli et al., 2009; Rich, 2009; Camm et al., 2010). As a result, AF represents a significant public health problem, as it has been associated with increased rates of stroke, systemic embolism, heart failure and left ventricular dysfunction, which in turn result in reduced quality of life and higher death rates (Camm et al. 2010; Kirchhof et al., 2007; Steward et al., 2002; Thrall et al., 2006; Korantzopoulos et al., 2012). Moreover, AF also generates significant health care services utilization and represents a great economic burden for the modern healthcare systems (Steward et al., 2001; Friberg et al., 2003; Wattigney et al., 2003; Steward et al., 2004; Coyne et al., 2006; Bruggenjurgen et al., 2007; Reynolds et al., 2007; Ghatnekar et al., 2008; Ringborg et al., 2008; McBride et al., 2009; Wolowacz et al., 2011; Karampli et al., 2012).

The primary goal in the treatment of AF patients using anticoagulation therapy is to reduce symptoms and to prevent complications. International guidelines issued by the European Society of Cardiology (National School of Public Health, 2012) provide guidance on how to manage patients based on their risk status, the latter being defined in terms of their CHADS2 (cardiac failure, hypertension, age, diabetes, stroke2) score. Anticoagulant therapy with warfarin decreases the risk of embolic stroke by 50%. However, warfarin poses a risk for major hemorrhagic events such as intracranial haemorrhage and gastrointestinal bleeding (Landefeld and Goldman, 1989; Fanikos et al., 2005).

Warfarin dose requirement depends on several demographic and nutritional factors, as well as the medical history of the patient, while it also has a strong genetic component. In particular, *CYP2C9* and *VKORC1* genotypes have been shown to relate to warfarin metabolism. In particular, carriers of *CYP2C9* genomic variants metabolize S-warfarin more slowly than patients bearing the wild-type allele, leading to elevated international normalized ratios (INRs) at

common initial doses of warfarin (Gage and Lesko, 2008), while carriers of *VKORC1* genomic variants require a lower warfarin dose as well, to appropriately inhibit coagulation. Obviously, variations in both genomic loci induce resistance to warfarin (Gage and Lesko, 2008). *CYP2C9* and *VKORC1* pharmacogenomic testing has been reported to have 50%-60% accuracy in predicting the warfarin maintenance doses, which can potentially decrease the incidence of bleeding, as a result to the elevated INRs. As such, genotyping of pharmacogenomic variants related to warfarin metabolism has the potential to improve clinical management of warfarin treatment and, reciprocally decrease the likelihood of bleeding. In this case, however, *CYP2C9* and *VKORC1* pharmacogenomic testing represents an additional cost item, which efficacy and economic outcomes still remains unknown for the majority of healthcare systems.

In Croatia, like in many developing countries, health resources are scarce and demographic and technological trends are pushing budgets upwards. Therefore, it is important to find ways that can aid decision makers to direct resources to the most efficient therapies. This is even more important in the context of the present global financial crisis and the pressures upon public budgets. Hence, to guide efficient resource allocation, an economic evaluation was undertaken in order to assess the therapeutic alternatives available for thrombophylaxis in the management of AF in elderly patients in Croatia. It must be noted that several cost-effectiveness studies have been conducted in general comparing pharmacogenomic-guided warfarin treatment, but this is the first one conducted in the local setting.

The aim of the present study was to conduct an economic evaluation comparing, pharmacogenomic (PGx)-guided warfarin therapy vs non-pharmacogenomic (N-PGx) warfarin therapy in the treatment of elderly patients who developed ischemic stroke predominantly due to atrial fibrillation.

5.3. Methods

5.3.1. Analysis perspective

The present economic analysis was carried out from the Croatian National Healthcare system perspective; as such, only direct healthcare provider costs

reimbursed by the payers were considered, namely costs which are associated directly with the care of patients and reflect all the resources expensed in delivering the treatments under investigation and managing any adverse events within the healthcare system of Croatia. Other costs that quantify the productivity loss associated with each therapy, or direct payments by patients for traveling or other resources, were not taken into consideration (Weinstein et al., 2003).

5.3.2. Data used

All patients included in this study with acute ischemic stroke (AIS) that were hospitalized in the Department of Neurology, University Hospital Center Zagreb for a period of six months were prospectively observed. In particular, the main inclusion criteria of patients were: a) to have previously taken warfarin due to AF, mechanical heart valves, deep vein thrombosis or pulmonary embolism; b) newly discovered AF patients confirmed by HOLTER ECG; c) patients with foramen ovale apertum (FOA) with septal aneurysm; d) acute dissection of extracranial or intracranial arteries; e) cerebral venous sinus thrombosis.

Exclusion criteria were: a) bleeding in the brain detected by CT scan except in patients with cerebral venous sinus thrombosis; b) malignancy, c) pregnancy for women; d) hepatic and renal insufficiency; and e) age<18 year. Eligible patients were centrally registered and stratified according to sex, age, and then, randomly assigned to the two different treatment arms which, as indicated in **Table 5.1**, is reasonably well balanced.

On admission, blood samples (10 ml) were taken for INR measurement in both groups and for genotyping (only in PGx). Low molecular weight heparin was administered before the initial dose of warfarin was introduced, during first five to seven days since admission. Patients were assigned to the group of respondents (genotype-guided dosing group, PGx) or to the control group (standard dosing group, N-PGx). In both groups, patients were permitted to receive symptomatic drugs like antihypertensives, statins, or antiepileptics as needed.

PGx consisted of 104 acute stroke patients, among whom analysis of *CYP2C9* *2, *3 and *VKORC11173*C>T gene polymorphisms was conducted before the introduction of warfarin. Using non-profit website published algorithm *http: //www.WarfarinDosing.org*, for each patient during the first two days we assessed

initial pharmacogenomically-predicted warfarin dose and introduced the calculated "mini loading dose" (dose of introduction) of warfarin according to the American College of Chest Physicians guidelines (Holbrook et al., 2012).

Table 5.1. Patients Characteristics [n (%)]

	Pharmacogenomics (PGx)	**Non-Pharmacogenomics (N-PGx)**	**p-value**
Number of patients			
All	104 (100%)	102 (100%)	0.555
Male	45 (43.3%)	40 (39.2%)	
Female	59 (56.7%)	62 (60.8%)	
Age [mean ± SD (years)]			
All	67.7±13.6	69.6±12.2	0.424
Male	66.5±12.0	67.2±11.3	0.919
Female	68.7±14.7	71.1±12.6	0.449
Weight [mean± SD (kg)]			
All	75.2±10.5	74.3±10.5	0.515
Male	83.9±6.5	83.2±7.0	0.557
Female	68.6±7.7	68.6±8.1	0.911
Reason for oral anticoagulant therapy			
Chronic Atrial Fibrilation	24 (23.1%)	21 (20.6%)	0.666
Artificial Aortic Valvule	7 (6.7%)	7 (6.9%)	0.970
Deep venous thrombosis (DVT) or pulmonary embolism (PE)	4 (3.8%)	1 (1.0%)	0.377
Newly diagnosed Chronic Atrial Fibrilation	53 (51.0%)	64 (62.7%)	0.08
Dissection	10 (9.6%)	5 (4.9%)	0.301
Thrombosis of venous sinuses	3 (2.9%)	2 (2.0%)	0.667
Foramen Ovale Apertum (FOA)	2 (1.9%)	2 (2.0%)	0.984
New Deep venous thrombosis (DVT) or pulmonary embolism (PE)	1 (1.0%)	-	
Concominant Therapy			
All	16 (15%)	8 (7.8%)	0.09
Male	6 (13.3%)	4 (10.0%)	0.634
Female	10 (16.9%)	4 (6.5%)	0.07

Further on, the doses were adjusted depending on the measured INR values. Only in patients with "wild" *CYP2C9* *1/*1, *VKORCl*-1173 CC genotype, we applied a double dose of estimated doses during the first two days of treatment since it is known that these alleles are the slowest to achieve the target INR. After that, the doses were adjusted depending on the INR measurement. The control group (N-PGx) consisted of 102 patients with the same indication for anticoagulation and with the same criteria for entry in the study. Among them, warfarin was introduced by a fixed dose of 6 mg for the first two days according to the standard criteria without pharmacogenetic analysis and doses were then adjusted depending on INR values. The initial fixed dose was reduced by 25% in three patients due to the concomitant use of amiodarone.

Treatment effectiveness was measured as time and percent of time spent in the therapeutic/supratherapeutic INR range, time to reach a stable maintenance dose (at which the patient was maintained within the therapeutic INR range and which did not change during three consecutive INR measurements for at least five days), warfarin dosage-dependent side effects and neurological deficit. Target INR value was ≥ 2, therapeutic INR range was 2-3, subtherapeutic INR values were defined as INR<2 and supratherapeutic values were determined as INR>3.1.

In the present analysis minor complications (minor bleeding) were defined as asymptomatic microhematuria, slight gingival or vaginal bleeding or small subcutaneous hematoma. More extensive bleeding ("Major complications") were classified into two subgroups: a) bleedings that did not require discontinuation of therapy, such as mild hemorrhage into the infarct zone without worsening of neurological deficit and b) bleedings that required discontinuation of warfarin therapy, such as large intracerebral hematoma with deterioration of neurological deficit, extensive urogenital or gastrointestinal bleeding.

In the control group, INR testing was performed on 2nd, 3rd, 5th and 7th day during the first week of warfarin therapy. In the 2nd and 3rd week of therapy, INR measurement was performed on every 2nd or 3rd day depending on the INR values and the need for dose correction. The study was conducted in accordance with the declaration of Helsinki and all patients give written informed consent in order to participate in the study.

Table 5.2. Probabilities, costs and utility values used in the model. *The SD referred herein was determined by using the mean value (p) as: SD=[p* (1-p)]/n, where n the corresponding sample of the study.

	Mean	SD*	Source
Transition Probabilities			
Minor bleeding (PGx)	0.087	0.028	Study calculations
Major bleeding (PGx)	0.029	0.016	
Minor bleeding (N-PGx)	0.157	0.036	
Major bleeding (N-PGx)	0.108	0.031	
No_event_to_mortality	0.044	0.003	
Major_Bleeding_to_Mortality	0.133	0.025	De Katerina et al., 2010
Minor_bleeding_to_mortality	0.053	0.011	
Values			
Mortality	6 months Alive		Assumption
Survive	12 months Alive		
Utility Values			
AF without complications	0.98	-	Patrick et al., 2009
Major Bleeding	0.8 for 1 month	-	
Death	0	-	
Drugs costs (€)			
1 mg of warfarin	0.0136		Local Economic Data
Extra costs in case of major bleeding:			
A. 1 day in hospital 105 euros, for 8 extra days	840		
B. CT scan x 2 (75.9 x 2)	151.8		
C. Additional tests for INR 10x 2,1 eur	21		
D. Frozen plasma and vitamin K for 1 day	350.5		
E. Colistin (polymyxin E) for 10 days	537.66		
F. Ciprinol (ciprofloxacin) for 10 days	208.36		
G. Meronem (meropenem) for 10 days	525.97		
H. Endoscopic interventions in case of gastrointestinal bleeding	373.5		
Cost of Genetic Analysis (€)	140.25		

5.3.3. Genotyping analysis

In the PGx group, DNA was isolated from whole blood and three SNPs were genotyped by TaqMan® Drug Metabolism Genotyping Assays: *CYP2C9**2 (rs1799853) with assay ID C25625805_10, *CYP2C9**3 (rs1057910) with assay ID

C27104892_10 and *VKORC1* 1173C>T (*rs* 9934438) with assay ID C30204875_10. Genotyping was performed by the Applied Biosystems 7500 Real Time PCR System according to the manufacturer's instructions (Applied Biosystems, Foster City, CA, USA). All assays were run in 96 well plates under the same instrument conditions: 2 min at 50°C, 10 min at 95°C, following 50 cycles of 15 sec at 92°C with 90 sec at 60°C extension time. For each SNP, the 25 μl PCR reaction mixture per well consisted of 1.25 μl TaqMan® Drug Metabolism Genotyping Assay Mix (specific for each polymorphism), 12.5 μl TaqMan® Universal PCR Master Mix and 5 -20 ng of genomic DNA diluted in 11.25 μl dH_20.

5.3.4. Model Structure

Based on the aforementioned available data and international literature, we constructed a pharmacoeconomic model to compare from an economic point of view, PGx-guided vs N-PGx warfarin therapy in the treatment of elderly patients with AF in Croatia in a 1-year time horizon. Our pharmacoeconomic model is a decision tree constructed in a TreeAge Pro Suite 2013 (TreeAge Software, Inc., Williamstown, MA). Our model was populated with cost data from Croatia public tariff lists, in line with current treatment guidelines on patient management, outcomes and economic consequences. Differences relate only to the cost of the resources 'consumed' at each corresponding node of the model and the corresponding transition probabilities.

The transition probabilities for the first 6 months of the model were based on available data from the study. The transition probabilities concerning the remaining 6 months beyond the duration of our data, was extracted by a study conducted by (De Caterina et al, 2010), while the utility values used in the model was extracted by a similar cost-effectiveness analysis published in 2009 (Leey et al., 2009).

The model structure is identical for each of the two assessed strategies. In short, the structure of the model is identical for both arms and the differences relate only to the cost of the resources expensed and the transition and outcome probabilities in different nodes of the model. The model simulates the progression of patients from the moment they start therapy, to various states based on specified probabilities which were collected from our study and from the

literature. The likelihood of moving between different states is influenced by the effectiveness of each therapy and hence the cost and quality-adjusted years of life. As illustrated in **Figure 5.1**, patients can transition from the initial state to three distinct states including "no event", "major bleeding" and "minor bleeding". From these states, each patient may "survive" or "die" within a one-year time horizon.

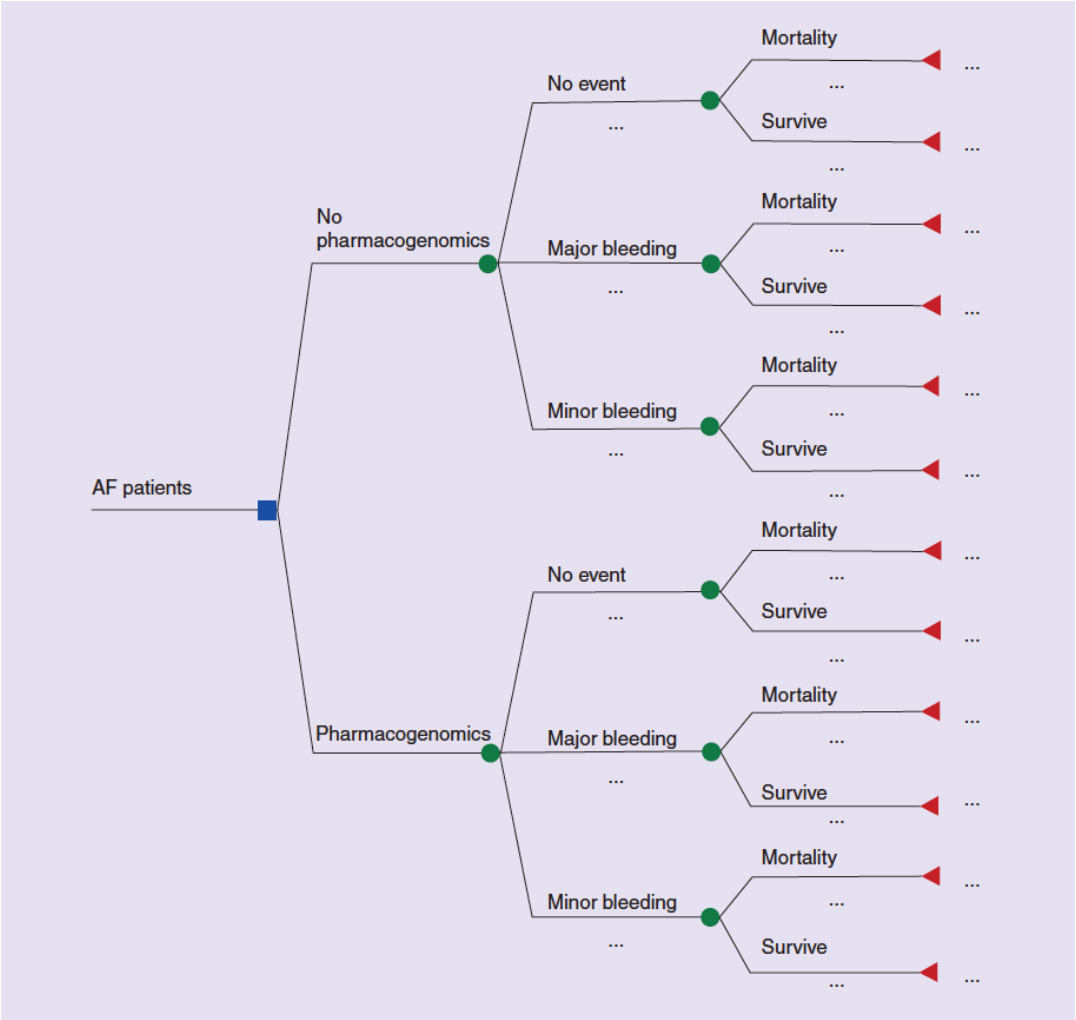

Figure 5.1. Model Diagram. Values used in the model are presented in **Table 2**.

5.3.5. Dealing with Uncertainty

Costs data are often skewed or do not follow normal distribution because there are often some small numbers of very costly cases which skew the results and heavily distort any statistical measures one may try to estimate (Desgagne et al., 1998). This is why we bootstrapped individual patient data 5000 times to get the mean of the bootstrapped mean and its standard deviations and confidence intervals. In particular, based on the initial data set of trial (including cost and

utility data), 5000 new data sets with the same number of observations were drawn at random with replacement. Mean values of the parameters of interest were obtained from each data set and were used to construct a new matrix with 5,000 observations. Their variability measures were used to estimate confidence intervals using the percentile method. The distribution of the bootstrapped means approximates the normal and their mean is a better (unbiased) estimator of the population mean.

5.4. Results

Our primary analysis indicated that the 97.07% (95%CI: 94.08%-99.34%) of patients belonging to PGx group have not any major complications, while in the N-PGx group the corresponding percentage was limited at 89.12% (84.00%-93.87%; $p<0.05$). The TC (time to achieve targeted INR) in case of the PGx group was estimated at 5.64 days (95%CI: 5.41-5.89), while in the N-PGx arm TC was 7.11 days (95%CI: 6.80-7.43; $p<0.05$) and the Tmd (time to achieve maintenance dose) was 10.35 days (95%CI: 10.05-10.65) in the PGx group compared to 13.87 days (95%CI: 10.05-10.65) in the N-PGx group (**Table 5.3**).

Details on each component of total treatment cost are presented in **Table 5.4**. The total cost per patient in the PGx arm was estimated at €187.68 (95%UI: €162.10-€5,901), while in the N-PGx arm the cost was €172.07 (95%UI: €100.67-€253.21), a non-significant difference of €-15.60 (95%UI: €-92.69-€67.45) in favor of N-PGx group. The main item driving total treatment costs was the cost of pharmacogenomic testing in the PGx group, accounting for approximately 75% of the total costs in this arm. The mean cost of bleeding was estimated at €28.07 (95%UI: €2.51-€63.52) in the PGx arm, whilst the costs in the N-PGx arm were €147.39 (95%CI: €76.14-€228.50), reaching a statistically significant difference at €119.32 (95%CI: €41.95-€202.69) in favour of the PGx group. The difference between the two arms concerning the cost of bleeding, was due to the fact that bleeding was more frequent in control group. The cost of INR testing and warfarin was lower in both arms.

Table 5.3. Main Results of the Primary Analysis. TC: time to achieve targeted INR; Tmd-time to achieve maintenance dose with warfarin; B: Bootstrap, SD: Standard Deviation; LCI: Lower Confidence Interval; UCI: Upper Confidence Interval. Results were based on 5,000 non-parametric bootstrap experiments.

	Tc days	Tmd days	No Major Complications
PGx Group			
B-Mean	5.7	10.4	97.07%
B-SD	0.1	0.2	1.39%
B-95% LCI	5.4	10.0	94.08%
B-95% UCI	5.9	10.7	99.34%
B-min	5.2	9.81	90.79%
B-max	6.1	10.9	100.00%
N-PGx Group			
B-Mean	7.1	13.9	89.12%
B-SD	0.2	0.2	2.53%
B-95% LCI	6.8	13.4	84.00%
B-95% UCI	7.4	14.3	93.87%
B-min	6.6	12.8	77.95%
B-max	7.8	14.8	96.71%
N-PGx vs PGx			
B-Mean	1.5	3.5	-7.95%
B-SD	0.2	0.3	2.70%
B-95% LCI	1.1	3.0	-13.37%
B-95% UCI	1.9	4.1	-2.77%
B-min	0.7	2.9	-18.56%
B-max	2.1	4.5	1.24%

Tables 5.5 and 5.6 show the results of the main model for the 1-year time horizon. Deterministic results indicate that PGx arm was associated with higher cost per patient and higher total QALYs gained compared with the N-PGx arm. The incremental cost-effectiveness ration was estimated at €31,225/QALY. In terms of QALYs gained, total QALYs was estimated at 0.954 (95%CI: 0.943-0.964) and 0.944 (95%CI: 0.931-0.956) for PGx and N-PGx, respectively. The true difference in QALYs was estimated at 0.01 (95%CI: 0.005-0.015) in favor of PGx. The results from the Probabilistic Sensitivity Analysis were illustrated by plotting the distribution of differences in costs and effects in the cost-effectiveness plane (**Fig. 5.2**). All the simulation experiments felt into the North East quadrant indicating

that the PGx arm was slightly more expensive but, at the same time, more effective than N-PGx.

Table 5.4. Cost Differences (in €) between Pharmacogenomics (PGx) and Non-Pharmacogenomics (N-PGx) groups per patient in the primary analysis. B: Bootstrap; SD: Standard Deviation; LCI: Lower Confidence Interval; UCI: Upper Confidence Interval. Results were based on 5,000 non-parametric bootstrap experiments.

	Cost of Bleeding	Cost of INR	Cost of warfarin	Cost of Test	Total Cost
PGx Group					
B-Mean	28.07	17.95	1.40	140.25	187.68
B-SD	15.72	0.14	0.04	-	15.74
B-95% LCI	2.51	17.68	1.32	-	162.10
B-95% UCI	63.82	18.23	1.49	-	223.44
B-min	0.00	17.46	1.26	-	159.16
B-max	103.39	18.51	1.58	-	262.90
N-PGx Group					
B-Mean	147.39	23.16	1.53	-	172.07
B-SD	39.04	0.19	0.02	-	39.03
B-95% LCI	76.14	22.79	1.50	-	100.67
B-95% UCI	228.50	23.52	1.56	-	253.21
B-min	24.76	22.43	1.46	-	49.32
B-max	310.47	23.87	1.59	-	335.47
Cost Differences (N-PGx vs PGx)					
B-Mean	119.32	5.20	0.12	-140.25	-15.60
B-SD	40.43	0.25	0.05	-	40.43
B-95% LCI	41.95	4.72	0.03	-	-92.89
B-95% UCI	202.69	5.69	0.21	-	67.45
B-min	-9.68	4.32	-0.08	-	-144.77
B-max	294.17	6.02	0.29	-	159.26

Table 5.5. Cost effectiveness results (deterministic analysis) for PGx vs non-PGx

	Cost per patient	Effectiveness (QALYs)	Incremental Cost	Incremental Effectiveness	ICER (per QALY)
PGx	538.7 €	0.954	319.4 €	0.01023	31,225 €
N-PGx	219.2 €	0.943	-		

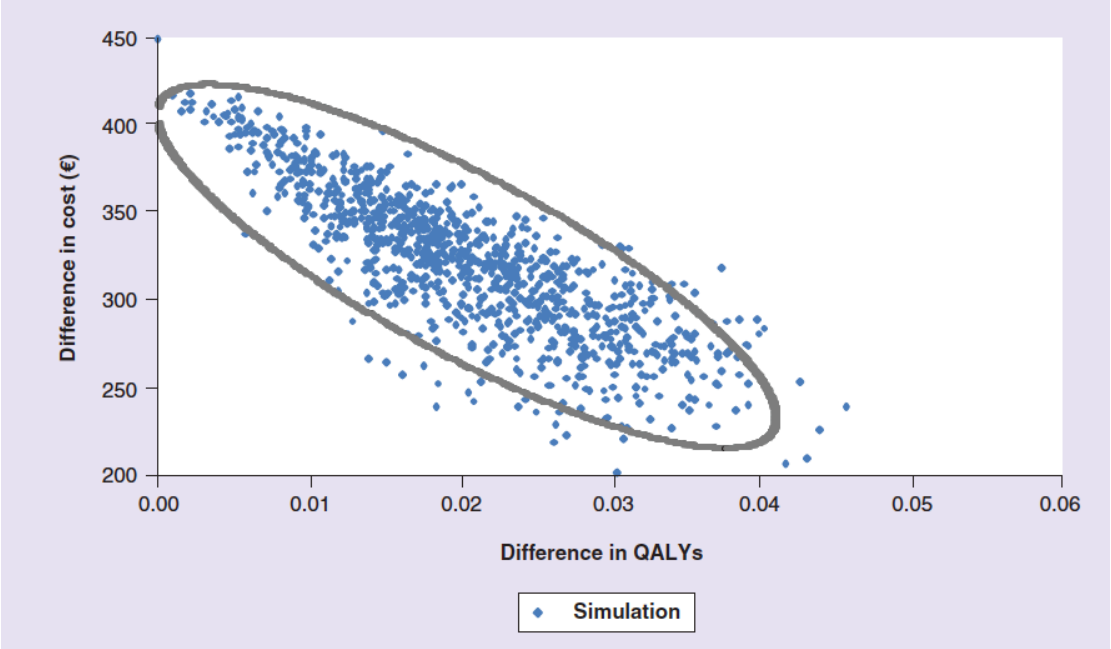

Figure 5.2. Scatter Plot of probabilistic analysis (PGx vs N-PGx)

We have then plotted the cost-effectiveness acceptability curve to demonstrate the probability (on the y-axis) that PGx may be cost-effective compared to the N-PGx for a range (on the x-axis) of maximum monetary values that a decision-maker might be willing to pay per QALY (Barton et al., 2008). Our data show that the probability of PGx being cost-effective increases significantly at a willingness-to-pay threshold in the range of €40,000 to €50,000 per QALY (Simoens, 2011), used in many jurisdictions; notably, at €60,000 per QALY its probability of cost-effectiveness is higher than 80%.

5.5. Discussion

Understanding the relative benefits of alternative strategies for elderly patients with AF is important in order to ensure that patients not only receive effective therapies, but also efficient care. In order to assess the economic impact of pharmacogenomic testing for AF patients to local budget, a cost-effectiveness analysis was considered as the appropriate approach for the case of Croatia. In this case, warfarin has been considered as an effective treatment for those suffering from AF and their use represent a standard practice in conventional medicine. The results of the analysis showed also that the PGx-guided warfarin

represents a prominent option for those suffering from AF in Croatia who developed ischemic stroke. It must be noted that the related literature in economic evaluation of pharmacogenomics is still limited. However, some data exist. For instance, in a recent economic evaluation the objectives were to evaluate the potential clinical and economic outcomes of genotype-guided warfarin therapy in elderly patients newly diagnosed with AF and to identify a threshold in bleeding risk at which such therapy may be cost-effective. The analysis concluded that genotype-guided warfarin therapy for anticoagulation in elderly patients with AF was potentially cost-effective, and its benefits were closely related to efficacy in preventing bleeding events (Leey et al., 2009).

Table 5.6. Probabilistic Results of the Model

	Statistics	N-PGx	PGx
Cost	**Mean**	219.7 €	538.7 €
	SD	43.2 €	6.3 €
	Minimum	96.2 €	520.3 €
	2.5%	137.9 €	526.3 €
	10%	163.1 €	530.4 €
	Median	218.0 €	538.6 €
	90%	274.5 €	546.7 €
	97.5%	304.2 €	551.2 €
	Maximum	395.5 €	561.9 €
	Variance	1,869.5 €	39.6 €
QALYs	**Mean**	0.944	0.954
	SD	0.007	0.005
	Minimum	0.919	0.931
	2.5%	0.931	0.943
	10%	0.935	0.947
	Median	0.944	0.954
	90%	0.953	0.961
	97.5%	0.956	0.964
	Maximum	0.962	0.968
	Variance	0.000	0.000

Similar conclusions were drawn from other studies under different methodological assumptions or comparators (Patrick et al., 2009; You et al., 2012). On the other hand, in a study which aimed to examine the cost-effectiveness of

genotype-guided dosing versus standard induction of warfarin therapy for patients with nonvalvular atrial fibrillation, the analysis showed that warfarin-related genotyping is unlikely to be cost-effective for typical patients but may be cost-effective in patients at high risk for hemorrhage who are starting warfarin therapy (Eckman et al., 2009).

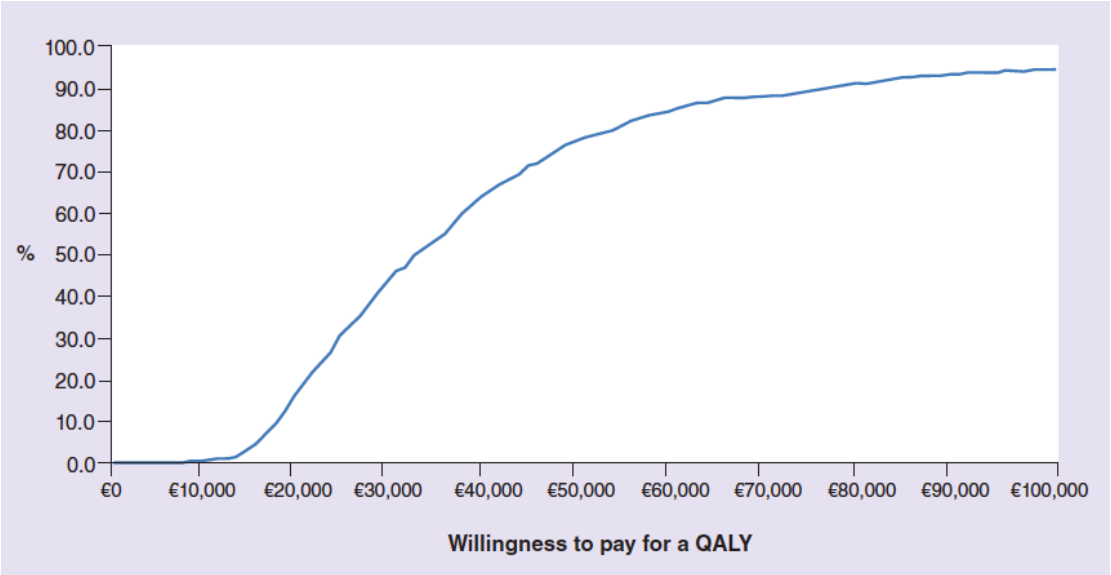

Figure 5.3. Cost effectiveness acceptability curve for PGx vs N-PGx. QALY: Quality-Adjusted Life Year

Similarly, in a study conducted by You and coworkers (2009) concluded that genotype-guided dosing for warfarin therapy does not appear to be cost-effective, with the potential ICER per QALY being greater than $50,000. Finally, a recent study by You and coworkers (2014) showed that pharmacogenomics-guided selection of warfarin versus novel oral anticoagulants for stroke prevention in patients with atrial fibrillation could be highly cost-effective under certain circumstances.

It must be noted that in our study the difference in effectiveness (QALYs) between PGx vs N-PGx is relatively small and someone could argue, from a statistical point of view, that there is not any meaningful difference. Nonetheless, in health economics the rules of classical statistical inference are inconsistent with the objectives of any coherent health care system and impose unnecessary opportunity costs. In case the objective is to maximize health gains for a given budget, programmes should be selected based on the posterior mean irrespective

of whether any differences are regarded as statistically significant. Therefore, analysts should focus their attention on estimation of cost-effectiveness rather than on hypothesis testing of cost or effect differences (Briggs and O'Brien, 2001).

Any model is by definition a simplification of the process they try to emulate and the present one is not the exception. In our study we preferred to model the course of the disease in a simple and intuitive manner based on data availability. In this case, no information has been provided -or has been modeled for both arms- regarding the complexity associated with the use of warfarin. In addition to that, certain assumptions have been adopted by the literature since it has not been provided by the raw data. In such a case, any dissimilarity between the populations would cause some alterations in the model results. Despite that fact, we believe that these simplifications could cause some amount of bias, but equally for both comparators, and thus, we are not expecting to cause alterations in the final conclusions.

The results of this model are not easily transferrable, as it is the case in the most of cases (Drummond et al., 2009), and have to be considered strictly in the context of the Croatian setting and on the basis of the present time and management practice of patients as well as drug and health resource prices. Hence is likely to change over time and thus, new economic analysis must be conducted periodically to assess the cost-effectiveness of comparators. Also, they have to be viewed in the context of the underlying model assumptions and data which were derived from an observational study conducted locally. To limit possible sources of bias, we conducted an assessment of the economic analyses in collaboration with experts and stochastic analysis in order to draw robust conclusions for the case of Croatia. In an economic analysis such as we discuss here, the estimation of the budget impact might be very useful for policy purposes. However, in this case, in order to have an appropriate analysis which we need some more data which is now missing. For that matter we prefer to stay focused only in our available data and the aforementioned cost-effectiveness analysis. Obviously, a comprehensive budget impact analysis could be the scope of a further future research in Croatia.

Overall, the present analysis indicates that, in Croatia, based on the current prices and resource utilization, pharmacogenomic-guided warfarin therapy may

represent a cost-effective therapy option compared with in the management of elderly patients with atrial fibrillation.

5.6. Acknowledgements

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Chapter 6

Economic analysis of pharmacogenomic-guided clopidogrel treatment in Serbian patients with myocardial infarction undergoing primary percutaneous coronary intervention

Mitropoulou C, Fragoulakis V, Rakicevic LB, Novkovic MM, Vozikis A, Matic DM, Antonijevic NM, Radojkovic DP, van Schaik RH, Patrinos GP.
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6.1. Abstract

Clopidogrel, which is activated by the CYP2C19 enzyme, is among the drugs for which all major regulatory agencies recommend genetic testing to be performed to identify a patient's *CYP2C19* genotype in order to determine the optimal antiplatelet therapeutic scheme. The *CYP2C19**2 and *CYP2C19**3 variants are loss-of-fucntion alleles, leading to abolished CYP2C19 function and thus have the risk of thrombotic events for carriers of these alleles on standard dosages, while the *CYP2C19**17 allele result in CYP2C19 hyperactivity. Here, we report our findings from a retrospective study to assess whether genotyping for the *CYP2C19*2* allele was cost-effective for myocardial infarction patients receiving clopidogrel treatment in the Serbian population compared to the non-genotype-guided treatment. We found that 59.3% of the *CYP2C19**1/*1 patients had a minor or major bleeding event versus 42.85% of the *CYP2C19**1/*2 and *2/*2, while a reinfarction event occurred only in 2.3% of the *CYP21C9**1/*1 patients, compared to 11.2% of the *CYP2C19**1/*2 and *CYP2C19**2/*2 patients. There were subtle differences between the two patient groups, as far as the duration of hospitalization and rehabilitation is concerned, in favor of the *CYP2C19**1/*1 group. The mean cost for the *CYP2C19**1/*1 patients was estimated at €2,547 versus €2,799 in the *CYP2C19**1/*2 and *CYP2C19**2/*2 patients. Furthermore, based on the overall *CYP2C19**1/*2 genotype frequencies in the Serbian population, a break-even point analysis indicated that performing the genetic test prior to drug prescription represents a cost-saving option, saving €13 per person on average. Overall, our data demonstrate that pharmacogenomics-guided clopidogrel treatment may represent a cost-saving approach for the management of myocardial infarction patientsundergoing primary percutaneous coronary interventionin Serbia.

Key words: pharmacogenomics, economic evaluation, clopidogrel, myocardial infarction, Serbian population

6.2. Introduction

Antiplatelet agent clopidogrel is an adenosine diphosphate (ADP) receptor blocker [Niitsu et al., 2005]. Patients with acute ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention (PCI) should receive a combination of dual antiplatelet therapy (DAPT) with aspirin and an ADP receptor blocker (Task Force for STEMI, 2012). The preferred receptor blockers are prasugrel or ticagrelor (Task Force for STEMI, 2012). Because these two drugs are contraindicated in some patients or are not available, still most commonly used antiplatelet drug is clopidogrel as a part of DAPT with aspirin (Mehta et al., 2010).

Clopidogrel is a prodrug that belongs to the drug class of thienopyridines, which activation – of a mere 15% of the prodrug, the rest being hydrolyzed and excreted – is mediated in the liver, mainly by CYP2C19 and also other enzymes (Niitsu et al., 2005).

Genomic variants in the *CYP2C19* gene have been shown to affect clopidogrel's activation, which directly impacts on the efficacy of the drug. The loss-of-function variants *CYP2C19**2, and *CYP2C19**3 abolish CYP2C19 activity, rendering the patients intermediate or poor metabolizers in which case clopidogrel is insufficiently activated and results in reduced efficacy (Scott et al., 2013). In the latter case, an alternative therapeutic agent is then recommended, such as prasugrel or ticagrelor (Sibbing et al., 2010]) On the other hand, the *CYP2C19**17 allele results in increased CYP2C19 enzyme activity and is thus associated with hypersensitivity to clopidogrel (Scott et al., 2013).

Major regulatory bodies, such as the US Food and Drug Administration and the European Medicines Agency, strongly recommend genetic testing to be carried out to identify a patient's *CYP2C19* genotype, prior to prescribing the necessary antiplatelet therapeutic modalities. This is particularly important considering that these variants are present in varying frequencies mostly in Asians but also in Caucasians and African Americans (Mizzi et al., 2016).

Contrary to the United States and European developed countries, in developing countries, there is often a scarcity in health resources. As such, policy makers must seek alternative strategies to make the optimal use of the resources available. In this case, economic evaluation plays an important role to assist decision makers to select the most optimal treatment modalities (Snyder et al., 2014). We have previously reported our findings from the first economic evaluation study in a developing country, where we prospectively showed that genotype-guided warfarin treatment may represent a cost-effective intervention in Croatian elderly patients suffering from atrial fibrillation (Mitropoulou et al., 2015). Here we report our results from a retrospective study, aiming to explore whether pharmacogenomics (PGx)-guided clopidogrel treatment is cost-effective in Serbian patients suffering from myocardial infarction, compared with the conventional non-PGx-guided clopidogrel treatment.

6.3. Materials and Methods

6.3.1. Study population

Overall, 1,059 consecutive ST Segment Elevation Myocardial Infarction (STEMI) patients were admitted for primary PCI between June 2010 and April 2011 at the Department of Cardiology Clinical Centre of Serbia, Belgrade. Of these, 66 patients experienced in-hospital bleeding and were included in the study together with 55 case-control STEMI, out of 993 (1,059-66), patients without bleeding from the same patient group. In total, 121 patients were subsequently genotyped for the *CYP2C19**2 and *CYP2C19**3 alleles (see below) and included in the economic analysis.

6.3.2. Study definitions

Acute STEMI definition was based on the history of chest pain/discomfort lasting for at least 20 minutes attributed to myocardial ischemia, accompanied by persistent ST-segment elevation of ≥ 1 mm in ≥ 2 contiguous limb leads or ≥ 2 mm

in precordial leads; or presumable new left bundle branch block; or true posterior myocardial infarction (MI) with ST depression of ≥ 1 mm in ≥ 2 contiguous anterior leads (van de Werf et al., 2003).

The Bleeding Academic Research Consortium (BARC) classification was used from the detailed clinical data of patients within hospital bleeding. All in hospital bleeding events were assessed using BARC and Thrombolysis in myocardial infarction (TIMI) criteria. Major adverse cardiovascular and cerebrovascular events (MACCE) were defined as a composite of death, reinfarction, target vessel revascularization for ischemia or stroke. Stent thrombosis (ST) (definite and probable) was defined according to Academic Research Consortium criteria (Cutlip et al., 2007).

6.3.3. PCI procedure and subsequent antithrombotic medication

All patients with STEMI underwent emergency coronary angiography using standard percutaneous techniques via femoral or radial artery, followed by primary PCI (angioplasty or intra coronary stent implantation), CABG or medical management. Unfractionated heparin was administrated as an intravenous bolus of 100 IU per kilogram of body weight or 50-60 UI/kg, if glycoprotein IIb/IIIa inhibitor (GPI) is given (van de Werf et al., 2008). Aspirin (300 mg orally) was preloaded in all patients, after which 100-300 mg was given orally every day during the first 30 days and 100 mg daily thereafter indefinitely.

Clopidogrel was given as a loading dose of 600 mg before insertion of the catheter, and 75 mg orally every day for one year. Use of GPI during primary PCI was left to physician's discretion. The only GPI used in our study was Tirofiban.

6.3.4. Endpoints and follow-up data

The primary endpoint was one year cumulative rate of adverse clinical events. The primary clinical safety endpoint was the incidence of bleeding, defined according to the BARC criteria. Overall bleeding events were also assessed using

the TIMI criteria (combined TIMI major and minor bleedings). The primary clinical efficacy endpoint was the cumulative incidence of definite and probable stent thrombosis (ST) during a follow up period. The primary ischemic endpoint was the composite of MACCE (death from any cause, nonfatal myocardial infarction, or stroke). Out of hospital clinical outcomes were obtained by telephone interviews of patients and families conducted by educated medical doctors or in the outpatient clinic at 30 days and one year follow up. The follow up mortality rate was 99.2%. The achieved rate of follow-up for MACCE was 98.4%. The study protocol was approved by the institutional ethics committee and was conducted in accordance with the Declaration of Helsinki.

6.3.5. Genotyping

Genomic DNA was isolated from peripheral blood and target region(s) of the *CYP2C19*gene were amplified by polymerase chain reaction (PCR) and sequenced using the Applied Biosystems 3130 Genetic Analyzer using the BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems) to detect the *CYP2C19**2 and *CYP2C19**3 variant alleles. Genotyping conditions are available upon request.

6.3.6. Analysis perspective and model structure

The perspective of the present analysis is based on direct health care cost items which are reimbursed by the Serbian health insurance fund and did not take into account other indirect costs. In particular the cost analysis included the costs of: a) genetic testing, b) hospitalization, c) single RePCI, d) vascular operation, and e) rehabilitation. Our economic analysis was restricted to the heterozygous and homozygous patients of the *CYP2C19**2 allele. The data for patients included in the economic analysis are presented in **Table 6.1**. **Table 6.2** indicates the cost items used in the analysis.

Based on the aforementioned available data, a simple economic model was constructed to compare two alternative treatment strategies for homozygous wild-type vs *CYP2C19**2 hetero- and homozygous patients that undergo clopidogrel treatment. The life horizon of the model was considered to be 1 year. This pharmacoeconomic model is, in principle, a decision tree, which is subsequently populated with cost data from the Serbian public tariff lists. Due to lack of appropriate data, no efficacy data were taken into consideration. As illustrated in **Figure 6.1**, in accordance with strategy "A", a random patient will be treated either "blindly", namely without taken their genetic profile into consideration. In this strategy, the economic advantages come from avoiding the cost of the genetic test.

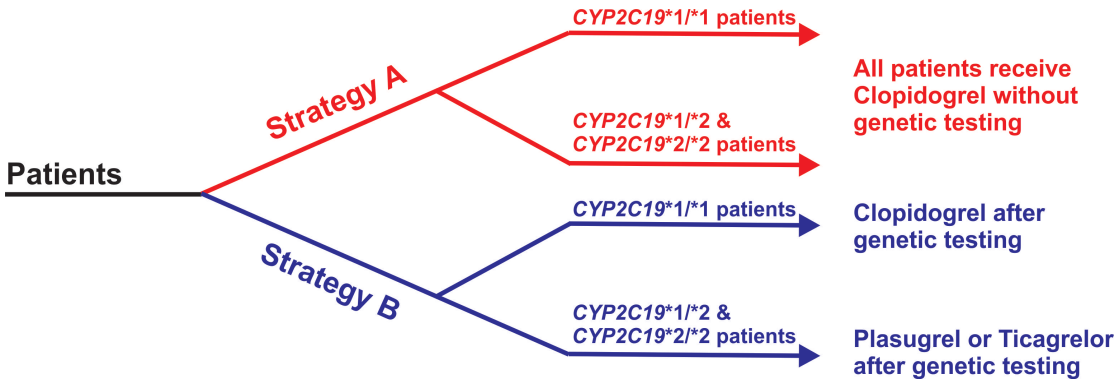

Figure 6.1. Model diagram, depicting the two alternative strategies. The conventional strategy (depicted in red) implies that all patients will receive clopidogrel without the need of performing a genetic testing. The alternative strategy (depicted in blue) implies that genetic testing will precede the drug prescription. In case of extensive metabolizers (*CYP2C19**1/*1 patients), Clopidogrel will be prescribed, while in case of intermediate (*CYP2C19**1/*2 patients) or poor metabolizers (*CYP2C19**2/*2 patients), Prasugrel or Ticagrelor will be prescribed instead to avoid adverse reactions.

On the other hand, the disadvantage in this case is that the *CYP2C19*2* hetero- and homozygous patients could be treated inappropriately, according to the guidelines. In strategy B, every patient receives the "appropriate" treatment, but all patients have an additional cost for the genetic test. As is usually the case in these types of models, differences relate only to the cost of the resources consumed at each node of the model.

Table 6.1. Sample characteristics (#ACE: Angiotensin Converting Enzyme). *CYP2C19* *1/*1: Extensive metabolizers, *CYP2C19* *1/*2: Intermediate metabolizers, *CYP2C19* *2/*2: Poor metabolizers.

	***CYP2C19* *1/*1**	***CYP2C19* *1/*2 *CYP2C19* *2/*2**
Number of Patients [n (%)]		
All	86 (100%)	35 (100%)
Male	37 (43.0%)	17 (48.6%)
Female	49 (57.0%)	18 (51.4%)
Age, mean ± SD (years)		
All	66.4±12.34	65.7+12.1
Male	62.0±14.30	60.1+12.10
Female	69.7±9.53	71.06+9.69
BMI, mean ± SD (kg)		
All	26.06±4.52	26.88+4.18
Male	26.16±3.83	27.14+3.60
Female	25.98±5.01	26.64+4.75
Smoking Status		
All	86 (100%)	35 (100%)
Non/Ex Smokers	74 (86.1%)	41 (88.6%)
Smokers	12 (14.9%)	4 (11.4%)
Male		
Non/Ex Smokers	28 (75.7%)	13 (76.5%)
Smokers	9 (24.3%)	4 (23.5%)
Female		
Non/Ex Smokers	46 (93.9%)	18 (100.0%)
Smokers	3 (6.1%)	0 (0.0%)
Hypertension		
All	63 (73.3%)	26 (74.3%)
Male	23 (36.5%)	12 (46.2%)
Female	40 (63.5%)	14 (53.8%)
Prior use of ACE# inhibitors		
All	42 (48.8%)	19 (54.3%)
Male	15 (35.7%)	6(31.6%)
Female	27 (64.3%)	13 (68.4%)
Prior use of statins		
All	11 (12.8%)	4 (11.4%)
Male	6 (54.5%)	2 (50.0%)
Female	5 (45.5%)	2 (50.0%)

Table 6.2. Unit cost per item used in the model.

Item	Cost (€)
Cost of genetic testing	63.0
Cost of hospitalization per day	200.0
Cost of single RePCI	1,000.0
Cost of vascular operation	4,400.0
Cost of rehabilitation per day	12.5

6.3.7. Dealing with uncertainty

The nature of the present analysis requires undertaking of uncertainty analyses. The management of patients, the probabilities associated with the various outcomes are subject to variation and the same applies to patient treatment costs. The data used also come from different sources and are subject to uncertainty, which is why computer-simulated clinical and economic models are used. In addition, costs data are often skewed or do not follow normal distribution because there are frequently some small numbers of very costly cases which skew the results and heavily distort any statistical measures one may try to estimate (Desgagne et al., 1998). As such, bias-corrected uncertainty intervals (UI) were calculated using the percentile method of nonparametric simulation (Fragoulakis et al., 2012).

In this case, the distribution of the bootstrapped means approximates the normal and their mean is a better (unbiased) estimator of the population mean. In particular, in every simulation, the value for each parameter is determined independently and at random from the prespecified distributions, and the results are recalculated.

The bootstrapping was run in total 5000 times and the results of the probabilistic analysis were used to calculate uncertainty intervals. It must be noted that this technique incorporates the probabilistic nature of variables, and thus, the results of analysis could be slightly different in a particular set of experiments and not “fixed” results produced in every case as opposed to “fixed results” with the classical statistical inference.

6.4. Results

In accordance with the main results of the model, 59.3% of the *CYP2C19* homozygous wild-type (*1/*1) patients (extensive metabolizers) had a minor or major bleeding versus 42.85% in the *CYP2C19* heterozygous (*1/*2; intermediate metabolizers) and homozygous mutant (*2/*2; poor metabolizers) patients arm. A reinfarction event occurred in 2.3% of the *CYP2C19**1/*1 patients, as compared to 11.2% in the *CYP2C19**1/*2 and *CYP2C19**2/*2 patients arm. The average number of hospitalization days for the *CYP2C19**1/*1 patients was estimated at 10.1±6.5 days, compared to 11.0± 6.9 days in the *CYP2C19**1/*2 and *CYP2C19**2/*2 patients arm. The mean stay in a rehabilitation center was estimated to be 24.1± 8.8 and 24.6± 6.2, for the *CYP2C19**1/*1 versus the *CYP2C19**1/*2 *CYP2C19**2/*2 patient groups, respectively. The detailed probabilistic results of the model are presented in **Table 6.3** and **Figure 6.2**.

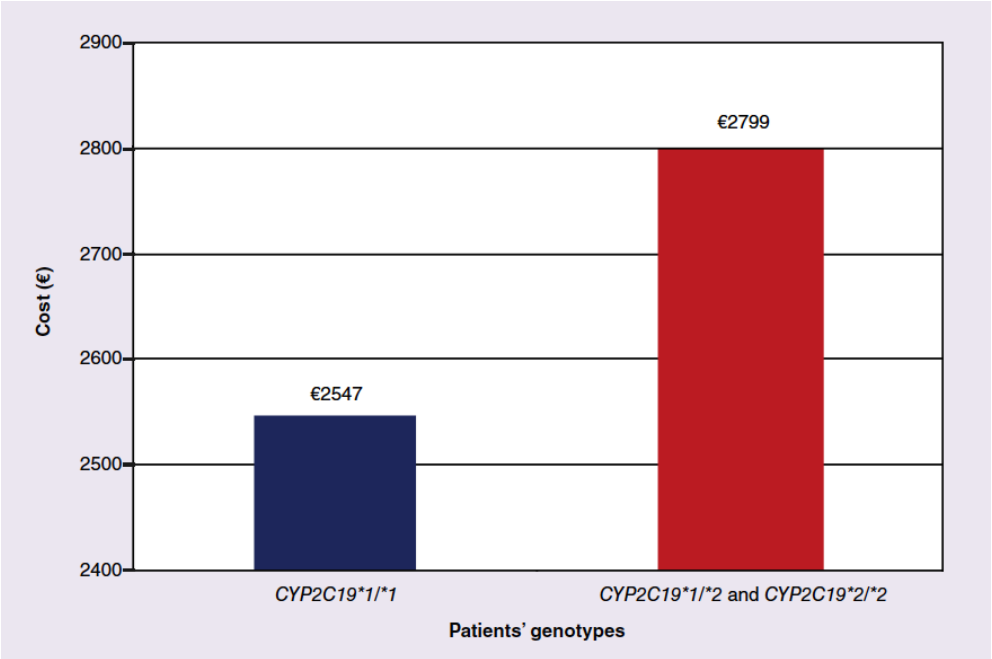

Figure 6.2. Cost per patient per patient group. *CYP2C19**1/*1 patients: Extensive metabolizers, *CYP2C19**1/*2 patients: Intermediate metabolizers, *CYP2C19**2/*2 patients: Poor metabolizers.

In short, the mean cost for the *CYP2C19**1/*1 patients was estimated at €2,547 (95%CI: €2,217-€2,966) versus €2,799 (95%CI: €2,251-€3,455) in the *CYP2C19**1/*2 and *CYP2C19**2/*2 patients, indicating a cost difference in favor of

the former patient group. For the *CYP2C19**1/*1 patient group, the main factor contributing mainly to the total cost was the hospitalization costs (79.2% on average of the total cost), followed by the cost of rehabilitation (11.2%), the cost of vascular operation (4.2%), the cost of RePCIs (2.6%) and the cost of genetic testing (2.4%). Similar results were obtained for the case of the *CYP2C19**1/*2 and *CYP2C19**2/*2 patient group. In particular, the main cost driver in this latter patient arm was also the cost of hospitalization (79.2%), followed by the cost of rehabilitation (11.6%). The remaining cost drivers have similar percentages as the previous ones in the other arm. We did not detect any *CYP2C19**3 alleles in the study population.

Table 6.3. Probabilistic results of the model (costs per patient group). Results were based on 5,000 bootstrap (B) replications; SD: standard deviation; 95% UCI: 95% upper confidence interval; 95% LCI: 95% lower confidence interval. *CYP2C19* *1/*1: Extensive metabolizers, *CYP2C19* *1/*2: Intermediate metabolizers, *CYP2C19* *2/*2: Poor metabolizers.

	Statistics	***CYP2C19* *1/*1**	***CYP2C19* *1/*2 *CYP2C19* *2/*2**
Cost (€)	B-Mean	2,547	2,799
	B-SD	189	310
	Number of Sample	86	35
	B-Minimum	1,939	1,936
	LCI	2,217	2,251
	B-Median	2,535	2,777
	UCI	2,966	3,455
	B-Maximum	3,404	4,212
	Variance	35.725	96.165

6.4.1. Break-even point analysis

In accordance with the sample analysis, the percentage of the *CYP2C19**1/*1 patients in the total population was estimated at 71.1% versus 28.9% in the *CYP2C19**1/*2 and *CYP2C19**2/*2 group. In the strategy analysis presented below, it is assumed that these percentages hold true and are representative to the entire Serbian population. Based on this assumption, we have conducted a break-even point (BEP) analysis. BEP is a type of analysis, which

indicates the point at which the total costs of two strategies (A versus B) equalize, based on changes in the percentage of the *CYP2C19**1/*1 patients in the total population (**Fig. 6.3**). In the base-case analysis (*CYP2C19**1/*1=71.1%), it was estimated that strategy B (performance of the genetic test) represents a cost-saving option, saving €13 per person on average, compared with strategy A. As expected, strategy B becomes less attractive as the percentage of the *CYP2C19**1/*1 patients increases, given that the potential chance of a "wrong" treatment (clopidogrel instead of prasugrel or ticagrelor) to a patient bearing the *CYP2C19**1/*2 or *CYP2C19**2/*2 genotype is reduced. In particular, the cost of two options potentially equalizes when the percentage of the *CYP2C19**1/*1 patients reaches 75%, while in higher percentages, strategy A represent a cost-saving option.

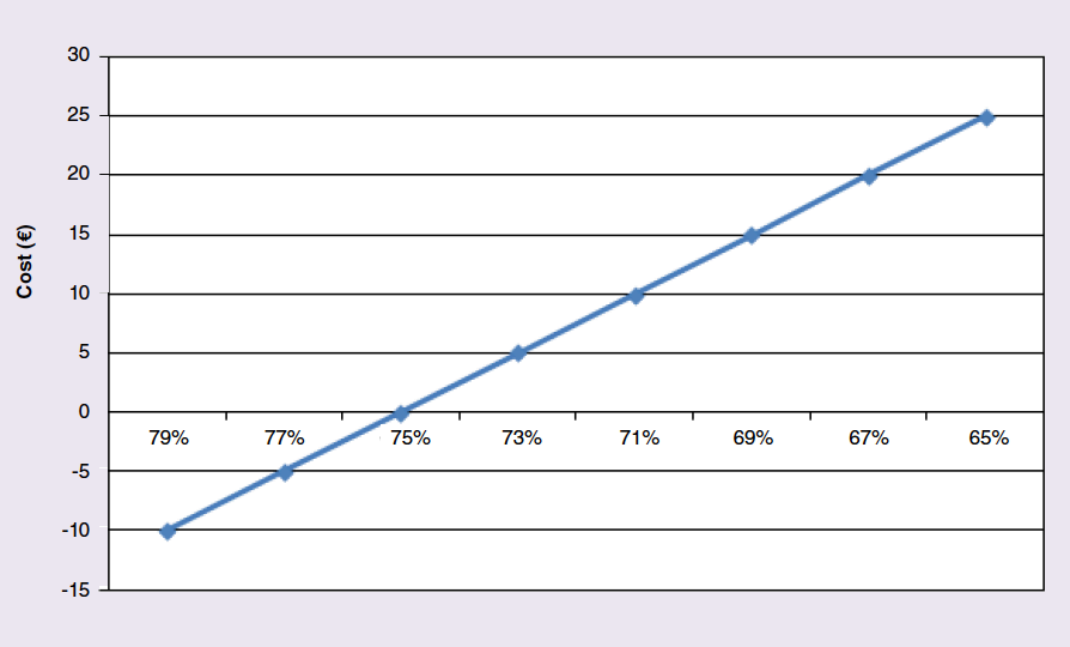

Figure 6.3. Break-even point analysis. *CYP2C19**1/*1 patients: Extensive metabolizers, *CYP2C19**1/*2 patients: Intermediate metabolizers, *CYP2C19**2/*2 patients: Poor metabolizers.

6.5. Discussion

Understanding the relative benefits of alternative strategies for patients with myocardial infarction is important in order to ensure that patients receive

standard therapies with few adverse events, but also economically viable. In the present model, an economic analysis was considered for *CYP2C19**1/*1 patients versus *CYP2C19**1/*2 and *CYP2C19**2/*2 myocardial infarction patients in Serbia. Although the present study has a number of similarities with the previous study conducted in a developing country environment, there are two main differences, as contrary to our previous study, since the present analysis (1) is based on a retrospective study, and (2) is a health economics rather than a cost-effectiveness analysis.

Clopidogrel represents a very well-studied example for economic evaluation, based on clinical trials and meta-analyses. Clopidogrel is commonly used in individuals with acute coronary syndrome (ACS) to reduce their risk of adverse cardiovascular (CV) outcomes. The introduction of new therapeutic alternatives to clopidogrel raised the question of whether a genotype-guided use of clopidogrel is more cost-effective compared to the universal use of newly developed drugs, such as prasugrel. Clopidogrel is an antagonist of the platelet ADP receptor $P2Y_{12}$ (Niitsu et al., 2005) and is converted to its active form by the CYP2C19 enzyme. Recently, a meta-analysis demonstrated that individuals who carry one or more *CYP2C19* loss-of-function (LoF) allele(s) are likely to have an increased risk of adverse CV outcomes, when clopidogrel is used for percutaneous coronary intervention (PCI), especially in populations of Asian descent (Sorich et al., 2014). Alternatively, the P2Y12 receptor antagonists ticagrelor and prasugrel were associated with improved efficacy. The Clinical Pharmacogenetics Implementation Consortium (CPIC) recommends these drugs as an alternate therapy to clopidogrel for *CYP2C19* poor metabolizers, if no contraindication is present (Scott et al., 2013).

In the clopidogrel and prasugrel scenario, the *CYP2C19* genotype-guided therapy was shown to be the most cost-effective choice, although it was dependent on the risk for developing MI stroke between carriers and homozygous wild type and heterozygous patients for a *CYP2C19* LoF allele. Recently, an evaluation on the cost-effectiveness of a *CYP2C19* genotype-guided strategy of antiplatelet therapy in ACS patients undergoing PCI (Patel et al, 2014) was performed from the US healthcare provider's perspective. Probabilities for clinical outcomes, costs and age-adjusted quality of life were obtained from a clinical trial (O'Donoghue et al.,

2009). The primary end point in the trial was the type, size, and timing of MI using the universal classification of MI. The cost-effectiveness analysis included the costs of MI, urgent target vessel revascularization, stroke and major bleeding events. One-way and probabilistic sensitivity analyses were performed, indicating that clopidogrel therapy was the least costly and the least effective, when compared to the *CYP2C19* genotype-guided therapy with an incremental cost-utility ratio of USD 4,200. Prasugrel therapy was costlier and less effective than both other strategies. Sensitivity analyses again showed the importance of the relative risk of developing MI or stroke between homozygous normal and heterozygous patients for a LoF *CYP2C19* allele. As the risk of developing MI or stroke between patients with and without the *CYP2C19* variant allele decreased, *CYP2C19* genotype-guided therapy became less attractive in comparison to the universal clopidogrel therapy. Similar results were also reported from others, where the *CYP2C19* genotyping-treatment arm was dominant to both clopidogrel and prasugrel treatment (Lala et al. 2013; Reese et al. 2012).

Interestingly, as far as the newly developed drugs are concerned, a randomized control study has shown a higher efficacy of ticagrelor treatment, compared to clopidogrel, irrespectively of the *CYP2C19* genotype (Wallentin et al., 2010). In particular, these authors suggested that the *CYP2C19* genetic testing prior to dual antiplatelet treatment is not needed in the case of universal ticagrelor therapy. The end point of this study was the composite outcome of cardiovascular death, myocardial infarction and stroke and major bleeding events were considered as safety outcomes. Taking these probabilities into account the cost-effective analysis was performed from the Australian health-care system prospective (Sorich et al., 2013). Only the costs of the primary outcomes without the cost of bleeding events were considered. The authors compared the universal clopidogrel therapy, the universal ticagrelor therapy and the genotyping of *CYP2C19* with the use of ticagrelor in individuals with a LoF allele and clopidogrel in individuals without a LoF allele. One-way deterministic and probabilistic sensitivity analyses were undertaken. It was concluded that the *CYP2C19* genotyping strategy was more expensive compared with the universal use of clopidogrel, but it provided greater effectiveness and the ICER AUS$ 6000 per QALY, was considered to be cost-effective. However, the most effective strategy

was the universal use of ticagrelor, as the ICER was AUS$ 23,000 per QALY compared with the genotyping strategy, being within what was considered acceptable in Australian health-care system (less than AUS$ 30,000-50,000 per QALY). Sensitivity analyses indicated that the routine *CYP2C19* genotyping would be cost-effective if the hazard ratio (ticagrelor vs clopidogrel) for the CV outcome was greater than 0.95. In addition, the results from Cerspin and co-workers (2011) that took the US health insurance provider perspective were generally consistent. They concluded that ticagrelor increases universally the QALY for ACS patients, when compared to the genotype-driven treatment at a cost below a typically accepted threshold (Crespin et al., 2011). Sensitivity analysis again showed that the hazard ratio of death for ticagrelor compared with clopidogrel sets the difference on which strategy is the most cost-effective.

Our study has a number of limitations. First of all, we opted to model the course of the disease in a simple manner based on data availability and any complexities associated with clopidogrel treatment were not taken into account in the model design. Also, certain assumptions have been obtained from the literature, as they were not available by the raw data. Nevertheless, we feel that these assumptions create some bias but for both arms of the model and as such we do not expect such bias to cause alterations in the final conclusions of this study. Another limitation of the study is the small number of patients. Furthermore, the results of this model have to be strictly considered in the context of Serbia and only on the basis of current drug, laboratory services and health resource prices. In other words, a new economic evaluation analysis is required, should these figures change over time. It must be noted that for the purpose of this study, we opted to stay focused only in our available data and the aforementioned health economic analysis, and not to perform a comprehensive budget impact analysis, which would not have been within the scope of the present study. In addition to that, the paper deals with outcomes/events which can be considered to be the result of adverse response to the therapy (and which can be caused due to the presence of a *CYP2C19**2 allele). Also, our example takes into consideration the price of dealing with consequences of adverse outcomes/events. Alternative therapy to clopidogrel in patients with a *CYP2C19**2 allele consists of drugs which are over 300 % more expensive than clopidogrel (e.g. clopidogrel vs ticagrelor).

For instance, in accordance with rough estimations, annual cost for a patient on clopidogrel is €130 and on ticagrelor is €445 which means that treatment with ticagrelor is about €300 more expensive. However, it is much cheaper than covering the costs of dealing with reinfarction (€1,000 for RePCI, plus €200 for hospitalization per day, plus €12.5 for rehabilitation per day). In this way, the use of ticagrelor becomes justified for patients with the *CYP2C19**2 allele. On the other hand, there is a tendency in practice to prescribe ticagrelor to all patients. This is irrational, since €300 is unnecessarily spent on every patient who would respond well to clopidogrel, particularly since these patients constitute the majority. Hence, the final goal of these considerations is to determine a balanced and rational approach to the treatment, *i.e.* substitution of clopidogrel only in patients with genetically confirmed presence of a *CY2C19 LoF* allele. In addition, with the present work, we emphasize the significance of this kind of approach for developing countries with modest budgets at disposal.

Lastly, considering the fact that our paper deals with retrospective analysis of data, precise conclusions related to the success of using the suggested therapy could be reached by subsequent prospective studies that would analyse genotype-guided clinical outcomes.

6.6. Conclusions and future perspectives

Based on the current prices and resource utilization in Serbia, our retrospective study indicates that genotype-guided clopidogrel treatment could represent, under certain assumptions, a cost-saving treatment option for *CYP2C19**1/*2 and *CYP2C19**2/*2 patients suffering from myocardial infarction and support results from previous studies involving *CYP2C19* LoF alleles. This study is one of the very few economic analyses to be conducted in a developing country clinical setting in Europe and Southeast Asia (Snyder et al., 2014; Mitropoulou et al., 2015) and provides the basis for rationalizing pharmacogenomics-guided treatment modalities towards cost-savings of national healthcare expenditure in developing countries. This study provides the basis for replication in other developing countries and for other pharmacogenomics-based treatments, ideally as part of multinational research networks to ensure large

multiethnic patient samples. A broader analysis with more real-life data could be the scope of a future work.

6.7. Acknowledgements

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Chapter 7

An alternative methodological approach for cost-effectiveness analysis and decision making in Genomic Medicine

Fragoulakis V, **Mitropoulou C**, van Schaik RH, Maniadakis N, Patrinos GP. ***OMICS***. 2016 May;20(5):274-82.

7.1. Abstract

Genomic Medicine aims to improve therapeutic interventions and diagnostics, the quality of life of patients, but also to rationalize healthcare costs. To reach this goal, careful assessment and identification of evidence gaps for public health genomics priorities are required so that a more efficient healthcare environment is created. Here, we propose a public health genomics-driven approach to adjust the classical healthcare decision making process with an alternative methodological approach of cost-effectiveness analysis, which is particularly helpful for genomic medicine interventions. By combining classical cost-effectiveness analysis with budget constraints, social preferences and patient ethics, we demonstrate the application of this model, the Genome Economics Model (GEM), based on a previously reported genome-guided intervention from a developing country environment. The model and the attendant rationale provide a practical guide by which all major healthcare stakeholders could ensure the sustainability of funding for genome-guided interventions, their adoption and coverage by health insurance funds, and prioritization of the Genomic Medicine research, development and innovation, given the restriction of budgets, particularly in developing countries and low-income healthcare settings in developed countries. We conclude with a discussion of the implications of the GEM for the policy makers interested in Genomic Medicine and new technology and innovation assessment.

Key words: Economic evaluation, willingness to pay, decision making, health policy, genomic medicine, public health genomics, Genome Economics Model, GEM

7.2. Introduction

Pharmacogenomics and Genomic Medicine play an important role in exploiting one's genomic profile to guide therapeutic interventions. As a result, not only pharmacogenomics and Genomic Medicine have the potential to improve the quality of life of patients but also to rationalize healthcare spending. In the latter case, and in order to fully exploit the potential of Genomic Medicine, one needs to strategically identify and adequately target evidence gaps for public health genomics priorities to create a more efficient healthcare environment. In other words, evidence on the value of pharmacogenomics and Genomic Medicine is needed to persuade policymakers and clinicians for genome-guided decision making, related to adoption and coverage by insurance funds, and to prioritize research, development and innovation (Snyder et al., 2014).

Economic evaluation aims to assess whether the financial investment in specific health care interventions will provide "value for money" in achieving policy aims and also to inform decision makers, comparing the costs and therapeutic consequences of new and innovative with existing interventions already used by the healthcare system. So far, and for the policy makers to access the value of innovative interventions, the commonly used investigation is implemented via the determination of incremental cost effectiveness ratio (ICER) (O'Brien and Briggs, 2002). ICER is the ratio of the average per-patient incremental cost (ΔC) of one intervention divided by an incremental health gain (ΔE), such as an additional stroke prevented, a case of cancer diagnosed, or gain of a Life Year (LY) or, primarily, an additional Quality Adjusted Life Year (QALY). Despite their shortcomings, QALY represents one of the widely accepted measures used to consider the ability of an intervention to extend life and to improve the quality of life for the patients.

In accordance with the current theory, if ICER is below a pre-determined amount a policymaker was willing to pay for an additional QALY, the new intervention is a "cost-effective option" and meets one of the criteria for reimbursement by the payers (McCabe et al., 2008) (**Fig. 7.1**). It must be

highlighted that this amount of money is not fixed (and may vary within a specific range), when taken into account other criteria for the reimbursement process, such as the particular features of the condition, the availability and clinical effectiveness of other interventions, the size of population who will use the technology, the innovative nature of the technology, the wider societal costs and benefits, equity concerns, the culture of every country and the available budget and, when appropriate, the reference to previous appraisals. Hence, it is known that it is necessary to consider the willingness to pay for a QALY in a disease and country-specific context, taking also into account the age and the gender of beneficiaries, their deservedness, and other ethical issues.

Because the above approach does not incorporate affordability when making judgments about cost effectiveness, an additionally separated budget impact analysis should also be implemented to determine the economic burden of short and medium-term effects on budgets and other resources to reach a final conclusion. Nonetheless, a "cost-effective" intervention, determined by the approach described above, may not necessarily be affordable from an economic point of view and the criteria for the final verdict of adoption or rejection, frequently, remains unclear. In addition to that, other concerns have also been raised regarding the methodological limitations of the present analysis in this existing form (Donaldson et al., 2002b; Whitehead and Ali, 2010; Donaldson et al., 2002a; Gafni, 1998; Barton et al., 2008; Eckermann et al., 2008). One of the main concerns, amongst others, is the fixed threshold (even in a disease specific context and/or determined in a range) approach might lead to controversial decisions (Gyrd-Hansen, 2005; Birch and Gafni, 2006; Sendi et al., 2002) and increased expenditures (Gafni and Birch, 2006). The classical theory assumes that all "cost-effective" interventions with increased effectiveness compared with the standard (conventional) intervention could or should be reimbursed by the payers. In that sense, the classical approach compares the ICER against the willingness to pay, a budget impact analysis is conducted independently, and an automatic/arbitrary adjustment of budget in the cost of new technology is assumed. In this case, there is a clear linkage between the budget affordability of a health care system and the cost-effectiveness approach. Nonetheless, even if the budget is not fixed, it is

reasonable to assume that there is an actual boundary, indicative of the budget limit. On a pragmatic basis, for instance in the UK, the government could finally judge if a particular intervention is unaffordable for the system, even though it had been judged previously as a "cost effective" option. On the contrary, where a new technology is far less effective compared with the standard one, the classical model, at least in theory, assumes that "infinitively" less effective technologies could be adopted based only on cost criteria. Even in the case of developing countries, there are important moral and ethical issues in the treatment of patients which make the possibility to adopt a new poor, in terms of effectiveness, technology unlikely, despite their cost-saving profile (**Fig. 7.1**).

To deal with this issue, a modified version of the classical model has been also proposed. Based on real life data, it have been estimated that the money which a society is willing to save in order to sacrifice a QALY is much greater than the willingness to pay for a QALY by 2-6 times on average (for details of this concept see (O'Brien et al., 2002). Even in this case, there should also be a boundary which prevents the adoption of a very poor technology in terms of effectiveness. Those boundaries described above, are not formally taken into consideration in the classical model. In addition to that, the classical theory assumes that the willingness-to-pay for a QALY is independent of the actual difference in effectiveness between different health technologies even within the same disease-specific context. In that sense, economic evaluation does not differentiate between a truly innovative health technology, a "me-too" health technology or even a generic health technology and reimburse proportionally equally each one of them.

Here, we provide an alternative, less restrictive model for economic evaluation for healthcare decision-making process, which takes into account the budget constraint criteria and relaxes the assumption that the willingness-to-pay is fixed and irrespective of the actual amount of incremental effectiveness among interventions. This model can be readily applicable for Genomic Medicine interventions and will be described hereafter as the "Genome Economics Model" (GEM).

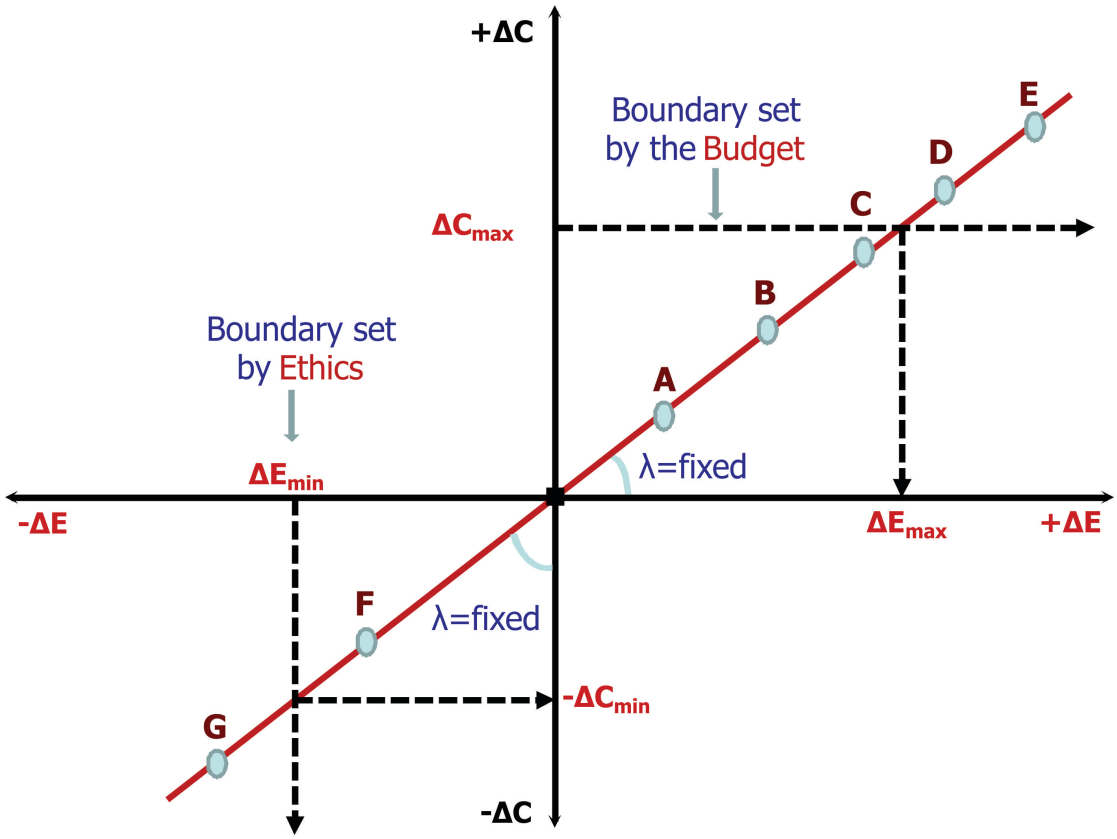

Figure 7.1. The basis of the proposed Genome Economics Model (GEM). Figure depicts the classical cost-effectiveness plane. Different health interventions are indicated as A-G, lie on the straight line and can be all adopted and reimbursed by the national healthcare systems, in accordance to the classical model, which assumes unlimited budget availability. According to GEM, interventions such as "A" or "B" represent "average cases" with increased Δ*E* and reciprocally higher costs, which together with "innovative" technologies, such as "C", e.g. those described in pharmacogenomics and Genomic Medicine, with a high Δ*E*, could be reimbursed by national healthcare systems. However, according to GEM, interventions with a much higher Δ*E*, such as "D" and "E" also bear higher costs, that make them unaffordable for adoption in a real-life situation, where unlimited budget availability is never the case. Similarly, intervention, such as "G", represent probably a technology with a cost-saving profile, but also less effectiveness, which again make it ineligible for adoption.

7.2. Methods

7.2.1. Description of the model and rationale

The basic concept of GEM is presented in **Fig. 7.1**. In accordance with GEM, a comprehensive decision-making process, should formally take into account both

the real therapeutic benefit in a patient's life and at the same time the payer's budget. Hence, technically, one should add in the decision-making process as regards the cost effectiveness of a new technology two boundaries:

(a) the right boundary which is imposed by the budget constraint (**Fig. 7.1**; upper right quadrant) and,

(b) the left boundary which is determined by ethics and standard medical practice (**Fig. 7.1**; lower left quadrant).

GEM implies that $\Delta C_{\max}$ represents the maximum amount of money per patient which could be spent by the payers only if a certain therapeutic gain from an innovative health technology was met by health providers.

It must be highlighted that this amount of money (or the range in which is supposed to fall into) has to be estimated based on a) the prevalence and the incidence of the disease, b) the available total budget for a specific disease, and c) the estimated market penetration of the new technology in the future. Hence in our proposed GEM model, in contrast with the classical model, the society defines ex-ante

(a) what is expected to be the upper limit of "innovation" in terms of effectiveness gains,

(b) what is the lowest acceptable effectiveness which could be accepted and judge ex-post every new technology within two boundaries,

(c) the maximum amount of money is willing to invest or save within two boundaries. Furthermore, the GEM model, contrary to the classical model does not conduct a separate cost-effectiveness and budget impact analysis, in order to avoid the problem of technologies which are "cost-effective" but not "cost-affordable". Every cost-effective technology in the GEM model meets also the cost criteria.

As such, health technologies "D" and "E" do not represent a cost-effective option anymore according to the GEM model, unless the budget is expanded or the costs of those interventions are lowered to meet the cost threshold (**Fig. 7.1**). In

addition, $\Delta E_{\min}$ represents the lowest acceptable level of effectiveness which could be offered by a new health technology in order to be accepted by the healthcare system. Hence, option "G" will be also rejected, according to GEM. In addition to those described above, contrary to the classical economic evaluation model (for details, see Fragoulakis et al., 2015), the GEM presents the variability of the actual incremental effectiveness of a new intervention, in correlation with the willingness to pay for a QALY in a formal manner (**Fig. 7.2**).

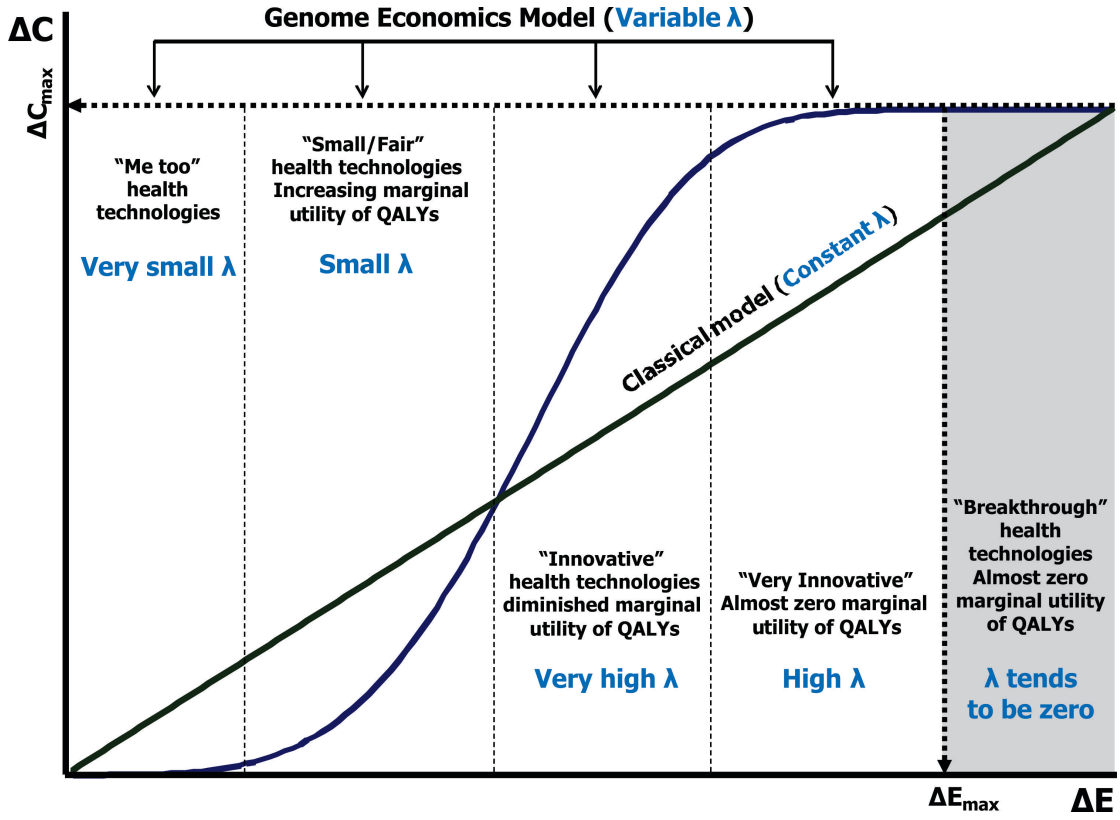

Figure 7.2. Cost Effectiveness Plane in the GEM versus the Classical Model. In the classical model, λ is constant, depicted as a straight line. However, in GEM, λ is variable, spanning from technologies with a very small innovation ("Me too") with a reciprocal small average λ to very innovative technologies with a high average λ. ΔE=difference in the effectiveness between the standard and the new intervention, depicted in the horizontal axis; ΔC=the difference in the total cost between the standard and new intervention per patient, depicted in the vertical axis; $\Delta C_{\max}$=the maximum available budget (per patient) is willing to afford the budget holder to capture the maximum expected effectiveness which can be additionally reimbursed (=$\Delta E_{\max}$); "marginal utility" referring to the additional satisfaction the society gains from the production of one more unit of effectiveness.

In this context, every potentially new unit of effectiveness which could be gained from future technologies has a different perceived value for the patients, the scientific community and the stakeholders.

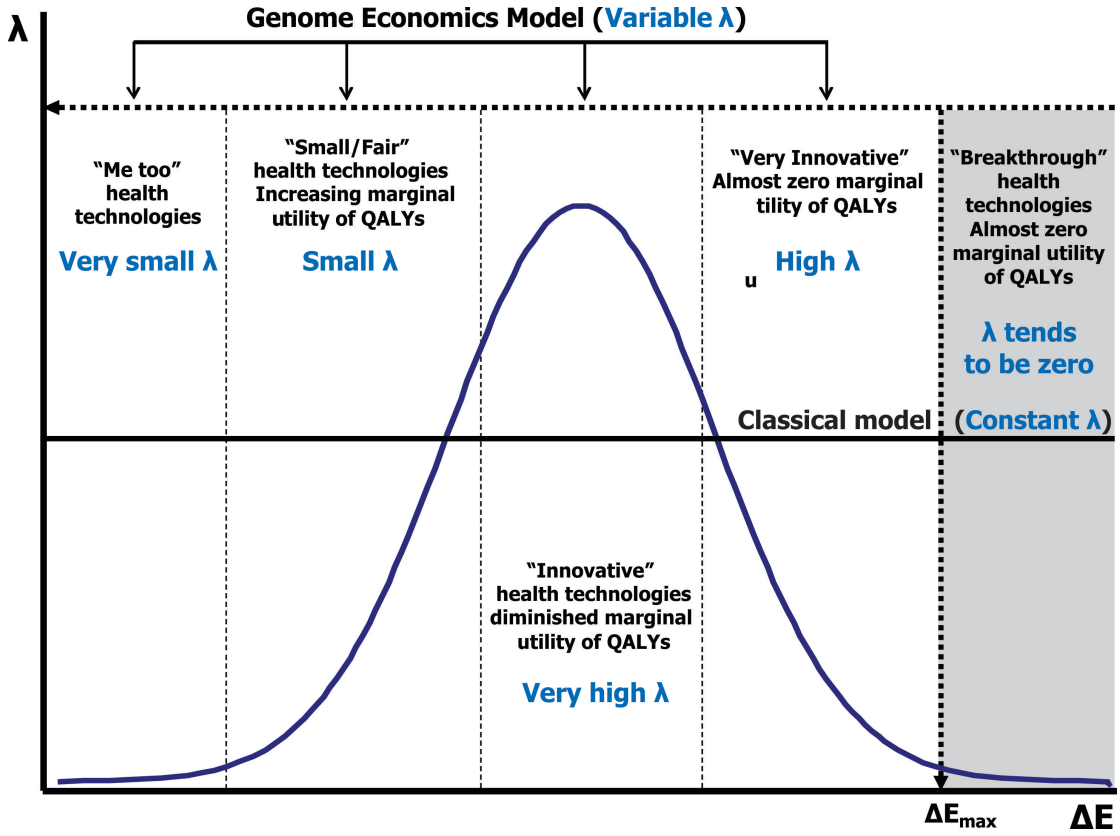

Figure 7.3. Willingness-to-Pay as a function of ΔE in GEM versus the classical model. In the classical model, λ is constant, depicted as a straight line. However, in GEM, λ is variable, and adopts a bell-shape appearance. Again, technologies with a very small innovation ("Me too") have reciprocally a very small marginal λ compared with the classical model; Technologies with fair/small benefits have higher but also small marginal λ compared with classical model; In the same concept, Innovative technologies have very high λ (which is determined by the difference in each point of the GEM minus the classical model), while very innovative technologies fall again to small marginal λ. As ΔE increases further, beyond the ΔE_{max}, λ tends to zero, since the available budget has been exhausted.

For a very small difference between two health technologies (i.e. "me too" intervention), and without any meaningful differentiation from existing interventions, the average willingness to pay for a QALY is expected to be low (**Fig. 7.3**). For more innovative interventions with some difference in terms of

effectiveness, ("small/fair" interventions), a higher average willingness to pay for a QALY (but also smaller than those offered by the classical model) can be expected, also in accordance to practical evidence (Kvamme et al., 2010). For innovative interventions with significant difference in terms of effectiveness, the average willingness to pay for every unit of QALY is expected to be very high in comparison with classical model. As the difference in effectiveness increases further (breakthrough technology), we meet the budget constraints criteria and, as such, we are unable to reimburse this technology further, the average willingness to pay is getting lowered, but the effectiveness of the adoption of this technology is offered by the health provider on behalf of the society. As such, the shape of willingness to pay for a QALY as the potential difference in effectiveness increases, resembles a bell-shape distribution, contrary to the classical model, in which willingness to pay is a straight line, determined by arbitrary assumptions, made by policy makers or the literature (**Fig. 7.3**). Finally, the new model is different compared with the classical one, in the sense that it drives healthcare providers to increase the effort for favorable treatments, "punishes" the less productive ones and "rewards" the true innovation, ensuring at the same time the sustainability of the healthcare system.

7.2.2. Implementation of the model

To demonstrate the usefulness of the proposed new model in pharmacogenomics and Genomic Medicine interventions, we have employed GEM to a recently published real-file example of pharmacogenomic (PGx)-guided versus non-pharmacogenomic (N-PGx)-guided warfarin treatment of elderly Croatian patients, who develop ischemic stroke predominantly due to atrial fibrillation (Mitropoulou et al., 2015). The model was populated with the cost data from the Croatian public tariff lists and current treatment guidelines on patient management. The main inclusion and exclusion criteria, the number or patients, and clinical features and genotyping is available elsewhere (Mitropoulou et al., 2015). The study was conducted in accordance with the Declaration of Helsinki and all patients give written informed consent in order to participate in the study.

The present model is only an indicative example and has been used only for illustrative purposes.

7.3. Results

We have previously shown (Mitropoulou et al., 2015) using the classical economic evaluation model in a one-year time horizon, that the probability of PGx-guided warfarin treatment being cost-effective increases significantly at a willingness to pay threshold in the range of €40,000 to €50,000 per QALY, used in many jurisdictions and, notably, at €60,000 per QALY, its probability of cost-effectiveness gets higher than 80% (Mitropoulou et al., 2015).

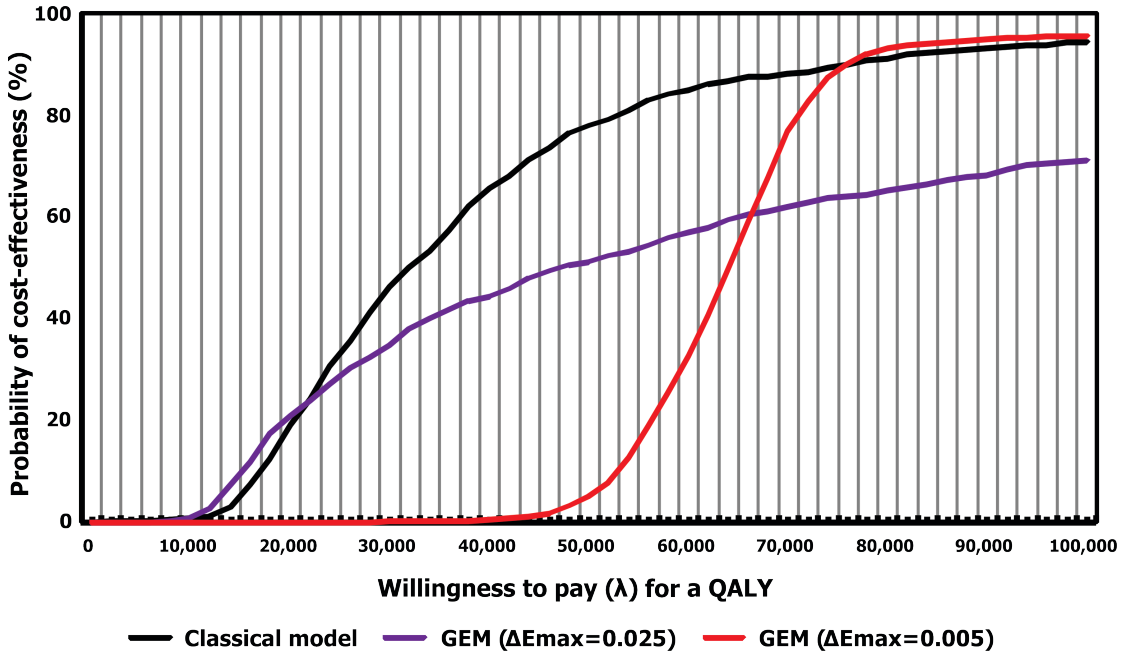

Figure 7.4. Cost effectiveness acceptability curve for PGx vs N-PGx guided treatment for the GEM and Classical Model for two different scenarios for ΔE_{max}. Cost effectiveness acceptability curve for PGx vs N-PGx guided treatment for the classical model (depicted in black) and for 2 different scenarios for GEM, namely ΔE_{max}= 0.025 (depicted in red) and ΔE_{max}= 0.005 (depicted in blue). See also text for details.

In particular, our findings indicated that the total cost per patient was estimated at €538.7 for the PGx-guided group vs €219.7 for the control group and total QALYs was estimated at 0.954 and 0.944 for the PGx-guided and the control groups, respectively (Mitropoulou et al., 2015). The incremental cost-effectiveness was estimated at €31,225/QALY ($\Delta C/\Delta E$= €319.4/0.01023). Based on data availability and related calculations, a specific cost-effectiveness acceptability curve for PGx vs non-PGx intervention is produced (**Fig. 7.4**, depicted in blue).

In the case of the GEM, we assumed two hypothetical scenarios:

(a) $\boldsymbol{\Delta E_{max}}$=0.025, and

(b) $\boldsymbol{\Delta E_{max}}$=0.005 (**Fig. 4**) lying at both sides of the actual difference (ΔE_{max}=0.01023).

For illustrative purposes a third scenario with (c) $\boldsymbol{\Delta E_{max}}$=0.01023 was also determined to indicate differences between the classical (scenario "c") and the new (scenarios "a" and "b") model **Fig. 7.5**).

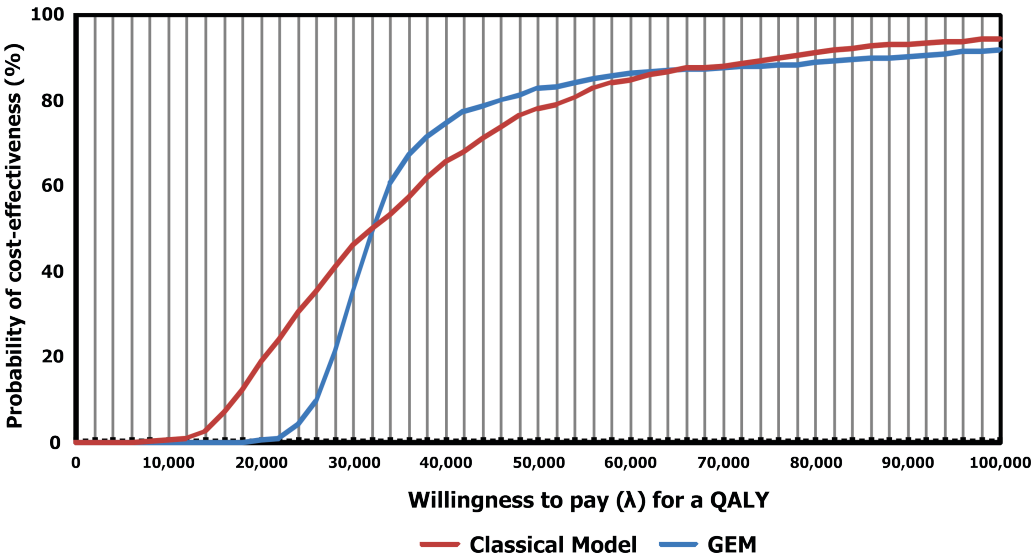

Figure 7.5. Cost effectiveness acceptability curve for PGx vs N-PGx guided treatment for the GEM and Classical Model based on the main results of the Croatian population. Cost effectiveness acceptability curve for PGx vs N-PGx guided treatment for the GEM and classical model for ΔE_{max}= 0.01023

It must be noted that these figures are indicative to highlight that different acceptability curves could be produced based on different assumptions. These assumptions represent decisions adopted by the policy makers.

The scenario with $\Delta E_{\max}$=0.025 represents an "ambitious" expectation and probably fits to the profile of the developing countries, since it requires that the PGx must have a fair difference in effectiveness (0.025 QALYs) gained against N-PGx in order to invest all the additional available amount of money. On the contrary, the scenario with $\Delta E_{\max}$=0.005 represents a society with low expectations from future innovations, since the available amount of money will be all invested even if the new technology (PGx) has only an insignificant incremental difference of 0.005 QALYs gained against N-PGx.

The present analysis of GEM indicates that the probability of a new technology being cost-effective is a function not only of a disease-specific willingness to pay as previously mentioned by the literature, but also the willingness of the society to transfer resources (and to which extent) from "me-too" health technologies to truly innovative ones taking into account the available budgets.

7.4. Discussion

As medical research is one of the leading priorities in the society, it is essential to improve the lives of patients and, at the same time, the economy as a whole. On the other hand, medical expenditure is expected to be covered by the Insurance Funds and usually lead to an uncontrolled growth in health care expenditure. In view of the limited resources, especially in developing countries and low-resource environments (Snyder et al., 2014), economic evaluation provides a criterion for the final decision concerning the adoption of certain new and innovative technologies. The classical approaches have, notwithstanding, some inconsistencies and drawbacks.

In this paper, we propose an alternative methodological approach, taking into account the budget constraint, the effectiveness of a new technology and

social preferences expressed by the willingness to pay in a flexible way. There are some distinct differences between the proposed (GEM) and the classical models. In the case of GEM, the maximum effectiveness which could be accepted by payers for reimbursement is determined before any new technology is introduced in the healthcare system, which is logical, considering the fact that the budget constrains vary between different countries. The model presented here describes, in a dynamic manner, the link between the willingness to pay threshold towards the budget limit. Thus, our model enables, at the same time, the combination of cost-effectiveness and budget impact analysis.

In an attempt to practically describe the real-world situation, the GEM relaxes the "fixed" and/or disease-specific assumption of willingness to pay for a QALY, allowing a flexible, upper bounded, budget. Furthermore, the model encourages the determination of willingness to pay to be different across different treatment areas, taking into account the differences in "production" of a QALY amongst patients' groups (e.g. cardiovascular patients, oncology patients etcetera), and even among the same patient groups but different healthcare systems. This argument of specific context and varying determination of willingness to pay is also in accordance with related literature (Bridges et al., 2010, Zhao et al., 2011). This model and its whole concept share the basis of methods used in the microeconomic theory, where the budget constraints and the preferences combined simultaneously at the same.

However, GEM is also a simplification of the process it tries to emulate, and it is therefore necessary to make assumptions and to accept limitations, which is common in similar models. For instance, the model demands the explicit mapping of preferences in a disease-specific context to reach some meaningful conclusions. Inevitably the problem becomes much more complex when taking into account the uncertainty of variables. Thus, further uncertainty is evident, concerning for instance the market penetration rate of innovative technology and the prevalence of a specific disease today and in the future. In addition to that, GEM assumed that the budget is exogenous and was set by the budget holders. Indeed, budget allocation lies on historical and political background in each country, and the optimal reallocation across healthcare sections or is not always desirable, when

sacrifices the transparency or consistency of decision making, the equality or other ethical issues (Schwappach, 2002). In that sense, the present model does not address the question of how to allocate available healthcare resources to different diseases based on a common measure for health. In order to do so, several limitations must be addressed which have already been mentioned in the literature and is out of the scope of the present work (Birch and Gafni, 2006; Sendi et al., 2002).

In this paper, our model is based on the economic evaluation of a specific disease context and for innovative interventions with greater effectiveness compared with the standard ones, when considering the introduction of a new treatment, while the case of decremental cost-effective medical technologies, which is probably of particular interest in developing countries, is still missing. It must be highlighted that the clinical determination of the "innovation" is beyond the scope of this article and this term is used only from a technical point of view, to indicate health technologies which provide greater effectiveness based on statistical measurements. The whole concept of innovation is controversial and still scientifically open (Vernon et al., 2009) and several attempts have been made to provide an overview of how innovation is currently valued amongst health care systems today.

Thus, the solution of GEM only offers a local maximum determined by the *de facto* budget availability in a specific disease context. The aggregate sum of costs and effectiveness across several disease areas does not necessarily represent the overall maximum, as the perceived importance by policy makers and society for different QALYs have not been fully addressed and the budget cannot be fully reallocated automatically across different therapeutic areas. Nonetheless, we argue that the "health optimization problem given a fixed budget" for the entire society, despite appealing as a mathematical problem in theory, cannot be so easily addressed in a real-world setting.

Uncertainty (Ramsey et al., 2005), lack of data or knowledge for preferences (Weyler and Gandjour, 2011), lack of training of policy makers (Veney et al., 1997), established status quo, and other policy and public health-related

issues, make the quantitative determination of constraints and the application of prominent instruments, such as mathematical programming, more difficult than GEM (Flessa, 2000). In this context, it must be noted that the determination of a general willingness to pay for a QALY irrespective of the disease as representative of social preferences, requires not only a scientific approach to evaluate the opportunity cost between comparable treatments, but also the knowledge of societal utility function and the knowledge of different weights for different QALYs as mentioned before (Wailoo et al., 2009). If, and only if, the above prerequisites were satisfied, one could estimate the true value of willingness to pay and the desired maximization treatment mix across several disease-specific areas. Despite the fact that mathematical programming could incorporate, in a quantitative form, some restrictions referred to ethical issues, exogenous (not scientific-based) information for the amount of this budget allocation must be also provided by the policy makers as an input in this kind of models.

7.5. Implications for policy makers

Based on the GEM model, a simple practical solution for policy makers in our context, is outlined in the next steps with a view to GEM's applications:

a) To determine (based on prevalence, incidence, market penetration and the available total budget for a disease), the maximum amount of money which could be invested per patient in the future only in case of specific requirements, in terms of effectiveness, are met,

b) To determine the amount of greater-than-the-standard effectiveness, which differentiate amongst "me-too", "fair", "innovative", "very innovative" and "breakthrough" technologies,

c) To determine the maximum amount of effectiveness, which could be sacrificed in the future for cost-saving purposes, compared with the current medical standard,

d) To define the amount of money that are willing to save from the least effective but also the least costly option,

e) To determine in a quantitative manner the proportional rule for reimbursement across the above-mentioned technologies (even those with greater or less effectiveness). For those technologies with greater effectiveness, the society is **willing to pay** a percentage of the maximum amount of money which could invest at most, in relation with the percentage of maximum expected effectiveness attained by the new technology. For those technologies with less effectiveness, the society is **willing to accept** a percentage of less effectiveness compared with the least acceptable, in relation to a percentage of the maximum acceptable amount of money we want to save from such a technology.

f) To assess every future technology in terms of (b) and (c).

g) To reimburse these technologies in terms of (e)

h) To update periodically all the above when new data becomes available

It must be highlighted that the actual issue of financial resource management, in practice, is primarily a political issue and requires a knowledge of the politics and sociology of technology and innovation-in-society (Sclove, 1989; Nowotny, 2015). Unfortunately, quantitative methods or logical approaches as those described above are not always adequate to resolve by themselves such issues and, in many cases, the translation of a theoretical model into a political decision involves other factors that lie mostly outside the province of the academic community.

Nonetheless, scientists and technology-driven academic communities can still play valuable roles in shaping of the knowledge trajectories from lab to innovation-in-society through greater transparency and a sociological read of the scientific laboratory and practices. In this regard, the readers are referred to the biography and contributions of the Nobel Laureate Frederick Soddy for his works to better understand the science and technology futures (Sclove, 1989) as well as the recent analysis by Helga Nowotny of scientific uncertainty (Nowotny, 2015)

In this context, we argue that decisions as those describe in the abovementioned steps must be carefully assessed from a large panel of experts, including the medical community, the patients, and the governmental stakeholders. The latter is of utmost importance in the case of Genomic Medicine interventions, where policy makers with high power of intervention, such as the Ministry of Health and Payers are often skeptical to adopt such innovative approaches due to the high anticipated costs (Mitropoulou et al., 2014).

It must be also noted that the numerical example presented herein refers to a specific group of patients suffering from a specific disease (atrial fibrillation) and in a specific setting (Croatia). Despite the fact that the results of the analysis only showed a marginal difference in QALYs between PGx- vs non PGx-guided interventions, intermediate results (percentage of major/minor bleeding, *etc*) demonstrated a statistically significant difference in favor of PGx-guided warfarin treatment, at least in terms of effectiveness. Also, a broader time horizon than the one used in the original analysis (1 year) could further (slightly) impact on the results in favor of the PGx-guided treatment group.

Our alternative model, described herein, attempts to unify cost-effectiveness, budget impact analysis, ethical issues and preferences into a same equation, improving some core drawbacks of the classical model. It must be noted that the potential added-value and novelty of the GEM approach presented in this paper can only be understood if compared to other approaches to overcome similar problems (Devlin and Parkin, 2004; Culyer et al., 2007; Gandjour, 2015, Rawlins and Culyer, 2004; Perleth et al., 2009; Cleemput and Van Wilder, 2009; Asaria et al., 2016; Thokala et al., 2015).

The validation of GEM and the estimation of the coefficients with real data sets might be some of the future avenues of research. Finally, although originally proposed for Genomic Medicine interventions, GEM might also be applicable for medical and health interventions other than genomic technologies that warrant further research and consideration.

7.6. Acknowledgements

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Chapter 8

Performance Ratio based resource allocation decision-making in Genomic Medicine

Fragoulakis V, **Mitropoulou C**, Katelidou D, van Schaik RH, Maniadakis N, Patrinos GP. **OMICS**. 2017 Feb;21(2):67-73.

8.1. Abstract

In modern healthcare systems, the available resources may influence the morbidity, mortality, and – consequently – the level of health care provided in every country. This is of particular interest in developing countries where the resources are limited and must be spent wisely to address social justice and the right for equal access in healthcare services by all the citizens in economically viable terms. In this light, the current allocation is, in practice, inefficient and rests mostly on each country's individual political and historical context and thus, does not always incorporate decision-making enabled by economic models. Here, we present a new economic model, specifically for resource allocation for genomic medicine, based on performance ratio, with potential applications in diverse health care sectors, which is particularly appealing for developing countries and low-resource environments. The model proposes a new method for resource allocation taking into account a) the size of innovation of a new technology, b) the relative effectiveness in comparison with social preferences, c) the cost of the technology, while permits the measurement of effectiveness to be determined differently in the context of a specific disease and then to be expressed in a relative form via a common performance ratio. The present work expands upon previous works by the authors and in the literature for innovation in economic models pertaining to genomic medicine and supports translational science that can address the knowledge gaps from cell to society. The present work represents the generalization of a previous recently work published by the authors in genomic medicine.

Key words: Resource allocation, cost-effectiveness, genomics, decision making, willingness to pay, public health genomics

8.2. Introduction

Genomic Medicine aims to exploit one's genomic profile to personalize therapeutic interventions, which has the potential to improve the quality of life of patients but also to rationalize healthcare expenditure. To this end, and in order to maximize the outcome of the various genome-guided interventions, one needs to create an appropriate healthcare environment by identifying and adequately targeting evidence gaps for public health genomics priorities so that not only clinicians are persuaded for the need to implement genome-guided decision making, but also policymakers and regulators for the need to adopt and reimburse genomic tests from insurance funds (Vozikis et al., 2016), and to prioritize research, development and innovation in all Genomic Medicine disciplines (Snyder et al., 2014).

Economic evaluation aims to assess whether a new health care technology or interventions provides "value for money" in terms of costs and therapeutic consequences compared to existing interventions (Fragoulakis et al., 2016). The most common research approach employed by policymakers to assess the value of innovative technologies and/or interventions is the determination of the Incremental Cost Effectiveness Ratio (ICER) (O'Brien and Briggs, 2002), defined as the ratio of the average per-patient incremental cost (ΔC) of one intervention divided by an incremental health gain (ΔE), determined, according to the medical specialty, as an additional stroke prevented, a case of cancer diagnosed, or gain of a Life Year (LY) or, primarily, an additional Quality Adjusted Life Year (QALY). In other words, ICER represents the difference in costs between a new intervention under consideration for adoption and the current approach to dealing with the same clinical problem/client group (the incremental cost) divided by the difference in outcomes between the new intervention and the current approach (the incremental effects). If ICER is below a pre-determined amount a policymaker is willing to pay for an additional unit of effectiveness (the desirable medical outcomes), the new intervention called a "cost-effective option" and meets one of the criteria for reimbursement by the payers. In the latter case and despite its

shortcomings, QALY represents one of the widely accepted measures used to consider the ability of an intervention to extend life and to improve the quality of life for the patients.

Until recently, the decision-making process was supported by the classical concept of cost-effectiveness analysis (Fragoulakis et al., 2015). In accordance with this theory, cost-effectiveness analysis represents a tool which has been used to maximize health gains from the use of available resources and this appears to reflect the needs of the decision-maker. However, this type of analysis has been criticised and has some distinct drawbacks in practical terms. A key concern is that this threshold approach might lead to controversial or contested decisions and to increase further the expenditures in a healthcare system as mentioned by Gafni and Birch, (2006). Indeed, the classical theory assumes that all "cost-effective" interventions with increased effectiveness compared with the standard (conventional) intervention could or should be reimbursed by the payers. In that sense, the classical approach assumes silently an arbitrary adjustment of budget in the cost of new technologies and thus unlimited budget availability. Hence, the above approach of cost-effectiveness does not incorporate the ability of a health care system to reimburse a new health technology, and thus in practice require an additional – and different – type of analysis to determine the economic burden of short and medium-term effects on budgets and other resources to reach a final conclusion. This type of analysis is called "budget impact analysis" (Goettsch and Enzing, 2014) but its criteria for the final verdict concerning the adoption or rejection of a new health technology remains unclear. Also, there are other drawbacks in this analysis. First of all, to adopt a new intervention the decision-maker must withdraw some existing interventions in order to find enough resources to support the new ones. However, in practice, very few, if any, economic evaluations state explicitly which specific health technologies and/or interventions must be withdrawn to meet the budget criteria (Birch and Gafni, 2006). In addition, the classical theory assumes that all decrementally cost-effective options (less costly, less effective but within the willingness-to-pay threshold; Nelson et al., 2011), could be reimbursed based on cost criteria. However, it is obvious, that there are important moral and ethical issues in the

treatment of patients which make the possibility to adopt an alternative "very poor", in terms of effectiveness, technology and/or intervention highly unlikely, despite their cost-saving profile. Furthermore, the classical model assumes that the willingness-to-pay for a unit of effectiveness is independent of the actual difference in effectiveness between different health technologies and thus, does not differentiate between a new truly innovative health technology, a similar-with-the-current health technology, or even a generic health technology and reimburse proportionally equally each one of them based on an arbitrary willingness to pay (Bridges et al., 2010; Cleemput et al., 2011). To deal with these drawbacks a modification of the present theory has to be conducted.

In this paper, we present a new economic model, specifically designed for resource allocation in genomic medicine, based on performance ratio, with potential applications in diverse health care sectors.

8.3. Methods

8.3.1. Where we stand: The Genome Economic Model

Based on the above consideration, we have recently proposed a new model to resolve these aforementioned drawbacks (Fragoulakis et al., 2016). Genome Economics Model (GEM) implies that there is a maximum amount of money per patient that could be spent by the payers only if a certain therapeutic gain from an innovative health technology was met by health providers. As such, in sharp contrast with the classical cost-effectiveness approach, under the GEM approach, the insurance funds define *ex-ante* what is expected to be the upper limit of ''innovation'' in terms of effectiveness/QALY gains, what is the lowest acceptable effectiveness that could be accepted and judge *ex-post* every new technology within two boundaries. In addition, GEM defines the maximum amount of money is willing to invest or save the budget holder within two boundaries. Furthermore, the GEM model, contrary to the classical model, does not conduct a separate budget impact analysis, as -by definition- every cost-effective technology in the

GEM model meets also the cost criteria. GEM was developed to be sensitive of the actual incremental effectiveness of a new intervention, in correlation with the willingness to pay for a QALY in a formal manner (for mathematical details see Yin et al., 2003). In this context, every potentially new unit of effectiveness that could be gained from future technologies has a different perceived value by policy makers. For a very small difference between two health technologies, the average willingness to pay for a QALY is expected to be low due to low additional value. For more innovative interventions with some fair differences in terms of effectiveness, a higher average willingness to pay for a QALY (but also smaller than those offered by the classical model) can be expected (Kvamme et al., 2010). For innovative interventions with significant difference in terms of effectiveness, the average willingness to pay for every unit of QALY is expected to be higher in comparison with classical model. As the difference in effectiveness increases further (breakthrough technology), we meet the budget constraints criteria and, as such, we are unable to reimburse this technology further and the average willingness to pay is getting lowered. The shape of willingness to pay for a QALY resembles, as the potential difference in effectiveness increases, a bell-shape distribution, contrary to the classical model, in which willingness to pay is a straight line, determined by arbitrary assumptions, made by policy makers or the literature (Fragoulakis et al., 2016).

Despite these appealing aspects, GEM does not address the very important issue of health resource allocation problem. Indeed, in this model a far less ambiguous approach was adopted to estimate the local equilibrium which is driven by the *de facto* budget availability in a disease-specific context without taking into account QALYs from different therapeutic areas. Hence, all conclusions and contributions of the GEM model were referred to a specific disease context without any comparisons with other therapeutic areas. To deal with such challenges, the identification of effectiveness, and consequently the amount of willingness to pay, could be attained/determined by ranking the available interventions for all diseases under a resource constraint with the use of a mathematical programming-type technique (Sendi et al., 2002).

8.3.2. Rationale and description of the model

The aim of the present model is to propose an alternative method for resource allocation taking into account a) the incremental innovation of a new technology, b) the relative effectiveness in comparison with social preferences, c) the cost of the technology, while permits the measurement of effectiveness to be determined differently in the context of a specific disease and then to be expressed in a relative form via a common performance ratio.

Contrary to GEM, the present new model aims to provide a practical solution for resource allocation in entire healthcare sector and to go a step further in the decision-making process. In practice, the scope of the present model was to determine an alternative and most precise way to share the available resources, maximizing a specific utility function in the same spirit as GEM. The model in the present form simplifies the complexities of real life, and thus does not take into account the uncertainty of variables (Briggs et al., 1994) and consequently determines its results in a deterministic way. In addition to that, the model is particularly applicable to developing countries, as assumes that the introduction of new innovative technologies improves the current medical practice and thus, it is connected with fewer adverse events and greater effectiveness compared with the technologies which are currently in use. Hence, the case of decrementally cost-effective choices does not taken into account in this form. Below we describe the main steps for the construction of the new model.

8.3.3. Methodological approach

The model is developed in a 6-step approach (**Fig. 8.1**). First of all, the decision makers must identify all the available health technologies (comparators) within different disease specific areas. These choices must include the “most expensive”, the “least costly”, and the “gold standard” intervention, which must be set in accordance with the standard medical practice, the literature and the current scientific research (Drummond et al., 1997). It must be noted that specific attention has to be given to this step, since some health care technologies are frequently presented as a “cost-effective choice” assuming that all available

knowledge has been incorporated is the evaluations, while in practice this term refers only in some of the available options which dominate the market share.

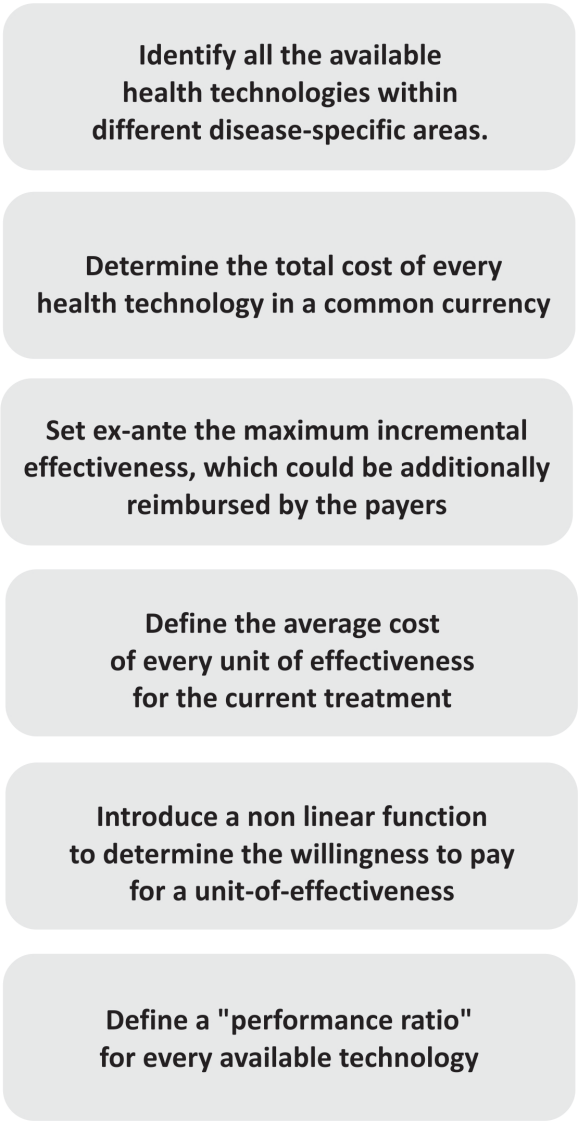

Figure 8.1. A stepwise approach for the proposed model for resource allocation and decision making in Genomic Medicine.

Secondly, the total cost of every health technology must to be determined in a common currency (e.g. €, £ or $). Cost determination must be in accordance to the current standards used in sounds economic evaluations (Husereau et al., 2013). Subsequently, the decision maker has to define how effectiveness in its separate disease-specific context needs to be determined. For instance, in GEM, there is no mandatory rule to express the effectiveness via the common measure of QALY, in order to avoid problems which are connected with this instrument

(Schwappach, 2002). Thus, several different disease-specific (but one-dimensioned) formulae must be used in each area. For instance, in oncology, it might be possible to use the "Progression Free Survival", as it defines the period over which the patient is free from disease progression, but must be used carefully in economic evaluation, since the correlation of this tool with the prolongation of life or improved quality of life is not always clear (Sullivan et al., 2011). Similarly, other specific tools have to be used for the other therapeutic areas. When all the available health technologies are expressed [as "Cost" (€, £, $), "Effectiveness" (PFS), *etc*)], then the second step of the model is completed.

The third step in the alternative model, proposed herein, is to set ex-ante what could be considered in the near future as the maximum incremental effectiveness (denoted as "ΔEmax"), which could be additionally reimbursed by the payers. This effectiveness expresses the most ambitious scenario in terms of effectiveness gains, which the policy makers is willing to additionally reimburse and must be set in every therapeutic area by the corresponding scientific and medical societies. This "ΔEmax", has to be expressed, as mentioned, in the terms of this particular tool used in every area. It must be noted that in a developing country with few available resources, the amount of ΔEmax, is expected to be relatively low, since the marginal utility of the limited resources is high. It must also be noted that the determination of ΔEmax might be a multi-criteria process, which has to take into account how a new technology has better effectiveness, how it affects patient quality of life, if it is easier to administer or safer to use and with fewer side effects. In addition to that, its therapeutic properties and mechanism of action must be taken into account, if (a) it constitutes an sound alternative enabling greater precision to individual patient needs, (b) and to which extent improves patient compliance through better dosage and administration mode, and (c) it extends the indications and gives multiple options in the same therapeutic class and/or reduces or substitutes other forms of therapy (http://www.who.int/medical_devices/innovation/en; accessed on 9/10/2016).

The fourth step is to define the average cost of every unit of effectiveness for the current treatment and this cost to be projected via a linear function form to meet the maximum incremental effectiveness. This step follows a similar concept of the "proportional rule" used by the German Organisation of Health

technology assessment (IQWIG; Lubbe, 2010), based on which every new health technology must provide at least a proportionally equal increase in percentage of effectiveness for an x% increase in the total cost of a technology. In other words, an increase in cost at x%, must be followed (at least) with an x% increase also in effectiveness. It must be stressed that the average cost per unit-of-effectiveness in each specific disease area will be different, which is logical, as the effectiveness in each area follows a different pattern concerning the cost and the effectiveness. For instance, it is much more difficult to produce a life month gain for an oncology patient than a cardiology patient and this feature is taken into account with our new model. This concept of a hypothetical example with 2 diseases is depicted in **Figure 8.2**.

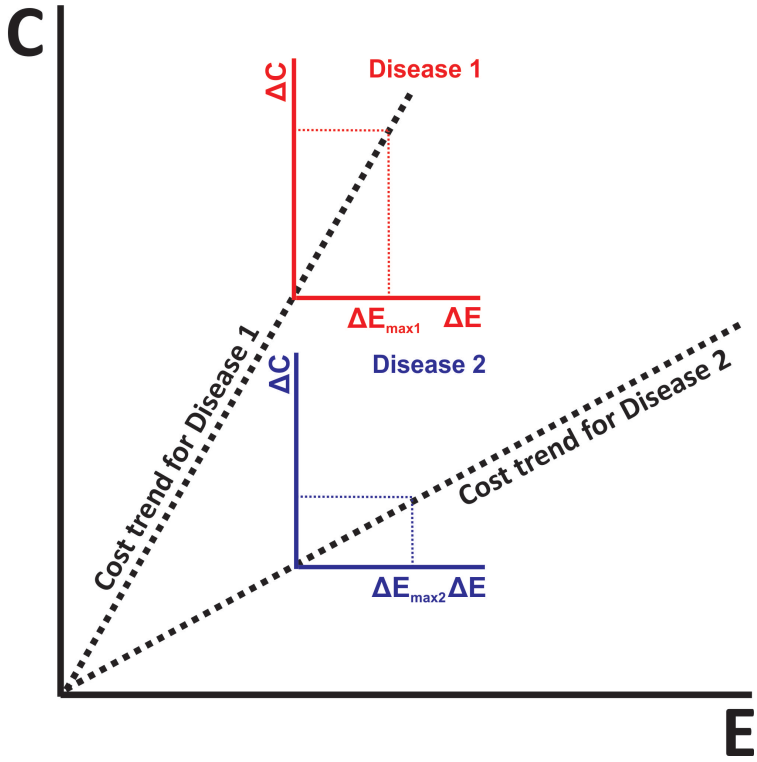

Figure 8.2. Average Cost and linear trend in a disease specific context. For every different disease ("disease 1", "disease 2", *etc*) we estimate the average trend for cost (based on the available historical data) and then we project it in the short-term, to meet maximum additional effectiveness we are willing to reimburse in a finite future (ΔEmax).

The fifth step, borrowed from the classical model described in Fragoulakis and co-workers (2016), is to introduce a non-linear function which determines

the willingness to pay for a unit-of-effectiveness in correlation with the actual difference produced by every new health technology. This non-linear function for willingness to pay drives healthcare providers to increase the effort for favourable treatments, "punishes" the less productive ones, and "rewards" those technologies which provide significant incremental innovation with viable economic terms (**Fig. 8.3**).

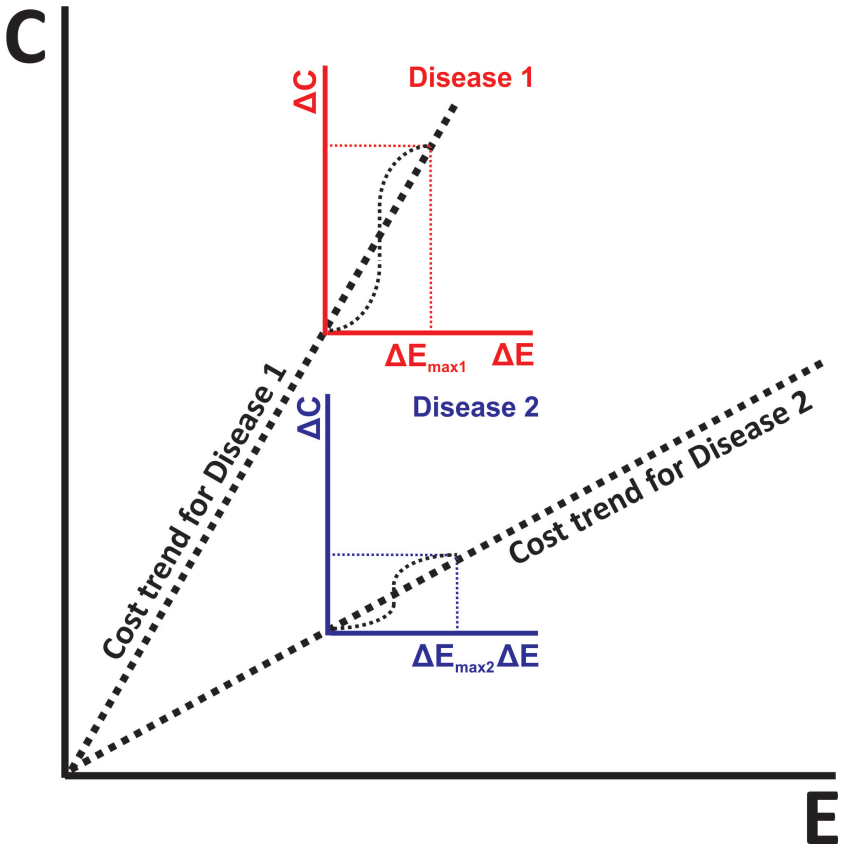

Figure 8.3. Willingness to pay for a unit-of-effectiveness in a disease specific context. Further to Figure 2, for each disease, we introduce also a nonlinear curve which determines the willingness to pay for an additional unit of effectiveness based on the projected cost and the ΔEmax.

Lastly, the proposed new model defines a "performance ratio" for every available technology, which is determined by the "one minus the ratio of the actual incremental cost of a new technology divided by the willingness to pay for the actual effectiveness gained" by this specific technology. If this ratio is negative, the policy makers are not willing to adopt and rejects this technology, since the cost of adoption is greater than what are they willing to invest. Of course, the most prominent options will be those technologies that will have the higher

performance ratio (near to one), as they have the biggest surplus. This concept on how to determine the results of each technology is depicted in **Figure 8.4**.

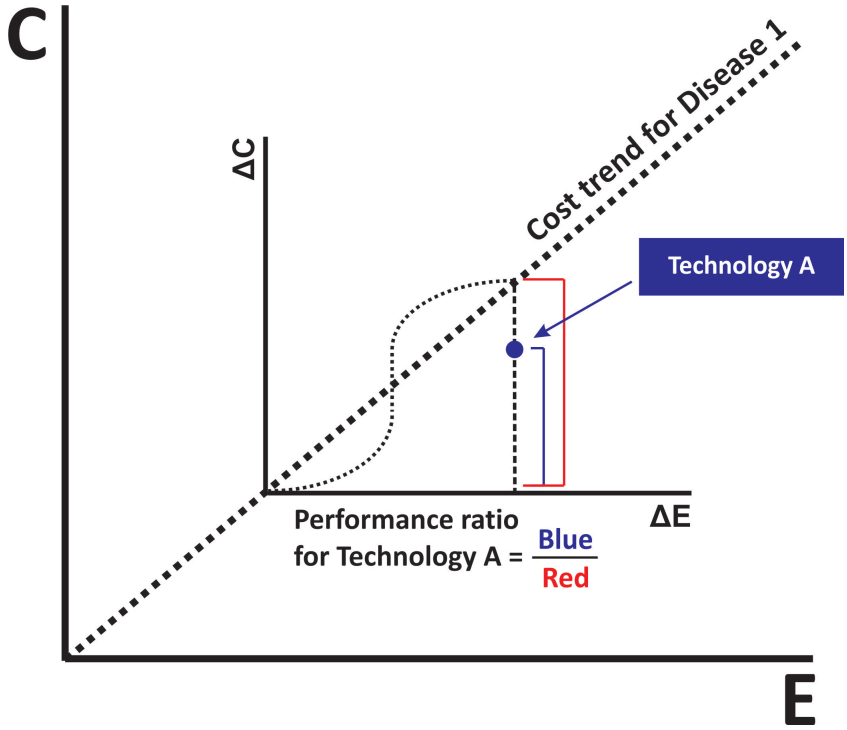

Figure 8.4. Definition of Performance Ratio, which determines the relative performance of a healthcare technology based on a relative basis. For instance, a 20% performance indicates that the cost of a technology is only 80% (1-20%) of the total cost that the Insurance Funds are willing to invest to gain the specific effectiveness this technology offers. When Performance ratio equals with 100%, this indicates that the new technology is offered in the same cost with the standard technology and thus, represents a dominant choice. A negative Performance ratio indicates technologies which have to be rejected by the healthcare system.

Finally, as a rule, the available resources will be spent for those technologies which provide the most attractive performance across the healthcare sector with a mathematical programming type of analysis until the budget is exhausted (Flessa, 2000). This model assumes that the policy makers are willing to maximize this performance ratio of health gains, and not to maximize QALYs as it is the normal (Weinstein et al., 2009). Hence in this model, the aspect of innovation has two different and distinct dimensions: (a) the actual difference in effectiveness which is on behalf of the patient in correlation with what is expected to be the true innovative health technology and (b) the containment of cost expenditures which plays an important role for all modern health care systems.

With this model, all health technologies ("me-too", "fair", "innovative", "very innovative", "breakthrough") in all specific areas become comparable via the "performance ratio" and thus the model provide a ground for comparisons (and reimbursement) amongst them. Of course, in order to meet meaningful conclusions, the model requires the explicit mapping of preferences via the non-linear forms of willingness to pay in a quantitative form.

It must be noted that in accordance with the maximization rule of performance ratio, the model gives a "premium" in innovative technologies and permit them to absorb proportionally higher amount of budget in comparison with a simple linear approach of classical model. In other words, for innovative interventions (in terms of effectiveness), there is a higher reimbursement as a reward for the successful research-and-development process, while the model is stricter in "me-too" technologies since it is expected only a marginal additional burden from them.

8.4. Results and Discussion

Understanding the relative benefits and drawbacks of alternative strategies for resource allocation, is important in order to ensure that patients receive effective but also economically efficient care and that healthcare systems have the chance to stay sustainable in the future (Sendi and Briggs, 2001). It is well known that in every developing country is crucial to establish a well-functioning health care system, to invest the necessary funds and to follow the major planning priorities for each country (Okebukola and Brieger, 2016).

Here, we have proposed an alternative methodological concept for resource allocation which represents the generalization of a previously published work (Fragoulakis et al., 2016) and could be particularly useful for developing countries. In the present work, it has been argued that "innovation" must be set as a priority and this term might also include: (a) the absolute benefit on behalf of the patients, and (b) the ratio of cost and effectiveness in terms of "social consumer surplus". In order to avoid theoretical issues with the use of QALY which is still under consideration (Wailoo et al., 2009; Baker et al., 2010; Lancsar et al., 2011), the present model uses a new index called "performance ratio", which

determines the proportional increase in effectiveness (the relative effectiveness as percentage) in accordance with social preferences. In this light, we have avoided the use of QALYs, despite the fact that it is possible to be also used as the variable which can be maximized in the present model. In that sense, the model maximizes a unified theoretical and abstractive index which takes into account three different "variables": namely the cost, the effectiveness and its size, and the social preferences. The present analysis pays particular attention only to deterministic results assuming that the cost and effectiveness are point estimates. In practice, due to limited knowledge, all these represent distributions and even the budget is not necessarily strictly defined in each country. It must be noted that the potential value of the present model must be judged in comparison with similar attempts previously made (Eckermann et al., 2008; see also www.york.ac.uk/che/pdf/mathprog.pdf). In the most of cases the analysis of this "maximization problem" is highly technical and uses advanced mathematical techniques to deal with all issues involved in this type of analysis under several different assumptions. In addition to that, the model implies a complex process in which formulae need to be created for every disease and effectiveness needs to be evaluated over a long time period, meaning that it is not easy to implement. This sort of evaluation would be costly, and therefore might limit the effectiveness of the present model.

Table 8.1. Differences between the previously published Genome Economics Model (GEM) and the new model presented in this paper. [a]: Although not necessary; [b]: It is a general model.

Model Features	**New Model**	**GEM Model**
Takes into account the level of innovation	YES	YES
Resolves the Budget Allocation problem	YES	YES
Maximizes QALYs	YES [a]	YES
Takes into account the uncertainty of variables	NO	YES
Takes into account only a disease-specific context	NO [b]	YES
Is Budget exogenous in a disease-specific context	NO	YES
Takes into account the decremental cost-effective choices	NO	NO

Even in this case, (in a restriction which our model is also subjective), ethical and political issues have to be identified and incorporated in these models.

Nonetheless, as previously mentioned, economic evaluation represents a useful tool, but despite the attractive veneer of objectivity given by the concise and elegant mathematical nomenclature, the actual subject of financial resource management is in practice fundamentally a political problem (Fragoulakis et al., 2015).

In essence, this alternative model provides a further insight in the decision-making process in Genomic Medicine and an improved management tool for the policy makers, particularly for developing and resource-limited countries, which warrant practical implementation. In summary, the main methodological differences amongst our previously proposed model (GEM) and the new one presented herein are described in **Table 8.1**. Despite the fact that this model is primarily meant for Genomic Medicine, it might also be used in healthcare sector in general and the exploration of this model in practical applications could be the scope of future research.

8.5. Acknowledgements

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Chapter 9

General Discussion

9. General Discussion

Pharmacogenetics is a core component of Personalized Medicine and has the potential to become an integral part of modern clinical practice. Pharmacogenetics aims to deliver "the right drug to the right patient at the right dose" (Piquette-Miller and Grant, 2007) with the ultimate goal to improve the quality of life of the patients by reducing ADRs and improving efficacy of therapy, both of which will reduce overall national healthcare expenditure (Patrinos and Mitropoulou, 2017). As such, studies have shown that over 150 genome-guided treatment modalities are a clinical reality, yet there is an urgent need to define whether these interventions are cost-effective, benefiting both the patient and the society overall. The availability of economic evaluation studies of pharmacogenomic-guided interventions and of specialized or generic economic models to perform such studies, will be key in the efforts to generate evidence for the clinical utility of these interventions. This will allow healthcare systems to reimburse pharmacogenomic testing costs, particularly since the testing costs are gradually declining. At the same time, a critical appraisal of the views of the various stakeholders involved in the provision of pharmacogenetics and personalized medicine interventions is of equal importance to smoothen the way of pharmacogenetics into the clinic.

Consistent with the challenges outlined above, this thesis aimed to (i) economically evaluate pharmacogenomic-based drug treatment modalities to demonstrate their cost-effectiveness, (ii) to develop economic models that could be used to perform these economic evaluation studies, and (iii) to critically appraise the current views and opinions of the healthcare professionals and the various other stakeholders in the provision of pharmacogenetics services. Particular focus was given into developing countries and low-resource environments, where application of genome-guided interventions is not so advanced compared to countries like the United Kingdom, the United States, the Netherlands, Switzerland, Germany, etc.

9.1.1. Economic evaluation of genome-guided interventions in developing countries

For a pharmacogenetics-based drug treatment modality to be integrated into the clinic, one should be able to demonstrate, apart from its clinical utility, its cost-effectiveness. As previously mentioned, economic evaluation studies of pharmacogenetics-guided treatment modalities are very scarce. Particularly in developing nations and low-resource environments, a cost saving approach using pharmacogenomic information could be valuable. Hence, we have decided to perform economic evaluation of two well-established genome-guided drug treatment interventions in cardiology, being warfarin and clopidogrel, delivered in low-resource environments in Croatia and Serbia, respectively, to analyze their cost-effectiveness as key examples.

Warfarin is the mainstream drug treatment modality for patients with atrial fibrillation. Our analysis showed that pharmacogenomic-guided warfarin treatment using the *CYP2C9*/*VKORC1* genotypes is a cost-effective option for those suffering from atrial fibrillation and developed ischemic stroke. Our findings were consistent with other studies under different methodological assumptions or comparators (Patrick et al., 2009; You et al., 2012), showing a general agreement. In our study, the difference in effectiveness (QALYs) between pharmacogenetics-guided and conventional warfarin treatment was relatively small (see **Chapter 5**), but there was a clear health gain demonstrated for these patients: less complications due to bleeding and a shorter time to reach the required maintenance dose. Overall, this analysis indicated that in Croatia, pharmacogenetic-guided warfarin treatment may constitute a cost-effective treatment modality and was assessed for the management of elderly patients with atrial fibrillation who developed ischemic stroke as compared to conventional therapy. This analysis was based on the current prices for drug treatment, genotyping costs and hospitalization to treat adverse drug reactions and resource utilization.

The issue of cost-effectiveness of warfarin treatment was also assessed in other healthcare systems. In particular, Pink and coworkers (2014) showed that

pharmacogenetics-guided warfarin treatment was cost-effective in the UK with an ICER of 13,226 GBP per QALY. These data were also confirmed by Verhoef and coworkers (2016), who also showed that pharmacogenetic-guided dosing of warfarin is a cost-effective strategy to improve outcomes of patients with atrial fibrillation in Sweden too. On the contrary, Verhoef and coworkers (2015) assessed the cost-effectiveness of pharmacogenetically-guided acenocoumarol and phenprocoumon treatment and showed that with ICER of €28,349 and €24,427 per QALY gained, respectively, these treatment modalities are unlikely to be cost effective compared with the clinical dosing. Availability of low-cost genotyping, however, would make this a cost-effective option. Similarly, in the United States, Meckley and coworkers (2010) showed that warfarin pharmacogenomic testing may provide a small clinical benefit with an ICER of <50000 USD per QALY, with the results being sensitive to the genotyping costs.

As far as the pharmacogenetically-guided clopidogrel treatment is concerned, we retrospectively assessed whether *CYP2C19* genotyping could be cost-effective in order to determine the optimal antiplatelet therapy in Serbian patients treated with clopidogrel, as compared to the non-genotype-guided treatment (see **Chapter 6**). Again, an almost 5-fold higher rate of reinfarction events in the case of patients bearing the *CYP2C19**1/*2 and *CYP2C19**2/*2 genotypes was observed as compared to *CYP2C19**1/*1 patients (11.2% versus 2.3%, respectively). Reciprocally, the mean treatment costs for the *CYP2C19**1/*1 patients were lower (2589 EUR) than these estimated for the *CYP2C19**1/*2 and *CYP2C19**2/*2 patients (2799 EUR). As such, our data indicate that, based on a break-even point analysis, performing the genetic test prior to prescribing clopidogrel represents a cost-saving option, saving €13 per patient on average in combination with a better health outcome. Also, considering the fact that treatment with ticagrelor, the alternative treatment modality to clopidogrel, is around €300 more expensive per patient, the use of the former is justified for patients bearing the *CYP2C19**2 allele and at the same time suggests that ticagrelor should not be generally prescribed to all patients, since *CYP2C19**1/*1 patients will respond well to clopidogrel.

When assessing cost-effectiveness of clopidogrel treatment in the US healthcare system, Lala and coworkers (2013) showed that acute coronary syndrome patients undergoing PCI, a pharmacogenetically-guided strategy yields almost similar outcomes compared to conventional treatment modalities, being only marginally less costly and more effective. On the contrary Jiang and You (2016) showed that in the US healthcare system, clopidogrel treatment was the preferred antiplatelet strategy for acute coronary syndrome patients with PCI, compared to alternative ticagrelor and prasugrel treatment, being both less costly and more beneficial. These data were consistent with the findings of by Patel and coworkers (2014). Similar findings were reported by Fragoulakis and coworkers (2019a) when analyzed a large number of Spanish patients with PCI, treated with clopidogrel. In addition, according to the systematic review by Zhu and co-workers (2019), pharmacogenetics testing was found to be cost-effective in 31 out of 46 studies (67%) involving genome-guided treatment in cardiology, from which 78% examined warfarin-CYP2C9/VKORC1 or clopidogrel-CYP2C19. In particular, in 13 out of 21 studies conducted in the United States (~62%) PGx testing was found to be cost effective and the same was true for both studies involved the Australian healthcare system, in 3 out of 4 studies originating from Canada and 3 out of 6 studies from the Netherlands. Interestingly, findings from the remaining countries, namely 9 out of 10 studies (90%), included in this study also demonstrated cost-effectiveness of the pharmacogenetics -guided treatment modalities in cardiology.

These results generated for the need of this thesis are applicable only for Croatia and Serbia, as they have been strictly considered in the context of the Croatian and Serbian healthcare settings and were performed on the basis of the time and management practice of patients as well as drug and health resource prices of the time the economic evaluation was conducted. In other words, these analyses should be done for every country individually, as we have demonstrated. In addition, these analyses could be repeated periodically, especially when the comparators change over time.

Although economic evaluation studies and cost-effectiveness analyses of genome-guided interventions are currently limited, they are not restricted to

cardiology alone. There are other medical specialties where economic evaluation of genome-guided interventions are performed.

In oncology, the cost-effectiveness of *KRAS* testing for cetuximab treatment of colorectal cancer patients was assessed is Germany (Behl et al., 2012) and Austria (Königsberg et al., 2012), indicating that the genome-guided intervention was cheaper and with the same effectiveness. The same intervention in Switzerland was shown to be cost-effective (Blank et al., 2011). In the case of DPYD genotyping for the treatment of colorectal cancer patients with capecitabine and fluorouracil, this was also shown to be slightly cheaper for the Netherlands (Deenen et al., 2015) and also a dominant choice (cheaper and with better effectiveness) in Italy (Fragoulakis et al., 2019b), respectively. Genome-guided treatment of colorectal cancer patients with irinotecan monotherapy, based on the UGT1A1*28 genotype was also shown to be a dominant choice for African and Caucasian patients (Obradovic et al., 2008), while in case of Asian patients this intervention was shown to be cost-effective (Obradovic et al, 2008). Also, *HER2* profiling to individualize Trastuzumab treatment on breast cancer patients was shown to be cost-effective (Blank et al., 2010).

In neurology, a key example is the cost-effectiveness analyses of *HLA-B*1502*-based carbamazepine treatment of patients with epilepsy. This variant is more prevalent in Asian, compared to Caucasian and African populations. In Singapore, a cost-effectiveness analysis involving all three ethnic groups bearing different allele frequencies of the *HLA-B*15:02* allele, indicated that *HLA-B*15:02*-based carbamazepine treatment was cost-effective in all three subpopulations (Dong et al., 2012; Liew, 2016).

In case of infectious diseases, there are also few economic evaluation studies previously performed. In HIV treatment, patients who carry the *HLA-B*57:01* allele are at high risk for experiencing a hypersensitivity reaction to abacavir [Mallal et al., 2008]. The first economic evaluation was performed in 2004 by Hughes and coworkers, indicating that the *HLA-B*57:01* testing strategy ranged from dominant (less expensive and more beneficial compared to no testing) to cost-effective. Similar findings were reported by Schackman and

coworkers [2008], indicating that the genetic testing strategy was a cost-effective intervention compared with no testing. In case of chronic Hepatitis C, it has been shown that *IL28B* genetic variants can predict treatment response with certain variants leading to a less favorable response. Bock and coworkers (2014) demonstrated that *IL28B*-guided therapy is cost-effective for each *IL28B* variant compared to the standard of care therapy for HCV genotype 2 and 3 patients.

Lastly, there are no economic evaluation studies of genome-guided interventions performed in psychiatric patients.

9.1.2. Developing economic evaluation models for genomic medicine

Economic evaluation is a key component in rationalizing healthcare expenditure, as the provision of optimal healthcare solutions is one of the leading priorities in society. An uncontrolled growth in health care expenditure would affect the national budget. Economic evaluation provides a criterion for the final decision for the adoption of certain new and innovative technologies, such as genome-guided drug treatment modalities (Snyder et al., 2014). To this end, there is an urgent need to establish economic models that can be used to evaluate these interventions.

In this thesis, we propose two alternative methodological approaches, which take into consideration the budget constraint, the effectiveness of a new technology and social preferences.

The first model (Genome Economics Model, GEM) describes the link between the willingness to pay threshold towards the budget limit, enabling the combination of cost-effectiveness and budget impact analysis (see **Chapter 7** for term definitions). In this context, every new unit of effectiveness that could be potentially gained from the innovative technologies has a different perceived value for the patients, the scientific community and the stakeholders. In other words, if the difference in effectiveness between two health technologies is very small, then there will be no meaningful differentiation between the two interventions. As the difference in effectiveness increases further for innovative

interventions, then this new intervention can be reimbursed, provided that the reimbursement costs are well within the budget constraints criteria. Hence, the new model encourages healthcare providers to increase the effort for favorable treatments, "punishes" the less productive ones and "rewards" the true innovation, ensuring at the same time the sustainability of the healthcare system. This model also attempts to unify cost-effectiveness and budget impact analysis, also taking into serious consideration ethical issues and patients' preferences, improving some core drawbacks of other models. Despite the potential added-value and novelty of the GEM model, it does not address the very important issue of health resource allocation. To deal with such challenges, the identification of effectiveness, and consequently the amount of willingness to pay, could be determined by ranking the available interventions for all diseases under a resource constraint with the use of a mathematical programming-type technique (Sendi et al., 2002).

As such, we designed an alternative method for resource allocation that takes into consideration a) the incremental innovation of a new technology, b) the relative effectiveness in comparison with social preferences, c) the cost of the technology, while permits the measurement of effectiveness to be determined differently in the context of a specific disease and then to be expressed in a relative form via a common performance ratio.

This alternative model uses a new index, termed as "performance ratio", which determines the proportional increase in effectiveness (the relative effectiveness as percentage) in accordance with social preferences. In essence, this alternative model provides (a) important insights into the decision-making process in Genomic Medicine, and (b) an improved management tool for the policy makers. This makes it particularly appealing for developing and resource-limited countries, which warrants practical implementation (**Chapter 8**).

This model is highly technical and uses advanced mathematical techniques to deal with all complex issues and processes that are implied. Different formulae need to be created for every disease and effectiveness needs to be evaluated over a long period of time. Also, this model must take into consideration various ethical

and political issues that have to be identified and incorporated into the equation. Despite the fact that this model is primarily meant for Genomic Medicine, it might also be used in the healthcare sector in general and the exploration of this model in practical applications could be the scope of future research.

9.1.3. Critical appraisal of the views of healthcare professional in respect of pharmacogenomics

In order to maximize the benefits of economic evaluation studies mentioned in the previous paragraphs and to expedite pharmacogenetics-guided treatment interventions into the clinic, one should ensure that the stakeholder environment in every country is clearly explored and the views of the various stakeholders critically appraised.

Given the potential of genomic medicine to grow in the coming years, it is imperative to comprehensively analyze the level of awareness of healthcare professionals in relation to genomics and personalized medicine so that the delivery of genomic services may be expedited in their various healthcare systems. Genetics education and communication will play an important role in increasing the level of awareness of the various stakeholders with respect to genomic medicine so that they come to appreciate the benefits that this new discipline can offer (Reydon et al., 2012).

In this thesis, we attempted to shed light on the level of awareness and education of healthcare professionals in relation to pharmacogenetics and genomic medicine, focusing again in a country with a large fiscal deficit, such as Greece. In Greece, like other developing countries in Europe and worldwide, there is very scarce knowledge as far as the level of genomics awareness and education of healthcare professionals is concerned (Mai et al., 2014 and references therein), contrary to other Western European countries where Genomic Medicine interventions are routinely implemented, such as the United States, United Kingdom, Germany, the Netherlands, and others. In particular, in the Netherlands, pharmacists strongly believe in the pharmacogenomics concept and being aware

of the Dutch Pharmacogenetics Working Group guidelines did not affect significantly their knowledge or adoption of pharmacogenetics in their practice (Bank et al., 2017). In countries like the United States and the United Kingdom, where large-scale genomics projects are run, such as the All-Of-Us and the 100,000 Genomes projects, respectively, there are well-established online resources to educate healthcare professionals in the fields of genomic medicine and pharmacogenetics (https://allofus.nih.gov, https://www.genomicsengland.co.uk/understanding-genomics). In the United Kingdom, integral to the success of the 100,000 Genomes Project is the education and training of both the healthcare workforce and patients and the public. This effort is coordinated and managed by the Health Education England (HEE) Genomics Education Programme (https://www.genomicseducation.hee.nhs.uk), aiming to: (a) underpin the delivery of the 100,000 Genomes Project and specific education and training needs, (b) upskill the existing workforce to respond to the changing genomics and stratified medicine landscape, and (c) provide broader prospective workforce transformation for the NHS and Public Health. The dedicated M.Sc. program that HEE has commissioned to seven leading universities in the United Kingdom, which is especially suitable for doctors, healthcare professionals and students with an interest in genetics and genomics, is another element that underlines the commitment of the United Kingdom towards the proper genomic education of British healthcare professionals.

Our results (**Chapter 3**) indicate that in Greece, approximately 2/3 of the pharmacists considered their level of genetics knowledge to be low, a proportion comparable to the pharmacists who admitted very limited or no knowledge of pharmacogenomics and its relationship with personalized medicine. A small proportion (5%) of pharmacists in Greece felt that their genetics and pharmacogenomics knowledge was high. As far as physicians are concerned, 24% admitted that the level of their knowledge over pharmacogenomics and personalized medicine was high or even very high. This difference can most easily be explained by the fact that genetics and molecular biology courses are included for a longer period of time in the medical schools in Greece as compared to the schools of pharmacy. Pharmacists are considered to be experts in medication, and

as such they are expected to be able to use pharmacogenomic information appropriately in order to individualize treatment regimens. As such, pharmacists can play an important role in the application of pharmacogenomics into clinical practice, jointly with the physicians, to improve the quality and safety of health care. Hence, pharmacogenomics should be taught at an increased rate in modern undergraduate curricula in schools of medicine and pharmacy, perhaps as a stand-alone module/course. The older generation of pharmacists and physicians have a positive view of pharmacogenomics and are willing to increase their knowledge of pharmacogenomics with a view to gradually integrating it into their practices. Proper continuous pharmacogenomics education must be encouraged to help them fill in their knowledge gaps for the benefit of their practices as well as to optimize the integration of pharmacogenomics into patient care.

In an effort to analyze the policy environment and identifying the role, the interests and the position of the key stakeholders related to pharmacogenomics and personalized medicine in Greece, we analyzed the views from representatives of all key stakeholders in the field of pharmacogenomics and genomic medicine policymaking, using Policy Maker's computerized version of political mapping. Based on this analysis, the Current Position Map of these stakeholders was generated, according to the extent of their support or opposition to pharmacogenomics and genomic medicine in Greece. Overall, half of the key stakeholders are highly supportive of pharmacogenomics and genomic medicine in Greece, among which were pharmaceutical and biotechnology companies, as well as molecular diagnostics laboratories (see **Chapter 4**). These also have strong influence and are driving forces to support clinical implementation of pharmacogenomics from a technology-driven point of view. On the other hand, there was a medium opposition from the Ministry of Health and the public health insurance funds, based on not yet fully proven cost effectiveness of a pharmacogenomics approach, both of which have high power to intervene against the implementation of pharmacogenomics and genomic medicine into mainstream clinical practice. The strong financial interest and responsibility of both stakeholders could in part explain this finding. Public health insurance funds may lack the information on how reimbursement of genetic testing could decrease

the overall healthcare expenditure, instead of increasing. This underlines the need to provide evidence of the value of genome-guided interventions (Patrinos and Mitropoulou, 2017) as an additional tool to convince these stakeholders of the need to reimburse these innovative interventions for the benefit not only of the patients but also of the healthcare system. The current lack of proper legislation to oversee the operation of private genetic testing laboratories (Kechagia et al., 2014) could also explain the medium opposition of these stakeholders. The neutral position of the Greek National Medicines Organization and the highly supportive position of the private health insurance companies were surprising, considering the fact that they both are at the opposite direction compared to that of the public health insurance funds. This warrants further investigation and possibly exploitation in order to convince the latter funds to also adopt a supportive attitude towards this emerging trend of genomic medicine.

According to the findings of this work, citizens and the general public, as well as biomedical scientists, such as geneticists, pharmacists and physicians are highly supportive towards genomic medicine and individualization of drug treatment, despite the fact that they professed that their level of genetics awareness is fairly low. The neutral position held by the Media and the Press could be attributed to their lack of knowledge and hence, if objective opinions and facts are presented by academics, qualified professionals, and regulatory bodies, it would help them towards adopting a more positive stance towards genomic medicine and pharmacogenomics, providing extra help to alter the position of governmental organizations that are currently opposed to genomic medicine, mostly due to the financial constrain imposed by the high fiscal deficit in the country.

Apparently, once the first tangible benefits from the implementation of pharmacogenomics become available, and more evidence regarding the value of genome-guided interventions is produced, the overall position of these key stakeholders will most likely change to a more favorable one. In any case, the results of this approach can not only help to adopt certain steps and measures necessary to maintain the overall positive attitude of most stakeholders towards genomic medicine and to shift the remaining stakeholders from a neutral-to-

negative opinion into a more supportive one but also to replicate this study in the coming few years in order to acquire further insight into the future views of these stakeholders in Greece.

This study can be also replicated in other countries in an effort to harmonize policies towards the establishment of the genomic medicine landscape into future medical practice.

9.2. Conclusions

Pharmacogenomics can clearly contribute to minimize adverse drug reactions and, as a result, help reducing morbidity and mortality rates. There are several studies that have highlighted the role of genomic variants, based on which the drug dose can be individualized in patients receiving medication for cardiovascular, oncological, psychiatric and other diseases. In order to implement a genome-guided treatment strategy, economic evaluations and cost benefit analyses are required. Generally, the need to perform cost-benefit analyses stems from the scarcity of resources in order to set priorities in the investments for health care. These benefits should be evaluated by means of proper economic analysis, taking into consideration ethical and societal issues as well as the available budget. This stepwise approach performed in this thesis could serve as an excellent model for replication, also and especially in low-resource environments. This can be particularly challenging, since results from medical and genomics research are often considered as intermediate indicators and should be converted/translated into tangible, final health outcomes on which policy and decision makers are based to draw their conclusions as to which intervention to adopt and reimburse. This economic evaluation process has been reported in **Chapters 5 and 6** to indicate that genome-guided warfarin and clopidogrel treatment is cost-effective in Croatia and Serbia, respectively.

We have also proposed alternative models to perform economic evaluation in genomic medicine, taking into consideration budget restrictions, where applicable (**Chapter 7**) and also performance ratio (**Chapter 8**), that takes into

serious consideration social preferences and acceptability of new technologies and rewards innovation. These models are particularly relevant to pharmacogenomics and genomic-guided interventions, since the latter interventions are highly innovative. As such, we propose that resources are transferred from existing low-innovation interventions, such as the conventional one-size-fits-all drug treatment modalities, to these genome-guided medical interventions that are highly innovative and hold promise not only to increase the quality of life of the patients but also to further reduce healthcare expenditure.

Lastly, it is highly recommended to critically appraise the views of society and the general public as well as of the various stakeholders, such as healthcare professionals, insurance bodies, regulators, policy makers, religious groups and their stance towards genomic medicine. At the moment, the vast majority of stakeholders are generally positive but continuous medical education and awareness is needed not only to maintain this position but also to better inform those stakeholders about the benefits of rationalizing drug use both for the patients and society overall. In the near future, it is expected that implementation of genomics into medicine will touch upon a much bigger proportion of patients and diseases, given the (i) generation of new knowledge, (ii) continuous decline of the genetic testing and interpretation costs and, (iii) advancement of genotyping technologies. This would provide the basis to encourage additional economic evaluation studies, which would yield more positive results regarding the cost-effectiveness of these interventions, hence facilitating the integration of personalized medicine into front-line patient care.

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Chapter 10

Summary

10. Summary

The central aim of Personalized Medicine is to exploit the individual's genomic information to support the clinical decision-making process. Although the concept of Personalized Medicine is relatively new, its intellectual ancestors have been around for some considerable time. Thus, around 400 B.C., Hippocrates of Kos (460–370 B.C.) stated that "… it is more important to know what kind of person suffers from a disease than to know the disease a person suffers".

In 1956, Fredrich Vogel introduced the term "Pharmacogenetics" when describing the adverse effect of soldiers on primaquine, an antimalarial drug, appeared to be the result of a genetic defect in the G6PD enzyme. In 1962, Evans and coworkers described the genetic backround of peripheral neuropathy occuring when patients where treated with isoniazide, and linked this response to geentic variations in the *NAT2* gene. A major contribution in this field was the discovery by Richard Smith in 1977 about the genetic basis of the response to the antihypertensive drug debrisoquine. The enzyme involved, the cytochrome P450 2D6, is involved in the metabolism of approximately 20-25% of all drugs, and in fact appears to be absent in 5-10% of the population. In addition, 20-25% of the population has a low activity of this enzyme, whereas 2-4% has an increased activity, all due to different *CYP2D6* genomic variants. In 1985, Richard Weinshilboum reported the hereditary component of the thiopurine S-methyl transferase, which was subsequently linked to genetic variants in the *TPMT* (thiopurinemethyltransferase) gene.

The term used for this field is "Pharmacogenetics", that is the relation between hereditary factors and drug metabolizing capacity. Later, the term "Pharmacogenomics" was introduced, covering pharmacogenetics, but also including other genomic variants identified in the genome as well as mRNA expression profiles affecting drug metabolism.

Also in the early 2000, the term *Personalised Medicine* was introduced, while in 2015, the newest term "Precision Medicine" was introduced by former US President Barack H. Obama, who announced the US Precision Medicine Initiative (PMI).

While there are many definitions of the term, the concept of personalized medicine involves the combined knowledge of genetics to predict disease susceptibility, disease prognosis, or treatment response of a person to improve the person's health. Progress made in the development of personalized medicine in recent decades has coincided with health care systems placing greater emphasis on evidence-based clinical practice, particularly as they are operating within an increasingly budget-scarce environment. It is often argued that personalizing treatment will inevitably improve clinical outcomes for patients and help achieve more effective use of health care resources. Hence, demand is increasing for demonstrable evidence of clinical utility and cost-effectiveness to support the use of personalized medicine in health care.

Pharmacogenomics is a core component of Personalized Medicine and as such, it will be used as an example to highlight the application of economic evaluation in Personalized Medicine. Pharmacogenomics attempts to enrich our understanding of how medicines work in each individual based on genomic contributions to a medicine's safety and efficacy. The latter can lead to a more efficient and effective approach to drug discovery. Furthermore, pharmacogenomics may lead to a more diversified and targeted portfolio of diagnostics and therapies, which, when used together, would yield greater health benefits to society.

Pharmacogenetics is a term that refers to the study of the effect of genomic variations on drug response, in terms of both drug metabolism (pharmacokinetics) and drug action (pharmacodynamics). Additionally, genetic variants have been shown to be associated with what had previously been considered to be idiosyncratic adverse drug reactions (ADR). In other words, this discipline aims to identify the best medicine for a specific disease when the disease occurs in a patient population with a particular genotype. Considering the fact that there are genetic factors that account for 20-95% of the observed responses to drug therapies, one could understand the impact of this new discipline in modern medicine. It is important to note that other factors such as age, food intake, drug-drug interactions, the simultaneous presence of other diseases (co-morbidity) influence an individual's drug response independent of, in conjunction with or in addition to genetic factors.

The aim of the present thesis was to assess the health benefits of genome-guided treatment interventions, in comparison with the standard interventions used in the current medical practice. We focus on the economic analysis of pharmacogenomic-guided warfarin and clopidogrel treatment, particularly since in recent years cardiology became the key medical specialty in which pharmacogenetics applications are emerging into practice. Furthermore, in this thesis, we investigated, through structural questionnaires, the views, opinions and attitudes of the various stakeholders and of the general public about genomic medicine and its impact to society. Lastly, we proposed an alternative methodological approach for cost-effectiveness analysis and developed a practical guidance for decision making by budget holders.

In **Chapter 2**, we provide some key examples of the applications of pharmacogenetics in modern medical practice, focusing on different medical specialties such as cardiology, oncology, psychiatric and infectious diseases and of these interventions that have been approved by all major regulatory bodies, such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Also, we emphasize the need to perform economic evaluation and its different types, summarize the main methodological aspects of economic evaluation and outline the few examples of economic evaluation in genomic medicine that have been performed so far. At first, we aimed to determine the level of awareness of healthcare professionals in Greece with respect to pharmacogenetics and personalized medicine using structured questionnaires addressed to a large number of pharmacists and physicians. These findings are presented in **Chapter 3**, indicating that approximately 60% of pharmacists consider their level of knowledge of personalized medicine to be very low, while over half of the pharmacists and physicians indicate that they would be unable to explain the results of pharmacogenomic tests to their customers or patients, respectively. This situation may be directly related to the low level of their undergraduate education in genetics and pharmacogenomics. These findings provide the basis for assessing the views of healthcare professionals in relation to personalized medicine in Greece and should help to facilitate the integration of genomics into the medical decision-making process.

In **Chapter 4**, we sought to enrich our understanding over the policies and opinions of the key stakeholders involved in the translation of genomic findings in the clinic. To achieve our goals, we used the computerized version of the *PolicyMaker* political mapping tool to collect and organize important information about the pharmacogenetics and genomic medicine policy environment, to assess the policy's content, the major players, their power and policy positions, their interests and networks and coalitions that interconnect. Our findings indicate that the genomic medicine policy environment in Greece seems to be rather positive, as the vast majority of the stakeholders express their medium to high support in the initially set goals of genomic medicine policy environment. The Ministry of Health and public healthcare insurance funds seems to oppose, most likely due to financial constraints. These findings would contribute in adopting those policy measures that will expedite the adoption of genomics into conventional medical interventions.

In **Chapter 5**, we present our findings from a prospective study to perform economic evaluation of genome-guided warfarin treatment in elderly Croatian patients suffering from atrial fibrillation, indicating that genome-guided warfarin treatment is a cost-effective therapy option for the management of elderly patients with atrial fibrillation in Croatia. In particular, our primary analysis indicated that more patients (97.07%) belonging to the pharmacogenetics-guided group did not have any major complications as compared to the control group (89.12%), while the total cost per patient was estimated at €538.7 for the pharmacogenetics-guided group as compared to €219.7 for the control group. In terms of QALYs gained, total QALYs was estimated at 0.954 and 0.944 for the pharmacogenetics-guided and the control groups, respectively and the incremental cost-effectiveness ratio of the pharmacogenetics-guided vs the control groups was estimated at €31,225/QALY.

Similar to the previous chapter, in **Chapter 6**, we report our findings from a retrospective study to assess whether *CYP2C19*-guided genotyping was cost-effective for myocardial infarction patients receiving clopidogrel treatment in the Serbian population compared to the non-genotype-guided treatment. Our data show that clopidogrel treatment coupled with *CYP2C19*-guided genotyping may represent a cost-saving approach for the management of myocardial infarction

patients undergoing primary percutaneous coronary intervention in Serbia. In particular, we found that 59.3% of the *CYP2C19**1/*1 patients had a minor or major bleeding event versus 42.85% of the *CYP2C19**1/*2 and *2/*2, while a reinfarction event occurred only in 2.3% of the *CYP21C9**1/*1 patients, compared to 11.2% of the *CYP2C19**1/*2 and *CYP2C19**2/*2 patients. The mean cost for the *CYP2C19**1/*1 patients was estimated at €2,547 versus €2,799 in the *CYP2C19**1/*2 and *CYP2C19**2/*2 patients, while, based on the overall *CYP2C19**1/*2 genotype frequencies in the Serbian population, a break-even point analysis indicated that performing the genetic test prior to drug prescription represents a cost-saving option, saving €13 per person on average.

In **Chapter 7**, we propose the Genome Economics Model (GEM), which is a public health genomics-driven approach to adjust the classical healthcare decision making process with an alternative methodological approach of cost-effectiveness analysis. In particular, we combine the classical cost-effectiveness analysis with budget constraints, social preferences and patient ethics. This model provides the rationale to ensure the sustainability of funding for genome-guided interventions, their adoption and coverage by health insurance funds, and prioritization of the Genomic Medicine research, development and innovation, especially in those countries with budget restrictions, making it particularly appealing in developing countries and low-income healthcare settings in developed countries.

Lastly, in **Chapter 8**, we describe a new economic model, specifically for resource allocation for genomic medicine, based on performance ratio, with potential applications in diverse health care sectors. Similar to the previous model described in Chapter 7, this model also addresses the needs of developing countries and low-resource environments and takes into account the innovation and costs of the new technology/intervention and its relative effectiveness in comparison with social preferences.

Appendix 1

Samenvatting

Samenvatting

Het centrale doel van Personalised Medicine is om de genetische informatie van het individu te gebruiken in het klinische besluitvormingsproces. Hoewel het concept van gepersonaliseerde geneeskunde relatief nieuw lijkt, bestaat de intellectuele voorouder ervan al geruime tijd. Zo verklaarde Hippocrates van Kos (460-370 v.Chr.) rond 400 v.Chr. dat het belangrijker is om te weten welke persoon aan de ziekte lijdt, dan te weten aan welke ziekte de persoon lijdt.

In 1956 introduceerde Friedrich Vogel de term "farmacogenetica" toen hij bijwerkingen van primaquine, een antimalariamiddel, beschreef bij een aantal soldaten die dit middel hadden voorgeschreven gekregen. Deze bijwerkingen bleken te zijn veroorzaakt door een genetisch defect in het glucose-6-fosfaat dehydrogenase (G6PD) enzym. In 1962 beschreven Evans en collega's de genetische oorzaak van perifere neuropathie die optreedt wanneer patiënten werden behandeld met isoniazide, een middel tegen tuberculose, en brachten deze reactie in verband met genetische variaties in het N-acetyl-transferase 2(*NAT2)* gen. Een belangrijke bijdrage op het gebied van de farmacogenetica was de ontdekking door Richard Smith in 1977 over de genetische basis van de te sterke reactie op het antihypertensivum debrisoquine die sommige mensen hadden ervaren. Het betrokken enzym, het cytochroom P450 2D6, is betrokken bij het metabolisme van ongeveer 20-25% van alle geneesmiddelen en blijkt structureel afwezig te zijn bij 5-10% van de bevolking. Bovendien heeft 20-25% van de bevolking slechts een lage activiteit van dit enzym, terwijl 2-4% van de bevolking juist een verhoogde activiteit ten opzichte van de gemiddelde bevolking heeft. Deze verschillen in enzymactiviteit konden voor een groot gedeelte worden teruggevoerd naar verschillende varianten van het *CYP2D6* gen. In 1985, publiceerde Richard Weinshilboum dat de omzetting van 6-mercaptopurine door thiopurine-S-methyltransferase (TPMT) een overerfbare component vertoonde. Dit ewrd vervolgens gekoppeld aan genetische variaties in het *TPMT* gen.

De term voor dit veld van onderzoek is “farmacogenetica”, ofwel “pharmacogenetics”, en beschrijft het onderzoek van overerfbare componenten en het metabolisme van geneesmiddelen. Later werd de term

"pharmacogenomics" ingevoerd als een breder veld, waarin naast overerfbare DNA varianten ook verworven mutaties en expressie/mRNA-profielen die invloed hebben op het metabolisme worden meegenomen.

Rond het jaar 2000 werd de term "*Personalised Medicine"* geïntroduceerd, en in 2015 de nieuwste term "*Precision Medicine*" door de voormalige Amerikaanse president Barack H. Obama, in het kader van het Amerikaanse Precision Medicine Initiative (PMI).

Hoewel er veel definities van dit begrip zijn, omvat het concept van *Personalised Medicine* de gecombineerde kennis van genetica om een ziekte/diagnose te kunnen vaststellen alsook de prognose en/of de reactie van een persoon op behandeling te voorspellen. De vooruitgang die in de afgelopen decennia is geboekt bij de ontwikkeling van *Personalised Medicine* viel samen met gezondheidszorgstelsels die meer nadruk legden op het gebruik van *evidence-based* medicine, vanwege de toenemende financiële druk op de gezondheidszorg. Er wordt vaak beweerd dat personalisering van behandeling de klinische uitkomsten voor patiënten zal verbeteren en zo zal bijdragen aan een effectiever gebruik van gezondheidszorgmiddelen. Daarom is er een toenemende vraag naar bewijs van klinische bruikbaarheid en analyse van kosteneffectiviteit om het gebruik van *Personalised Medicine* in de gezondheidszorg te ondersteunen.

Pharmacogenomics is een kerncomponent van *Personalised Medicine* en zal daarom als voorbeeld worden gebruikt om de toepassing van economische evaluatie van *Personalised Medicine* toe te lichten. Pharmacogenomics tracht ons inzicht te vergroten in hoe geneesmiddelen werken in ieder individu, gebaseerd op genetische informatie, om de veiligheid en effectiviteit van geneesmiddelen te vergroten. Dit kan resulteren in een efficiëntere en effectievere benadering bij het ontdekken van nieuwe geneesmiddelen. Bovendien kan pharmacogenomics leiden tot een meer gediversifieerd en meer gericht portfolio van diagnostiek en therapieën, die, wanneer ze samen worden gebruikt, grote gezondheidsvoordelen voor de samenleving kunnen opleveren.

Farmacogenetica is een term die verwijst naar de studie van het effect van overerfbare genetische variaties op geneesmiddelrespons, en betreft zowel het geneesmiddelmetabolisme (farmacokinetiek) alsook de geneesmiddelenwerking (farmacodynamiek). Bovendien is aangetoond dat genetische varianten ook

verklaren dat wat voorheen werd beschouwd als idiosyncratische bijwerkingen (adverse drug reactions: ADRs). Met andere woorden, deze discipline heeft tot doel het beste geneesmiddel voor een specifieke ziekte te identificeren wanneer de ziekte voorkomt in een patiëntenpopulatie met een bepaald genotype. Gezien het feit dat er genetische factoren zijn die verantwoordelijk zijn voor 20-95% van de waargenomen reacties op medicamenteuze therapieën, zal men de impact van deze nieuwe discipline in de moderne geneeskunde begrijpen. Het is belangrijk om op te merken dat andere factoren zoals leeftijd, dieet, -geneesmiddelinteracties en de aanwezigheid van andere ziekten (comorbiditeit) de geneesmiddelrespons van een individu beïnvloeden, onafhankelijk van, in combinatie met of juist in additie op genetische factoren.

Het doel van dit proefschrift is om de gezondheidsvoordelen van genoomgeleide behandelingsinterventies te beoordelen in vergelijking met de standaardinterventies die in de huidige medische praktijk worden gebruikt. We richten ons op de economische analyse van farmacogenetisch-geleide behandeling met warfarine en clopidogrel, vooral omdat de laatste jaren cardiologie het belangrijkste medische specialisme is geworden waarin farmacogenetische toepassingen in de praktijk worden toegepast. Bovendien hebben we in dit proefschrift, door middel van structurele vragenlijsten, de opvattingen, meningen en attitudes van de verschillende belanghebbenden en van het grote publiek over genomische geneeskunde, en de impact hiervan op de samenleving, onderzocht. Tenslotte hebben we een alternatieve methodologische benadering voor kosteneffectiviteits-analyse voorgesteld en een praktische leidraad ontwikkeld voor besluitvorming door budgethouders.

In **Hoofdstuk 2** geven we enkele belangrijke voorbeelden van de toepassingen van farmacogenetica in de moderne medische praktijk, waarbij we ons concentreren op verschillende medische specialismen zoals cardiologie, oncologie, psychiatrie en infectieziekten en die zijn goedgekeurd door alle belangrijke regelgevende instanties, zoals de Amerikaanse Food and Drug Administration (FDA) en de European Medicine Agency (EMA). We benadrukken de noodzaak om economische evaluatie, en de verschillende soorten hiervan, uit

te voeren, we vatten de belangrijkste methodologische aspecten van economische evaluatie samen en we schetsen de schaarse voorbeelden van economische evaluaties in de genomische geneeskunde die tot nu toe zijn uitgevoerd. In eerste instantie wilden we bepalen in hoeverre gezondheidswerkers in Griekenland bekend zijn met farmacogenetica en *Personalised Medicine*, door middel van gestructureerde vragenlijsten die aan een groot aantal apothekers en artsen zijn voorgelegd. Deze bevindingen worden gepresenteerd in **Hoofdstuk 3** , waar we aangeven dat ongeveer 60% van de apothekers hun kennisniveau van *Personalised Medicine* als "zeer laag" beschouwen, terwijl meer dan de helft van de apothekers en artsen aangeven dat ze niet in staat om de resultaten van farmacogenetische testen uit te leggen aan hun klanten of patiënten. Deze situatie houdt mogelijk rechtstreeks verband met het geringe niveau van hun vooropleiding aangaande (farmaco-)genetica. Deze bevindingen vormen de basis voor het beoordelen van de mening van beroepsbeoefenaren in de gezondheidszorg met betrekking tot *Personalised Medicine* in Griekenland en zouden de integratie van genetica in het medische besluitvormingsproces kunnen vergemakkelijken.

In **Hoofdstuk 4** hebben we getracht ons begrip te verrijken over het beleid en de meningen van de belangrijkste belanghebbenden die betrokken zijn bij de vertaling van genomische bevindingen in de kliniek. Om dit te bereiken hebben we de geautomatiseerde versie van *PolicyMake,* een politieke mapping tool, gebruikt om belangrijke informatie over beleidsomgeving van de farmacogenetische en genomische geneeskunde te verzamelen en te ordenen aangaande de inhoud van het beleid, de belangrijkste spelers, hun invloed en beleidsstandpunten, hun belangen en netwerken en de coalities die met elkaar in verbinding staan. Onze bevindingen geven aan dat de beleidsomgeving voor genomische geneeskunde in Griekenland relatief positief lijkt, aangezien de overgrote meerderheid van de belanghebbenden gemiddelde tot hoge steun uitspreekt aan de aanvankelijk gestelde doelen van de beleidsomgeving voor genomische geneeskunde. Het ministerie van Volksgezondheid en de openbare ziekenfondsen lijken hier echter tegen te zijn, hoogstwaarschijnlijk vanwege financiële beperkingen. Deze bevindingen zouden bijdragen aan het aannemen

van die beleidsmaatregelen die de acceptatie van genetica in conventionele medische interventies zullen versnellen.

In **Hoofdstuk 5** presenteren we onze bevindingen van een prospectieve studie om een economische evaluatie uit te voeren van genoomgeleide warfarine-behandeling bij oudere Kroatische patiënten die lijden aan atriumfibrilleren. We laten zien dat genoomgeleide warfarine-behandeling een kosteneffectieve therapie is voor de behandeling van ouderen patiënten met boezemfibrilleren in Kroatië. Met name onze primaire analyse gaf aan dat er meer patiënten (97,07%) die tot de farmacogenetica-geleide groep behoren zonder belangrijke complicaties bleven, in vergelijking met de controlegroep (89,12%). De totale kosten per patiënt werd geschat op € 538,70 voor de farmacogenetica-geleide groep, in vergelijking met € 219,70 voor de controlegroep. In termen van gewonnen QALY's werden de totale QALY's geschat op 0,954 voor de farmacogenetica-geleide groep en 0,944 voor de controlegroep; de incrementele kosteneffectiviteitsratio van de farmacogenetica-geleide versus de controlegroepen werd geschat op € 31.225/QALY.

In **Hoofdstuk 6** rapporteren we onze bevindingen van een retrospectieve studie om te beoordelen of een *CYP2C19*-geleide therapie rendabel was voor myocardinfarct patiënten die behandeld worden met clopidogrel in vergelijking met een niet-genotype geleide behandeling in de Servische bevolking. Onze gegevens tonen aan dat behandeling met clopidogrel, in combinatie met *CYP2C19* genotypering, kostenbesparend kan zijn voor de behandeling van myocardinfarctpatiënten met een primaire percutane coronaire interventie. We vonden dat 59,3% van de *CYP2C19 *1/*1* patiënten lichte of ernstige bloedingen ondervonden, versus 42,85% van de *CYP2C19*1/*2* en *CYP2C19* *2/*2 patiënten. Een re-infarct trad op bij 2,3% van de *CYP21C9 *1/*1* patiënten, vergeleken met 11,2% bij de *CYP2C19 *1/*2* en *CYP2C19* *2/*2 patiënten. De gemiddelde kosten voor *CYP21C9 *1/*1* patiënten werden geschat op € 2.547, versus € 2.799 voor *CYP2C19 *1/*2* en *CYP2C19* *2/*2 patiënten. Op basis van het algehele *CYP2C19*1/*2* genotype frequenties in de Servische bevolking toonde een break-even point- analyse aan dat het uitvoeren van de genetische test voorafgaand aan het voorschrijven van geneesmiddelen een kostenbesparende optie is, met een gemiddelde besparing van € 13 per persoon.

In **Hoofdstuk 7** stellen we het Genome Economics Model (GEM) voor, een genetica-gedreven benadering voor de volksgezondheid, om het klassieke besluitvormingsproces in de gezondheidszorg aan te passen met een alternatieve methodologische benadering van kosteneffectiviteitsanalyse. Hiervoor combineren we de klassieke kosteneffectiviteits-analyse met budgetbeperkingen, sociale voorkeuren en patiënten-ethiek. Dit model biedt de rationale om de duurzaamheid van financiering voor genoomgeleide interventies en de acceptatie en dekking ervan door ziektekostenverzekeraars te waarborgen, en prioriteit te geven aan onderzoek, ontwikkeling en innovatie op het gebied van genomische geneeskunde, vooral in die landen met beperkingen qua budget, waardoor het bijzonder aantrekkelijk wordt om toe te passen in ontwikkelingslanden en in ontwikkelde landen voor low-income gezondheidszorginstellingen.

Ten slotte beschrijven we in **Hoofdstuk 8** een nieuw economisch model, specifiek voor de toewijzing van middelen voor genomische geneeskunde, gebaseerd op prestatieverhouding, met mogelijke toepassingen in diverse sectoren van de gezondheidszorg. Vergelijkbaar met het model beschreven in Hoofdstuk 7, richt dit model zich ook op de behoeften van ontwikkelingslanden en gebieden met weinig hulpbronnen en houdt het rekening met de innovatie en de kosten van nieuwe technologieën/interventies en de relatieve effectiviteit ervan in vergelijking met sociale voorkeuren.

Appendix 2

Supplementary Information

Appendix 2

Item 1 - Questionnaire A - This questionnaire was addressed to physicians

SECTION 1

1. Year of birth
2. Gender
3. Did you complete your undergraduate studies abroad?
4. Did you complete your specialization (or post-internship medical training) abroad?
5. Do you hold a master/doctoral degree?

SECTION 2

6. What is your specialized filed/in which filed would you like to be specialized
7. You are currently employed in (multiple choices possible)
    a. Health Unit of the NHS
    b. University college hospital
    c. Private Hospital
    d. Insurance Agency
    e. Non-profit Organization
    f. Private Clinic
    g. Other
    h. I am not employed
8. What is the title of your position (multiple choices possible)
    a. Expert
    b. Registrar
    c. Consultant Physician
    d. Lecturer
    e. Associate director/ attending physician – Assistant Professor
    f. Attending physician–Associate Professor
    g. Attending physician – Professor
    h. Private doctor
    i. Other

SECTION 3

9. To what extent are genetics and genetic tests involved in your work?
10. To what extent are pharmacogenomics and pharmacogenomic tests involved in your work?
11. The results of genetic tests will affect medical care for my patients (e.g. medication, dosage, frequency of appointments, diagnoses, etc).
12. Are you familiar with pharmacogenomics and its relations with individualized drug treatment?
13. Have you ever advised any of your patients to undertake a genetic test? If yes:
    a. A genetic test (e.g. to control a hereditary disease)?

    b. A cytogenetic test (e.g. for dysmorphology and/or mental retardation syndromes)?

    c. A pharmacogenomic test (e.g. to reduce significantly the chances of developing side effects and/or to control responses to a medication)?

14. Have you had any patients who asked about undertaking a genetic test in the last two years?
15. Have you had any patients who asked your advice about the results of genetic tests in the last two years?
16. I could provide detailed information about genetic and pharmacogenomic tests and explain the results of the tests correctly to my patients.
17. Genetic tests can be performed directly to the patient, without any instruction from a specialist (e.g. doctor, or genetic counselor).
18. The expenses of genetic and pharmacogenomic tests should be covered by insurance companies.
19. An adequate regulatory and legal framework exists in the field of genetic tests (privacy of patients, cost analysis, quality assurance of laboratories that provide the tests, etc.) in Greece.
20. My undergraduate studies at the university provided me with sufficient knowledge on genetics so that I can efficiently consult my patients on these matters.
21. Regarding genetic tests, what is the most reliable source of information for you?
    a. Databases
    b. Scientific Journals
    c. Conferences
22. Have you attended any conferences on genetics in the past?
    a. Yes, in Greece
    b. Yes, overseas
    c. Yes, in Greece and overseas
    d. No
23. Would you like to attend workshops on applications of genetics and pharmacogenetics in modern medicine with units of further medical education?

Item 2 - Questionnaire B - This questionnaire was addressed to pharmacists

SECTION 1

1. Year of birth
2. Gender
3. Did you complete your undergraduate studies abroad?
4. Do you hold a postgraduate (master/doctoral) degree?
5. Did you complete your postgraduate studies abroad?

SECTION 2

6. How long have you been working as a pharmacist?
7. You are currently employed in (multiple choices possible):
    a) Health Unit of the National Healthcare System
    b) University Hospital
    c) Private hospital
    d) Insurance company
    e) Non-profit Organization
    f) Private Pharmacy
    g) Other _____
    h) I am not employed

SECTION 3

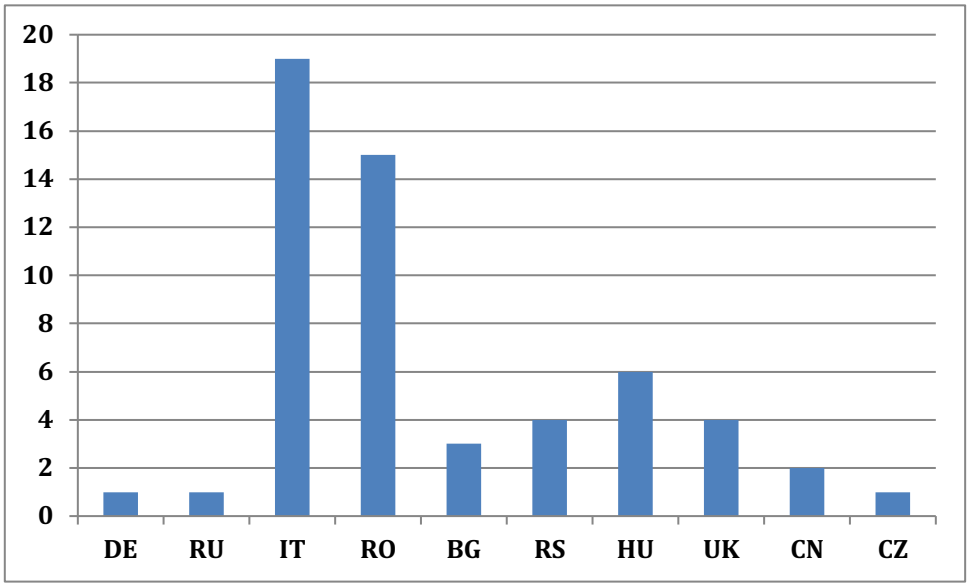
8. About 99.9% of human DNA sequence is identical.
9. Humans have 48 chromosomes.
10. Adenine (A) only pairs with cytosine (C) and thymine (T) only pairs with guanine (G).
11. Inherited diseases are caused by changes in the genetic material.
12. Pharmacogenomics seeks to individualize therapy based on a patient's genetic profile.
13. Genetic changes can affect the patient's response to a certain drug.
14. Genetic changes do not cause any adverse reactions, resulting from drug use.
15. Nowadays pharmacogenomics applies to most medications.

SECTION 4

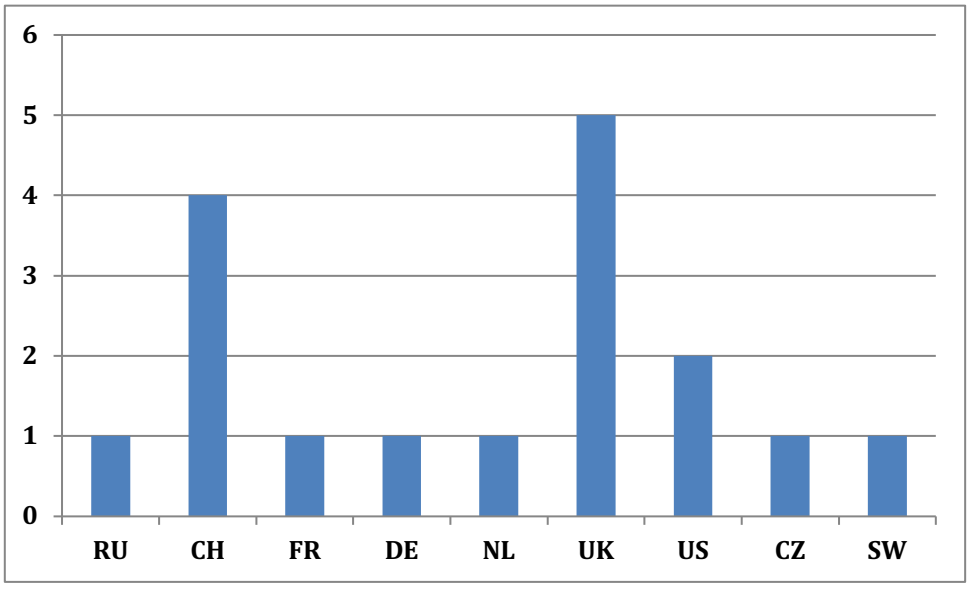
16. To what extent are you familiar with genetics?
17. To what extent are you familiar with pharmacogenomics and its relations with individualized drug treatment?
18. To what extent are pharmacogenomics and pharmacogenomic tests involved in your work?
19. The results of pharmacogenetic tests will affect medical care for the patients (e.g. medication, dosage, frequency of appointments, diagnoses, etc).
20. My studies at the university provided me with sufficient knowledge on genetics and pharmacogenomics.
21. Would you like to learn more about the Pharmacogenomics?
22. Do you provide genetic analysis kits in your pharmacy?
23. Are you aware that the genetic analysis kits are considered a medical device and as such require regulatory clearance?
24. Have you ever advised any of your customers to undertake a genetic test?
25. Have you had any customers who asked you about undertaking a genetic test in the last two years?
26. Are you aware that in the drug label of certain drugs, undertaking of a pharmacogenomic test is recommended before taking the drug to prevent adverse reactions?
27. I could provide detailed information about pharmacogenomic tests and correctly explain the results of these tests to my customers.
28. Genetic tests can be performed directly to the patient, without any referral from a medical specialist (e.g. a doctor, or genetic counselor).
29. The expenses of pharmacogenomic tests should be covered by insurance companies.
30. An adequate regulatory and legal framework exists in the field of genetic tests (privacy of patients, analysis costs, quality accreditation of genetic laboratories, etc.) in Greece.
31. Do you believe that pharmacogenomics helps in the reduction of the occurrence, frequency and severity of *drug*-induced *side effects?*
32. Do you believe that pharmacogenomics helps in reducing the cost of developing new drugs ?
33. Do you believe that pharmacogenomics helps in *reducing health care costs by rationalizing drug dose?*
34. Do you believe that pharmacogenomics could be exploited by employers, insurance companies, *etc* to discriminate certain population groups or patients?
35. Would you be interested in attending conferences or seminars on applications of genetics and pharmacogenomics?

Item 3 – Details of the physicians' sample characteristics

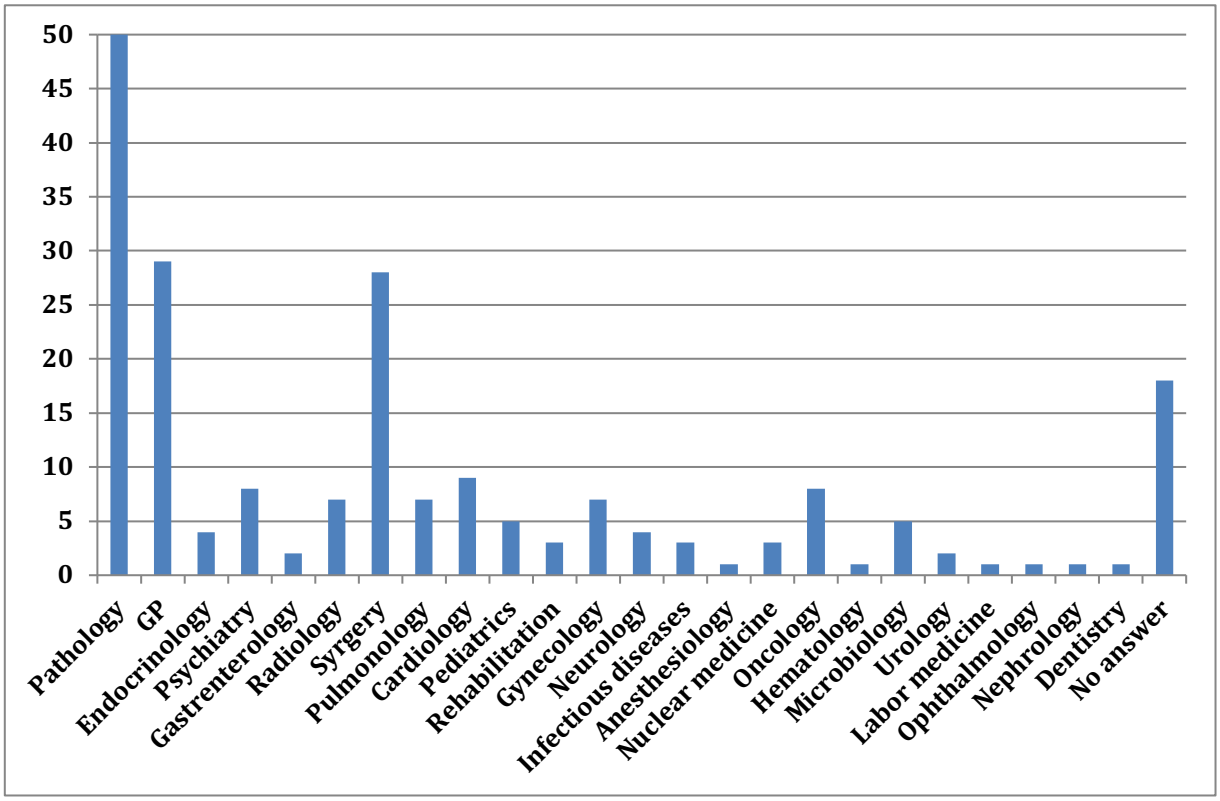
Q3A. In which country did you complete your undergraduate studies abroad?



Q4A. In which country did you complete your specialization (or post-internship medical training) abroad?

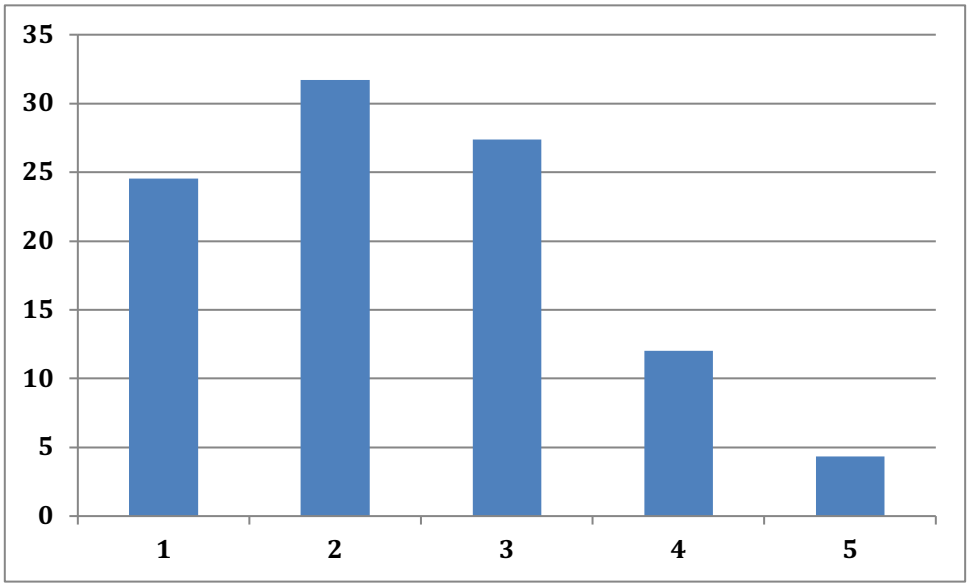


Q6A. What is your specialized filed/in which filed would you like to be specialized?

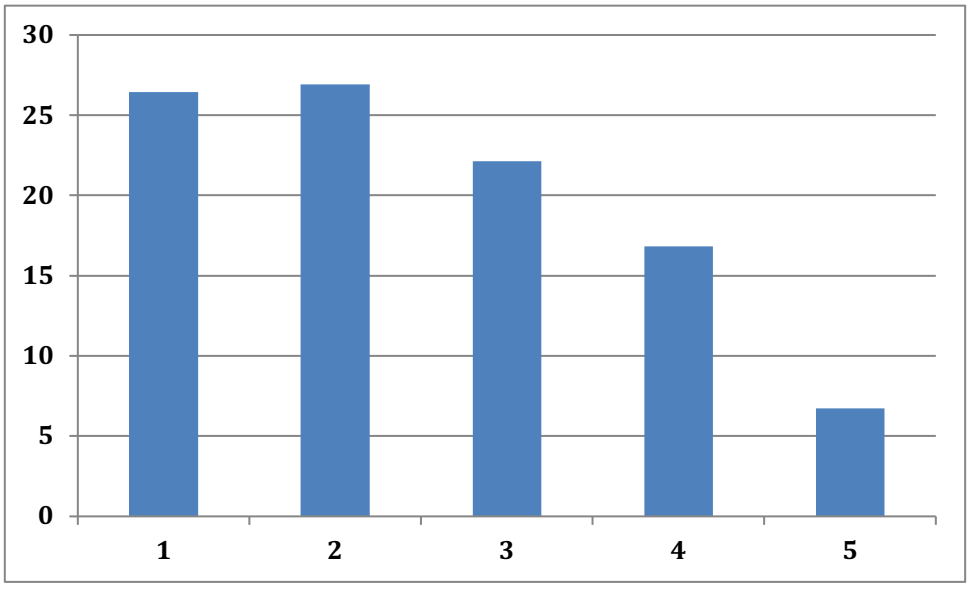


Item 4 – Results of Section 3 questions of survey A, addressed to physicians

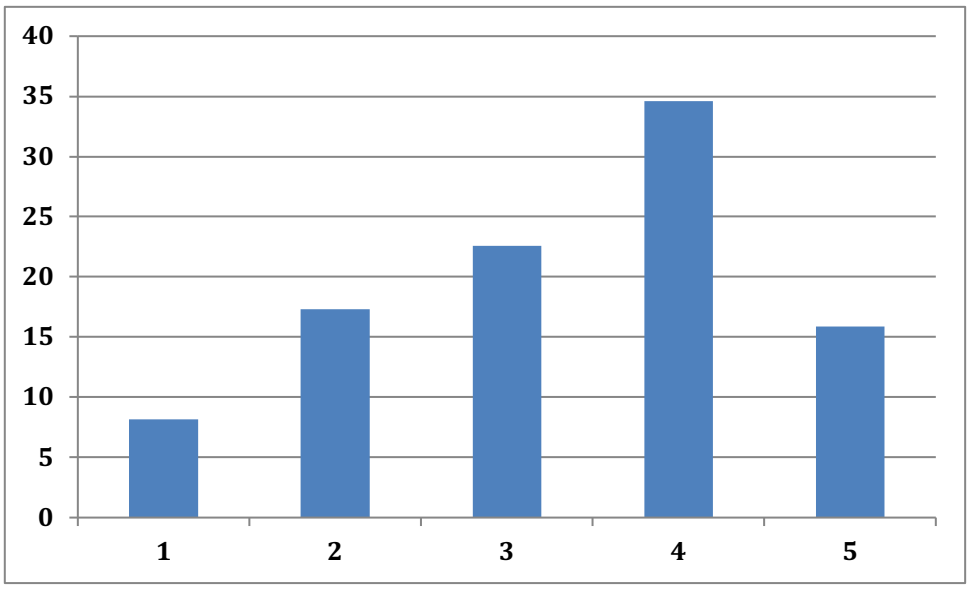
Q9A. To what extent are genetics and genetic tests involved in your work?



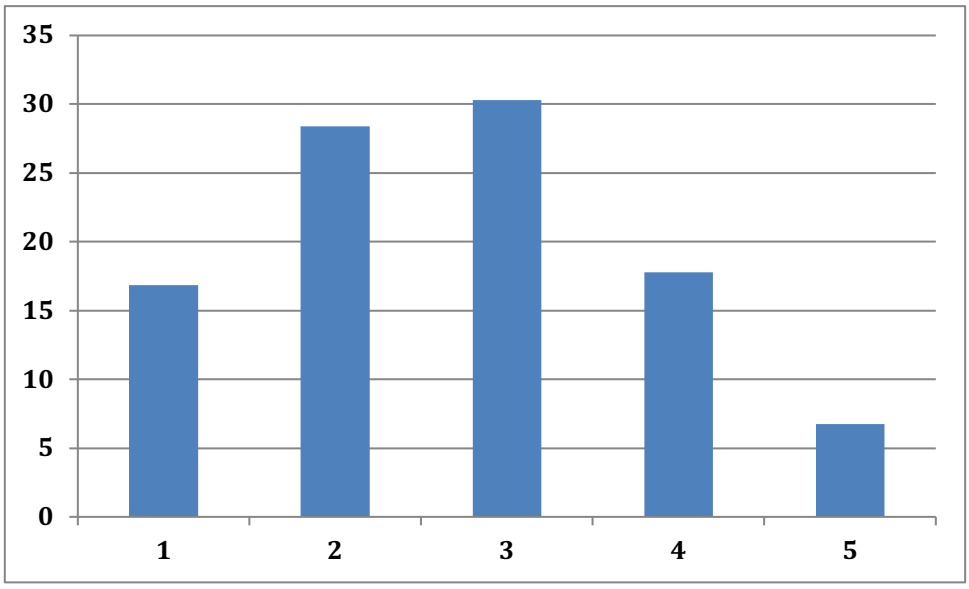
Q10A. To what extent are pharmacogenomics and pharmacogenomic tests involved in your work?



Q11A. The results of genetic tests will affect medical care for my patients (e.g. medication, dosage, frequency of appointments, diagnoses, etc).



Q12A. Are you familiar with pharmacogenomics and its relations with individualized drug treatment?

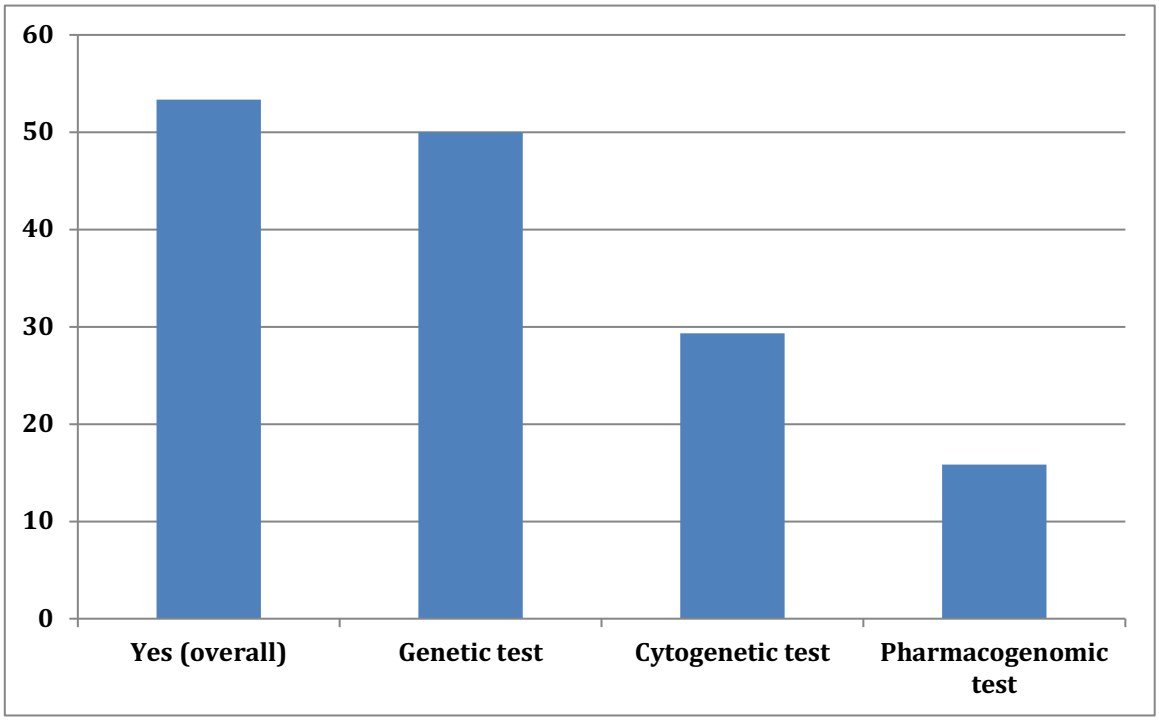


Q13A: Have you ever advised any of your patients to undertake a genetic test? If yes:

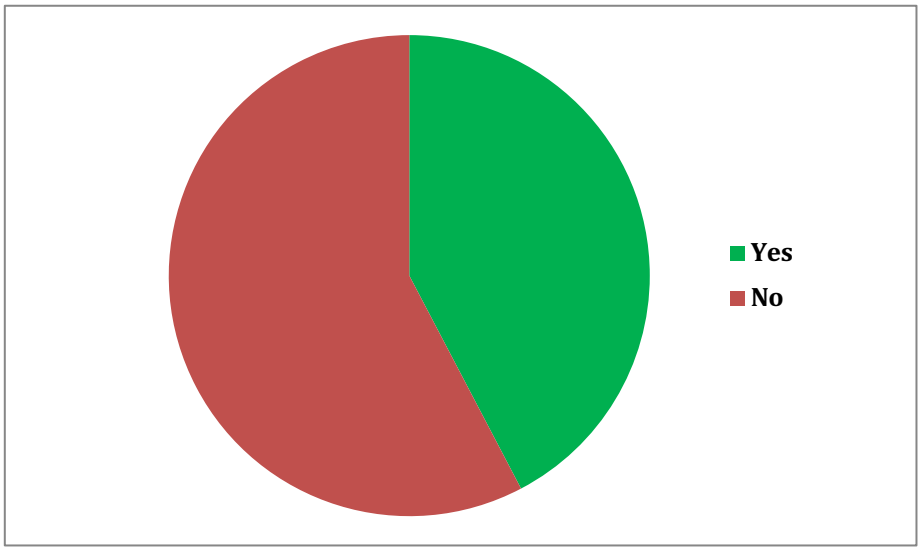
a. A genetic test (e.g. to control a hereditary disease)?

b. A cytogenetic test (e.g. for dysmorphology and/or mental retardation syndromes)?

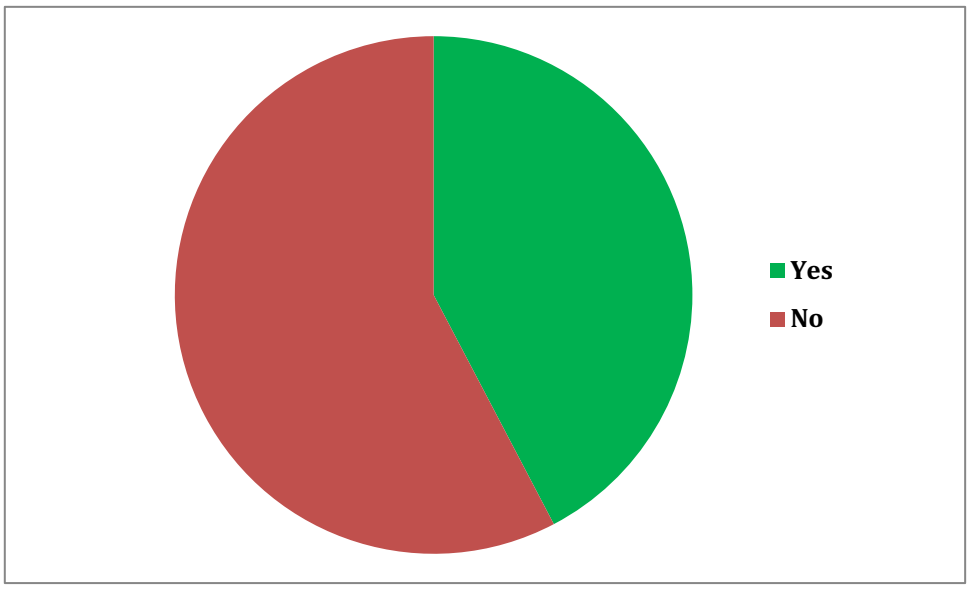
c. A pharmacogenomic test (e.g. to reduce significantly the chances of developing side effects and/or to control responses to a medication)?



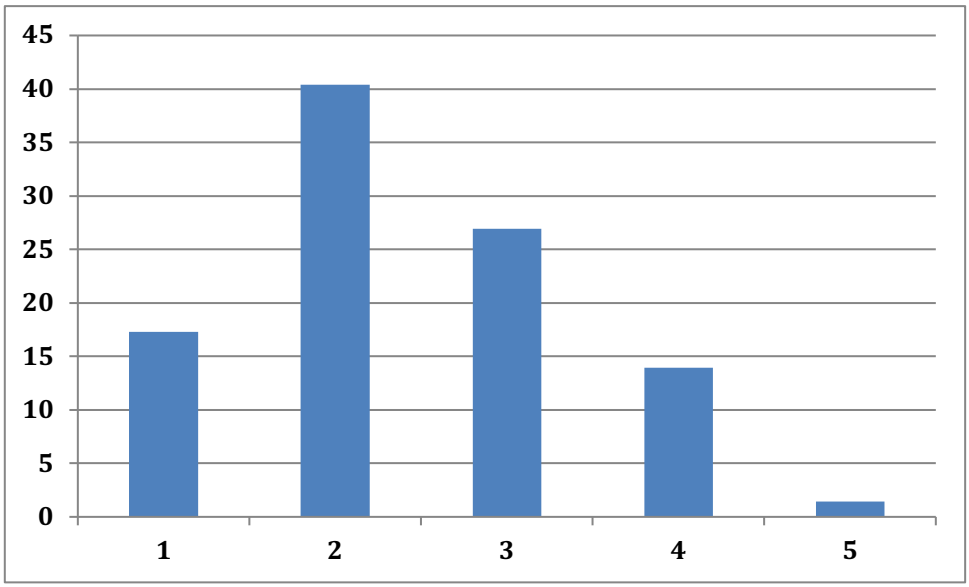
Q14A. Have you had any patients who asked about undertaking a genetic test in the last two years?



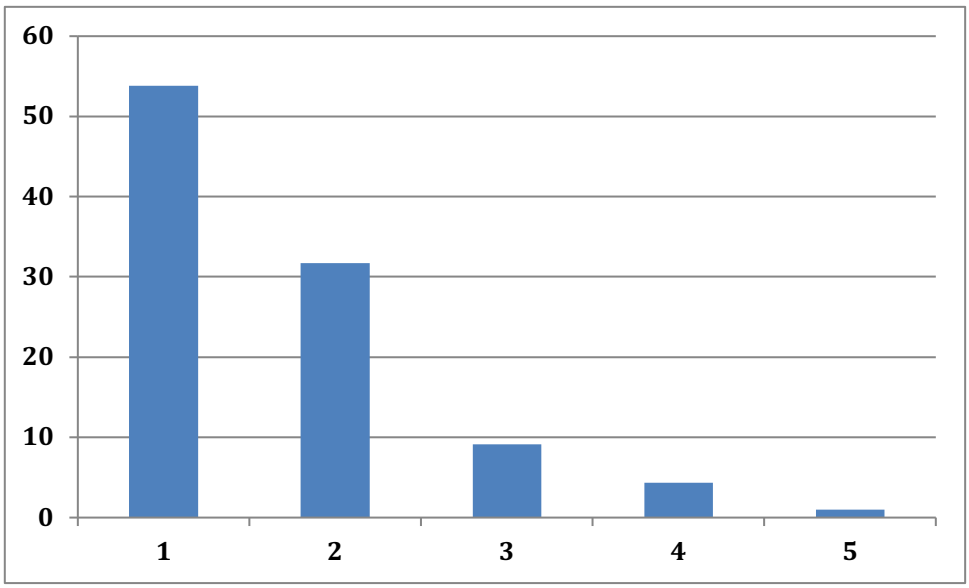
Q15A. Have you had any patients who asked your advice about the results of genetic tests in the last two years?



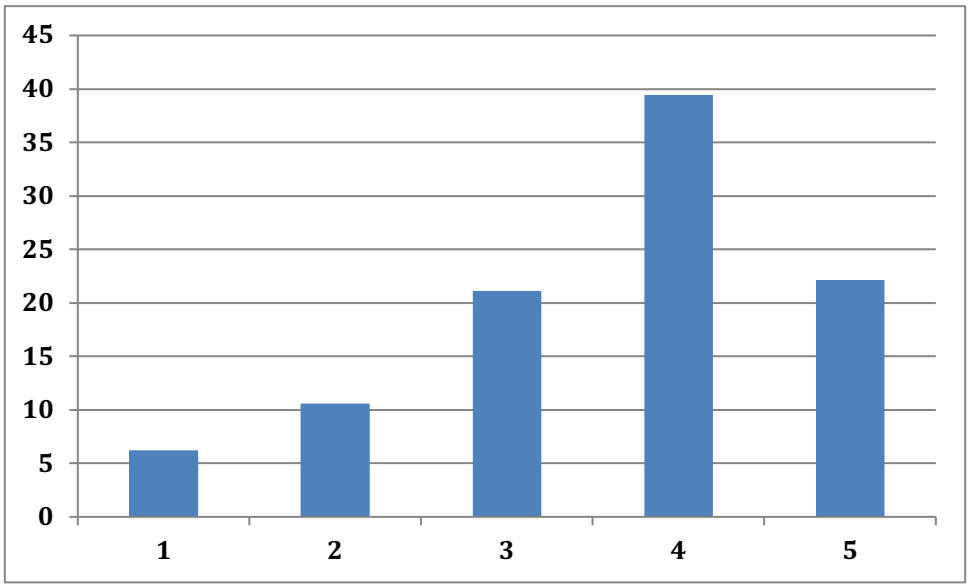
Q16A. I could provide detailed information about genetic and pharmacogenomic tests and explain the results of the tests correctly to my patients.



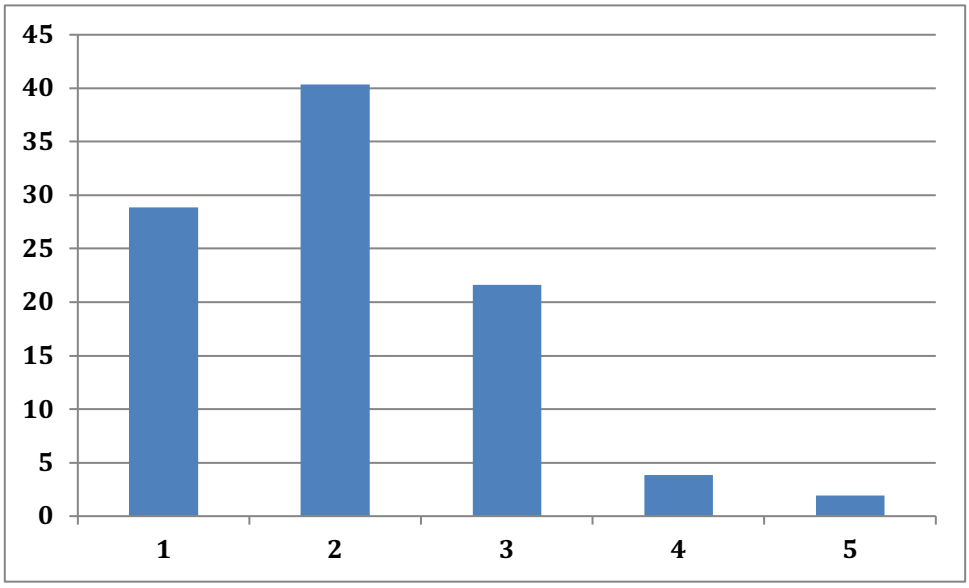
Q17A. Genetic tests can be performed directly to the patient, without any instruction from a specialist (e.g. doctor, or genetic counselor).



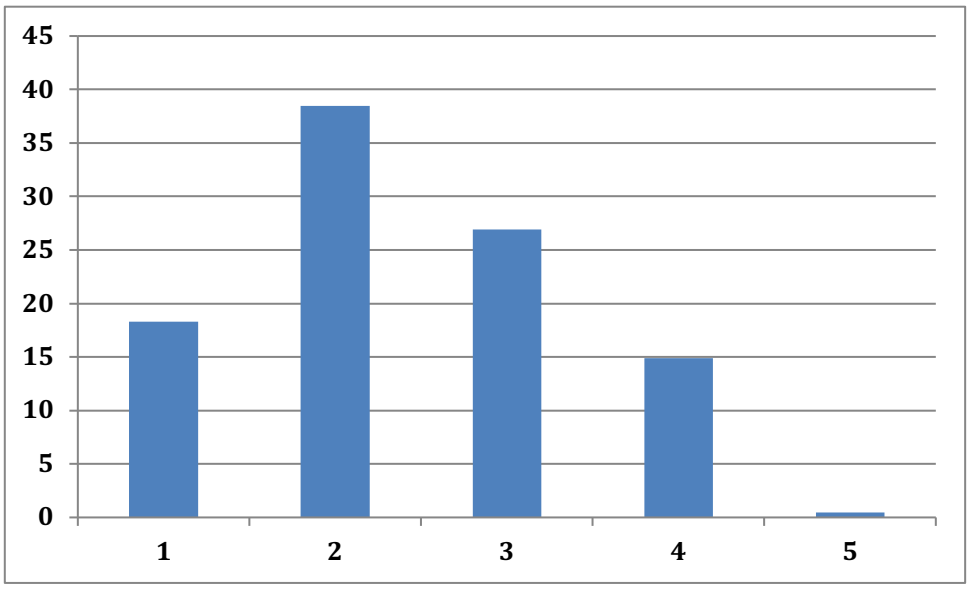
Q18A. The expenses of genetic and pharmacogenomic tests should be covered by insurance companies.



Q19A. An adequate regulatory and legal framework exists in the field of genetic tests (privacy of patients, cost analysis, quality assurance of laboratories that provide the tests, etc.) in Greece.

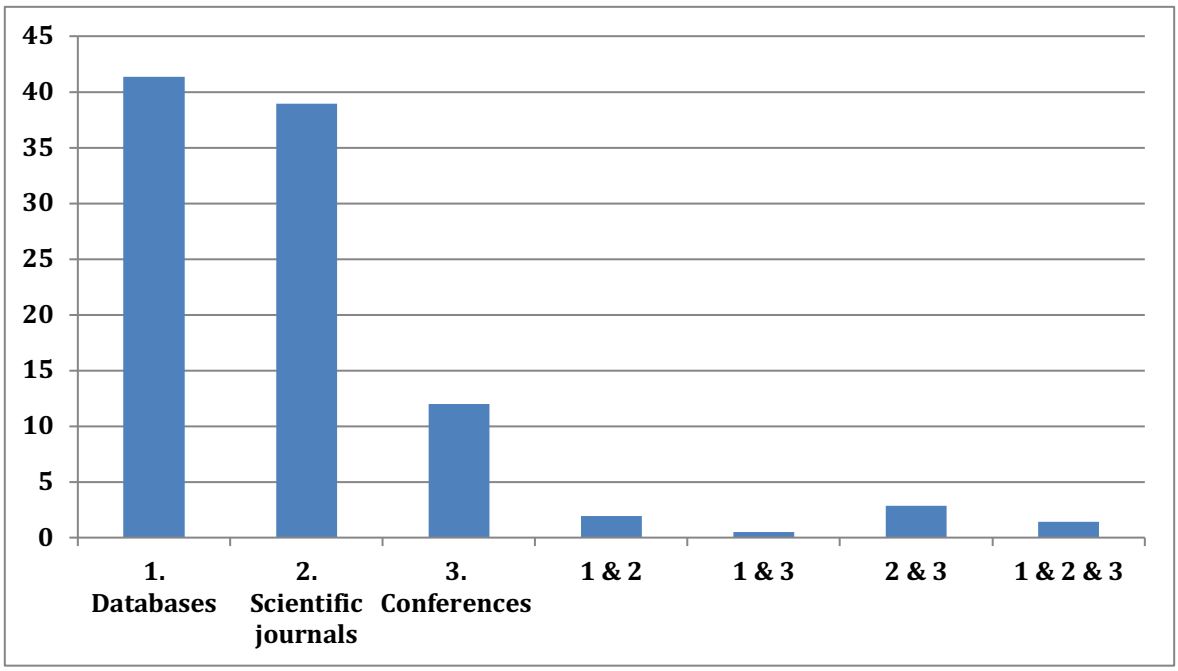


Q20A. My undergraduate studies at the university provided me with sufficient knowledge on genetics so that I can efficiently consult my patients on these matters.



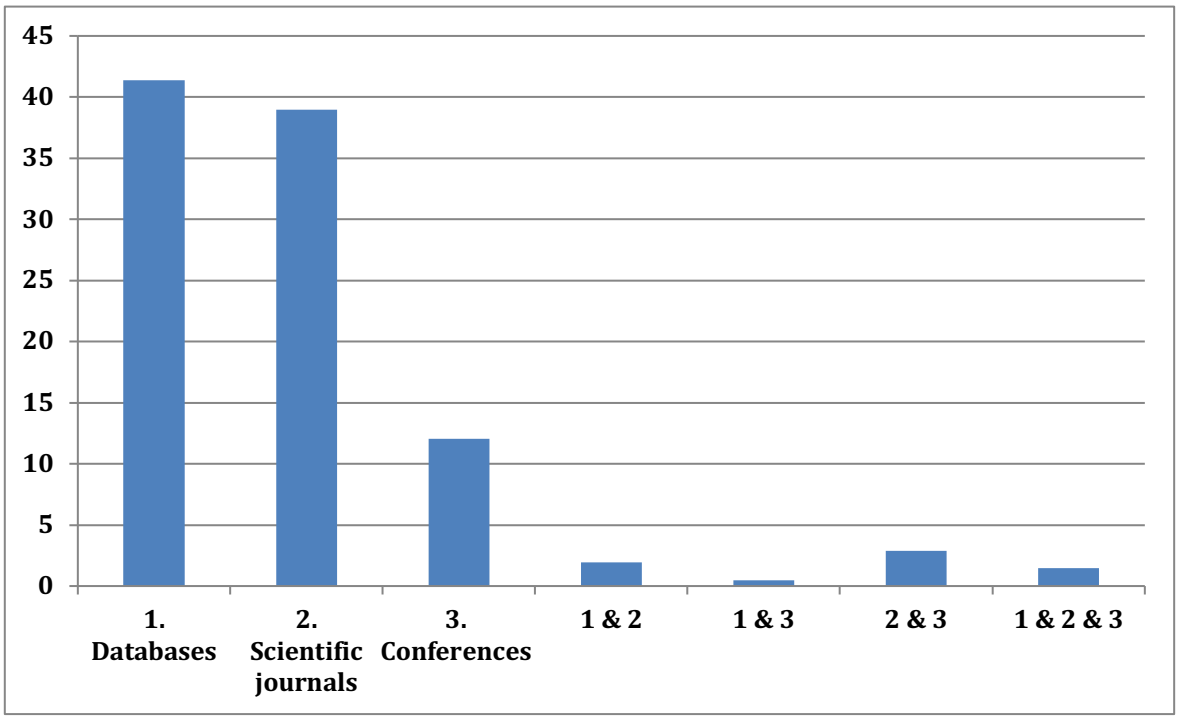
Q21A. Regarding genetic tests, what is the most reliable source of information for you?

1. Databases, 2. Scientific Journals, 3. Conferences

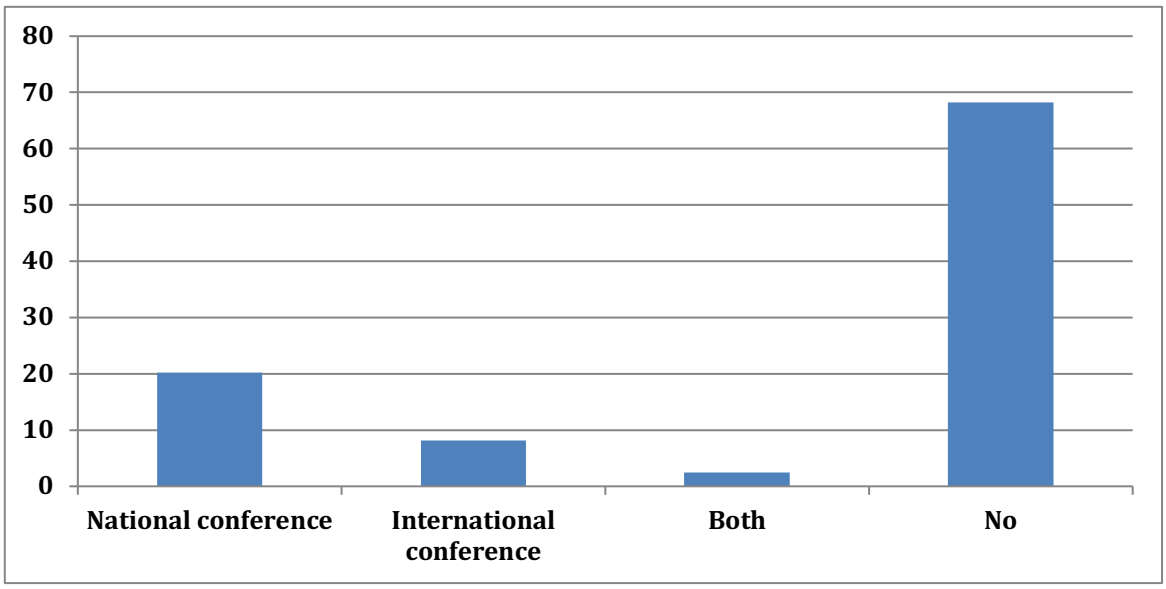


Q22A. Have you attended any conferences on genetics in the past?

1. National conference, 2. International conference, 3. Both

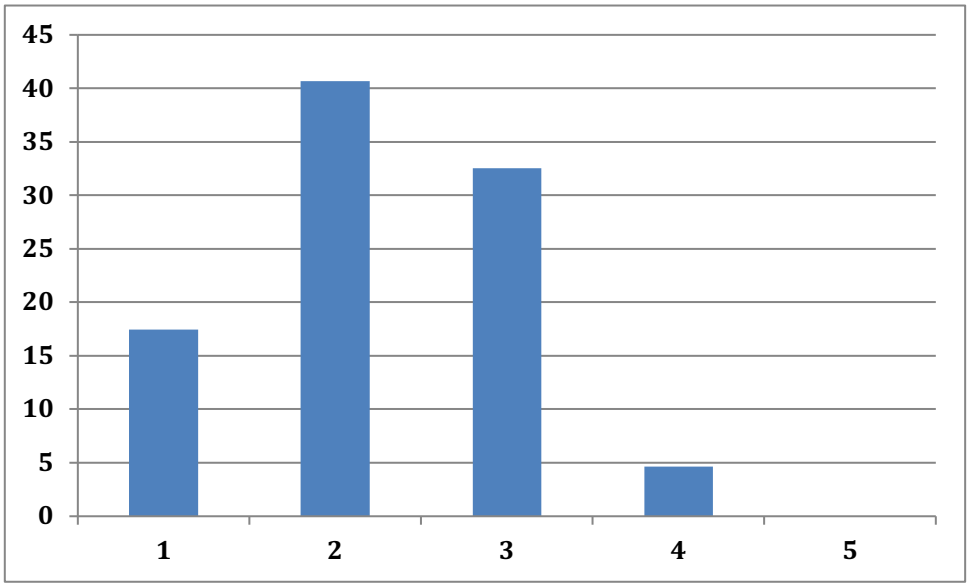


Q23A. Would you like to attend workshops on applications of genetics and pharmacogenetics in modern medicine with units of further medical education?

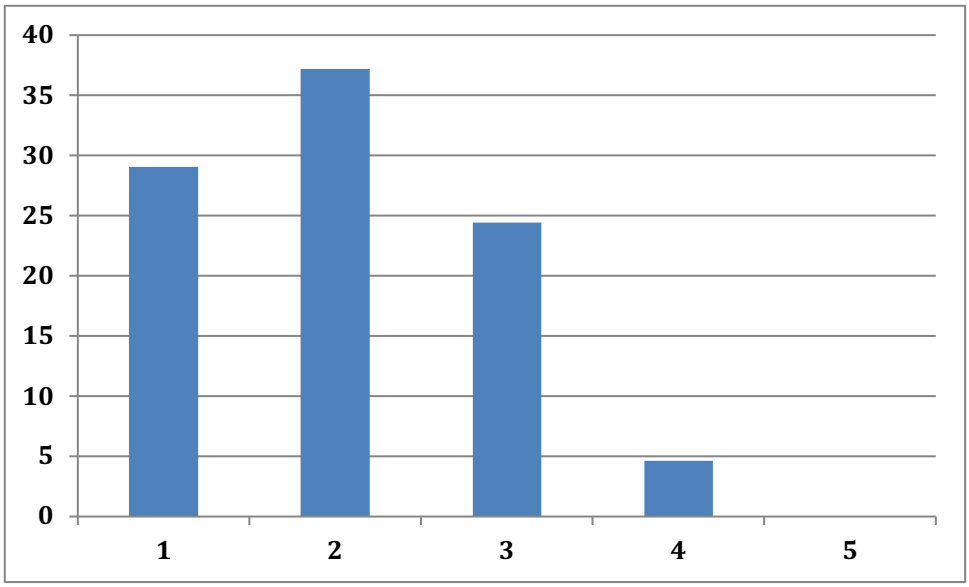


Item 5 – Results of Section 4 questions of survey B, addressed to pharmacists

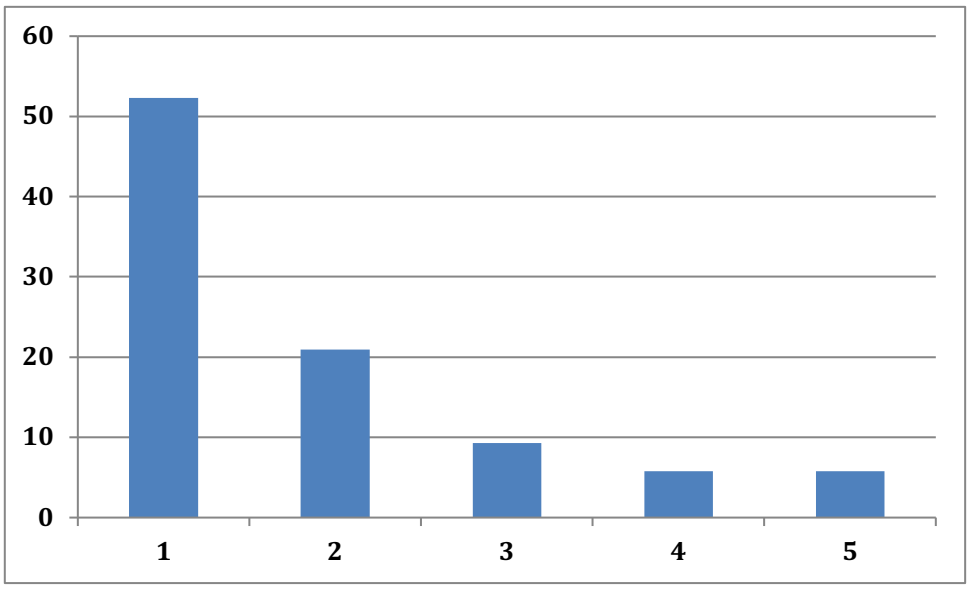
Q16B. To what extent are you familiar with genetics?



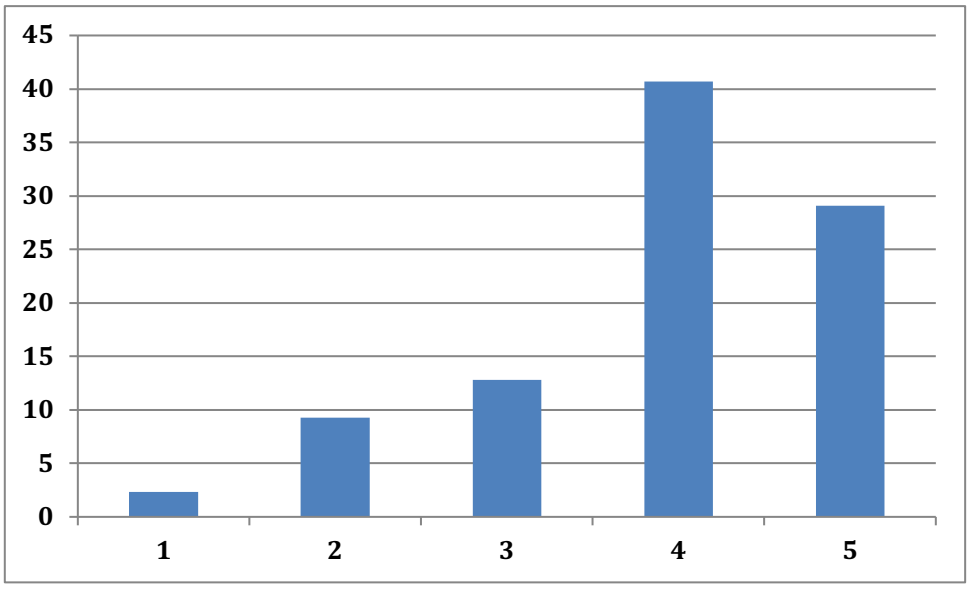
Q17B. To what extent are you familiar with pharmacogenomics and its relations with individualized drug treatment?



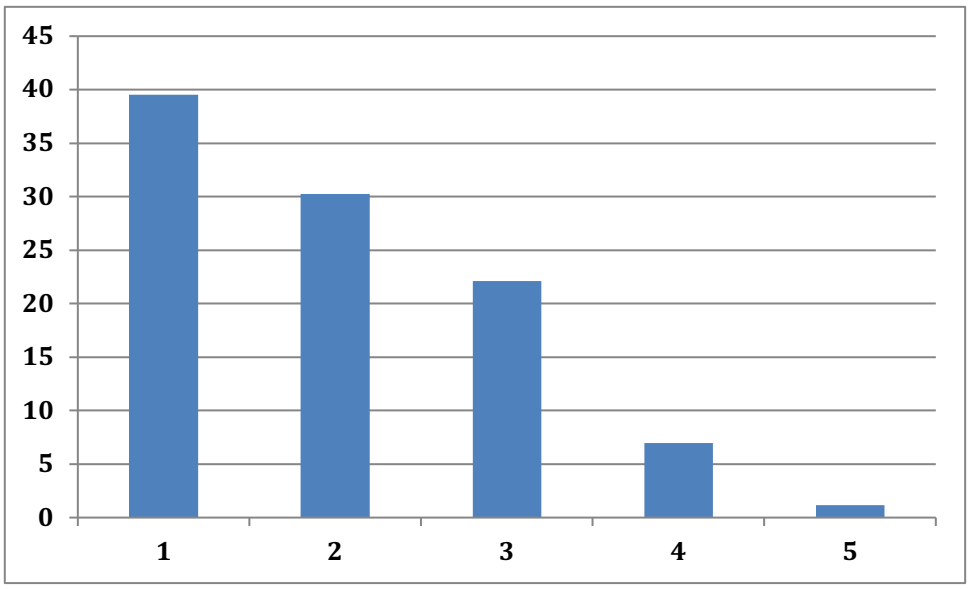
Q18B. To what extent are pharmacogenomics and pharmacogenomic tests involved in your work?



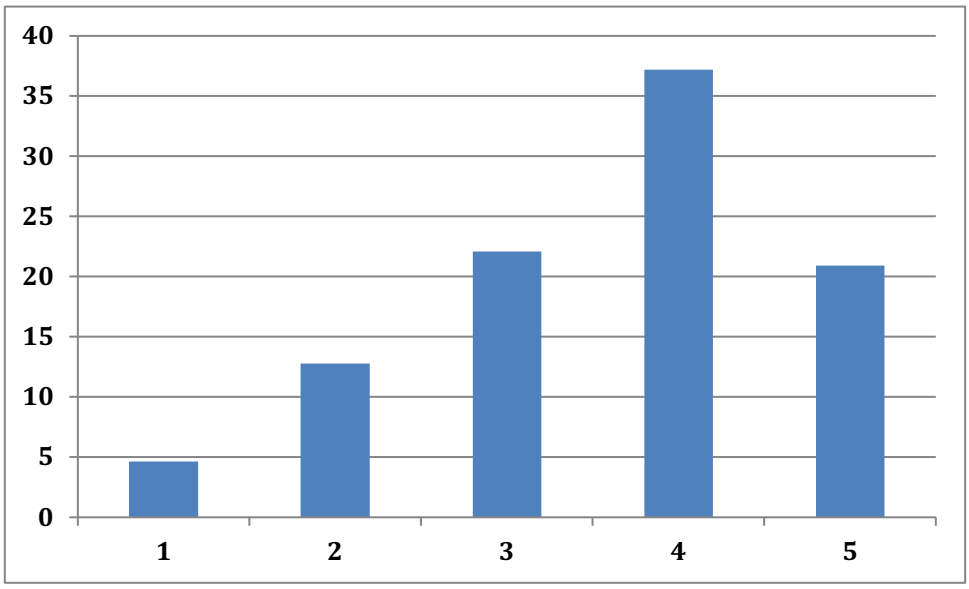
Q19B. The results of pharmacogenetic tests will affect medical care for the patients (e.g. medication, dosage, frequency of appointments, diagnoses, etc).



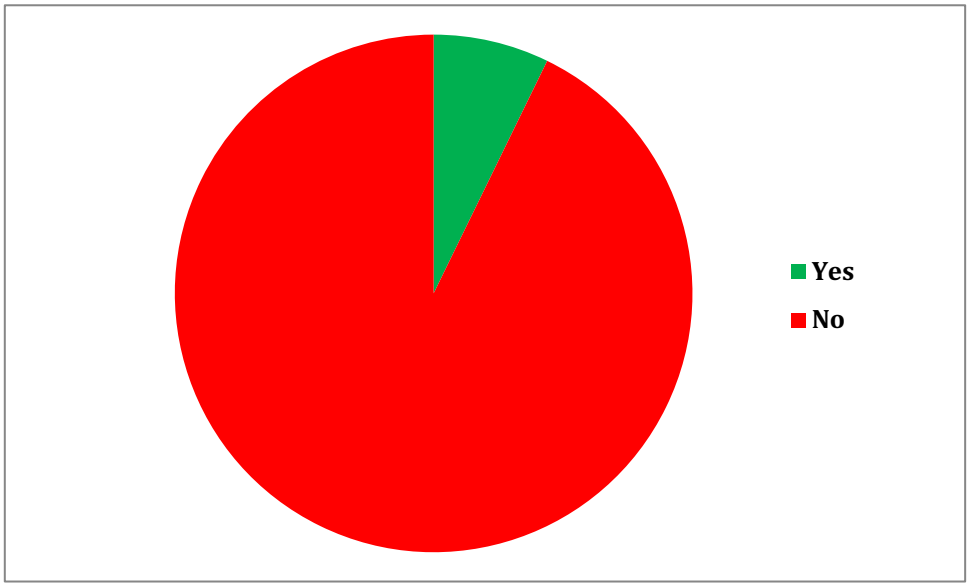
Q20B. My studies at the university provided me with sufficient knowledge on genetics and pharmacogenomics.



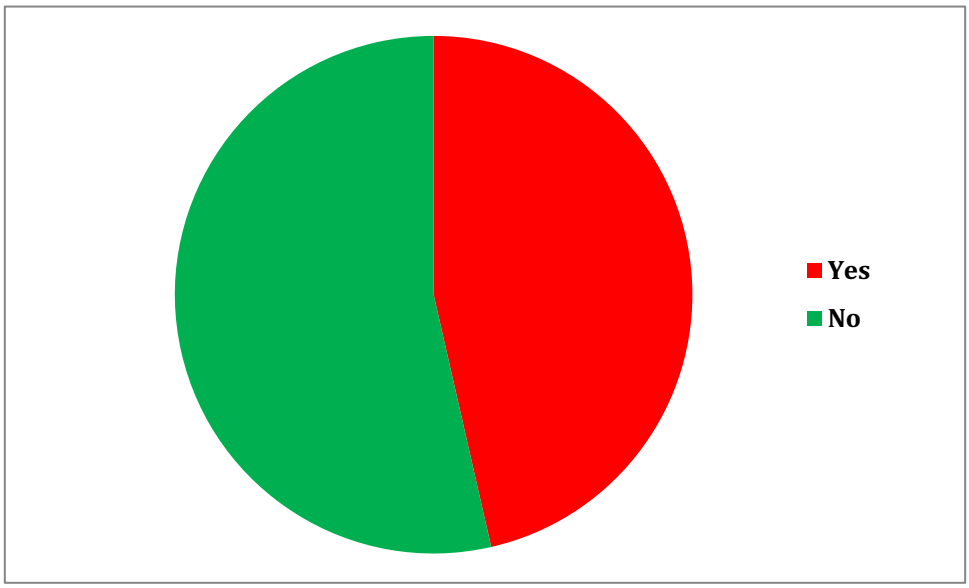
Q21B. Would you like to learn more about the Pharmacogenomics?



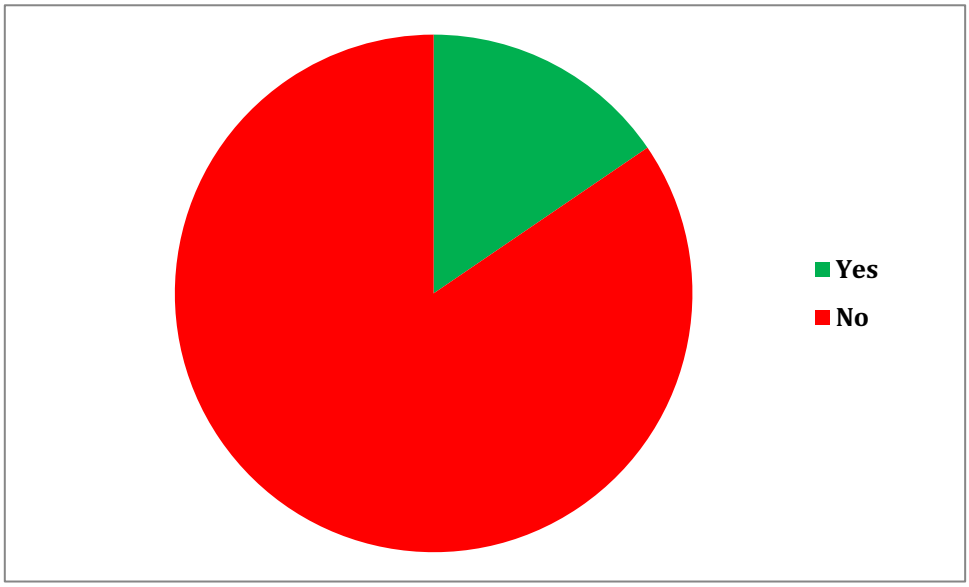
Q22B. Do you provide genetic analysis kits in your pharmacy?



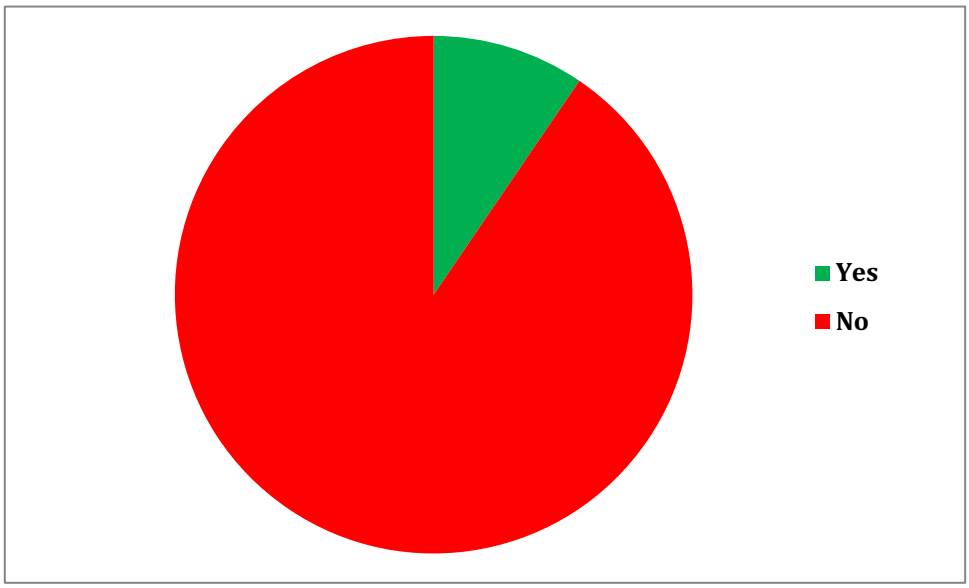
Q23B. Are you aware that the genetic analysis kits are considered a medical device and as such require regulatory clearance?



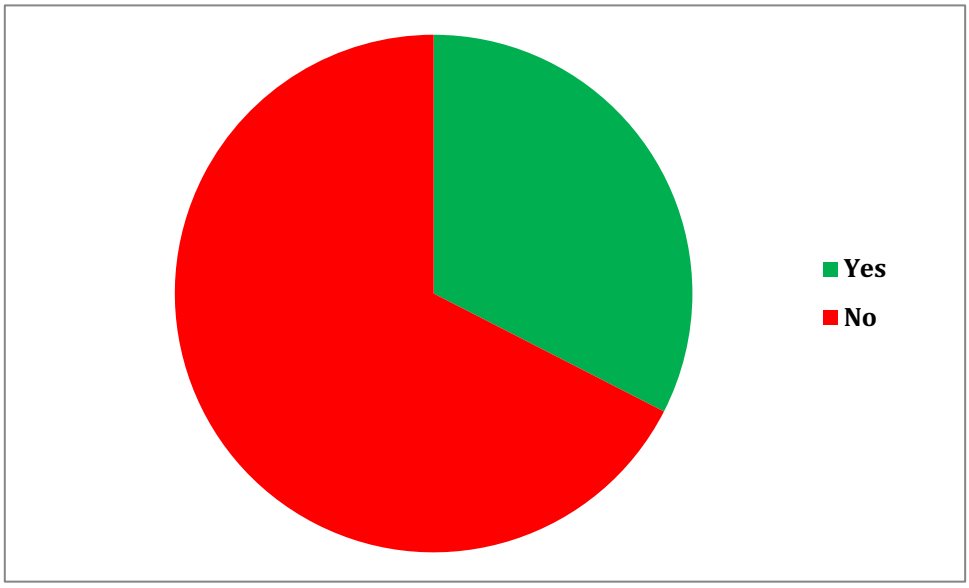
Q24B. Have you ever advised any of your customers to undertake a genetic test?



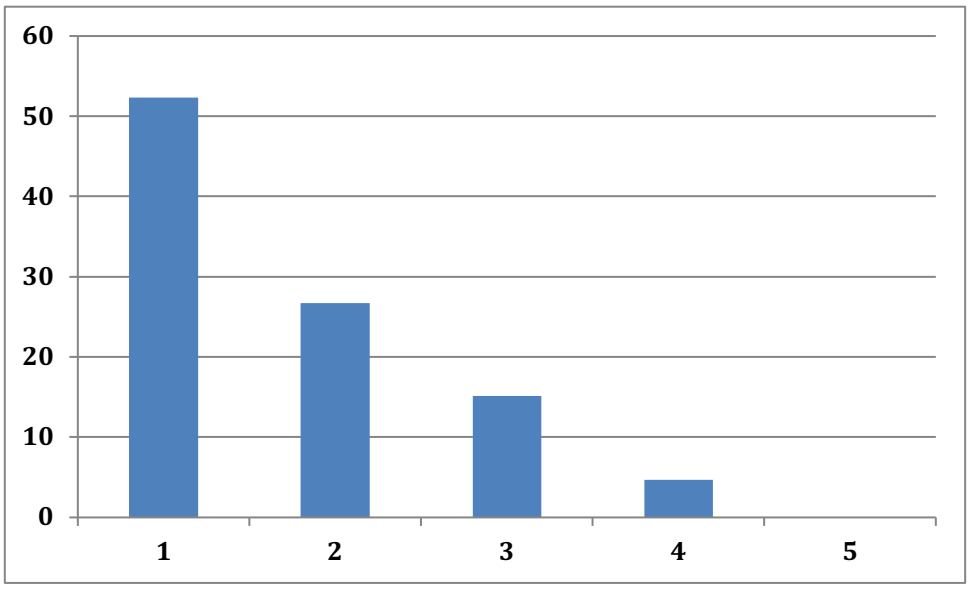
Q25B. Have you had any customers who asked you about undertaking a genetic test in the last two years?



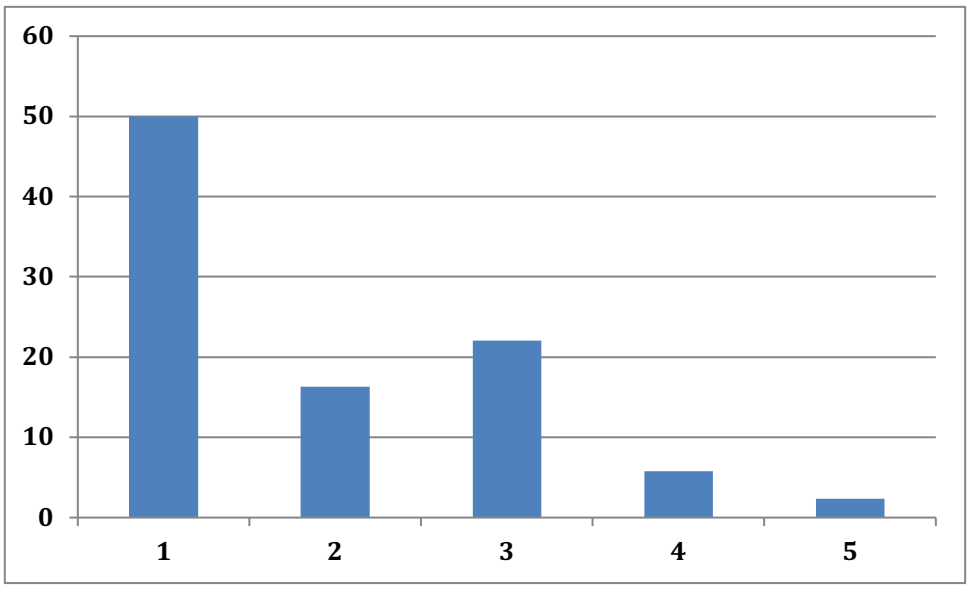
Q26B. Are you aware that in the drug label of certain drugs, undertaking of a pharmacogenomic test is recommended before taking the drug to prevent adverse reactions?



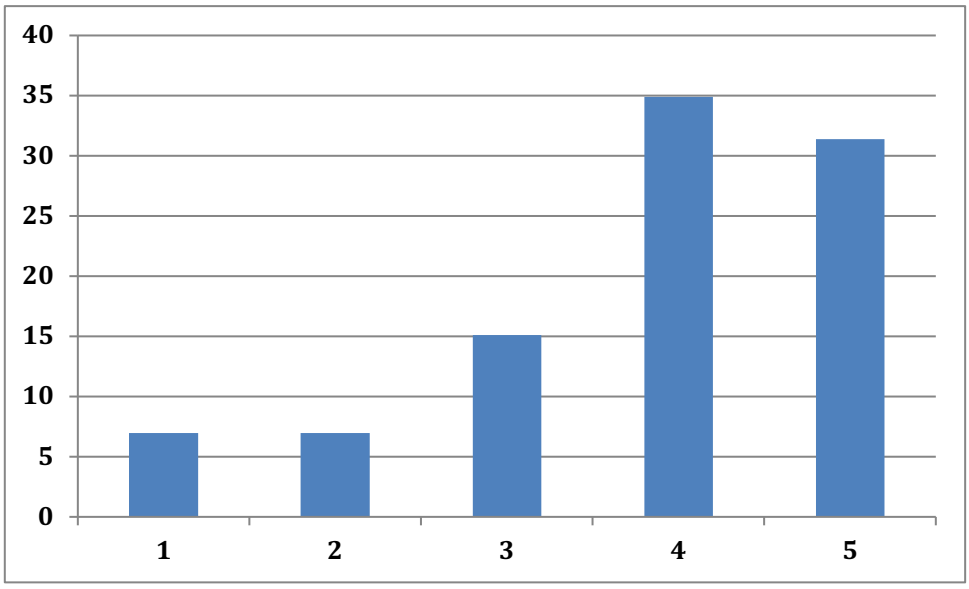
Q27B. I could provide detailed information about pharmacogenomic tests and correctly explain the results of these tests to my customers.



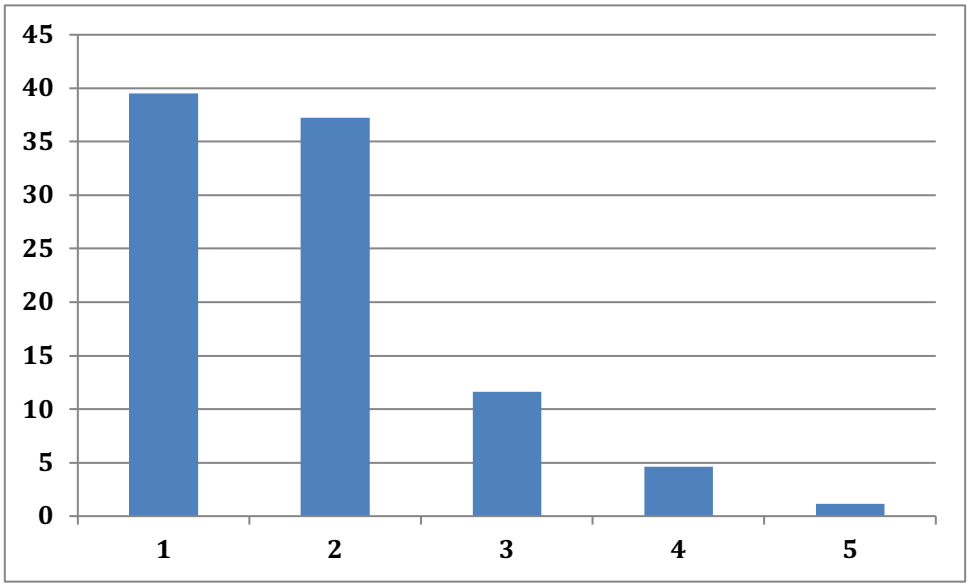
Q28B. Genetic tests can be performed directly to the patient, without any referral from a medical specialist (e.g. a doctor, or genetic counselor).



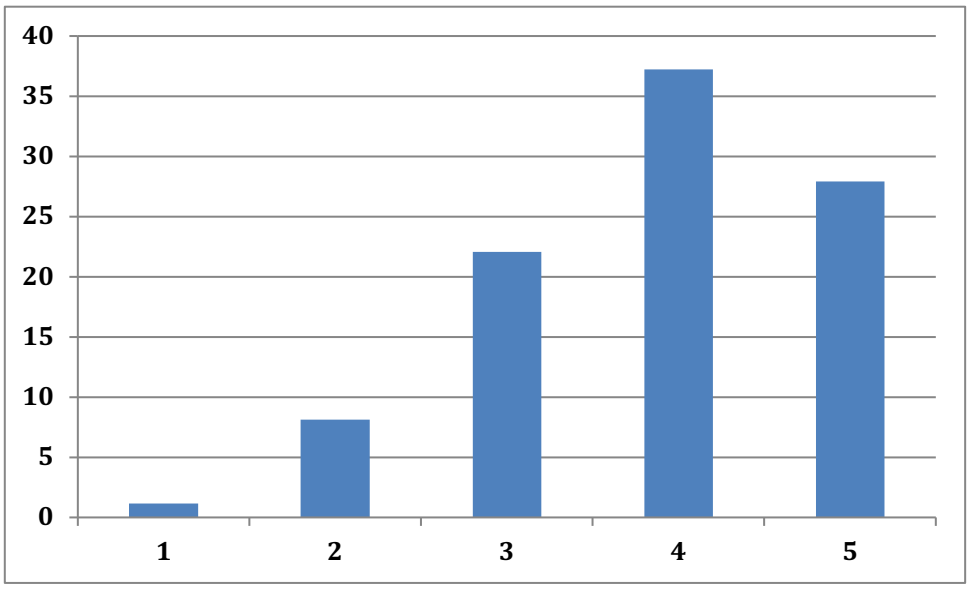
Q29B. The expenses of pharmacogenomic tests should be covered by insurance companies.



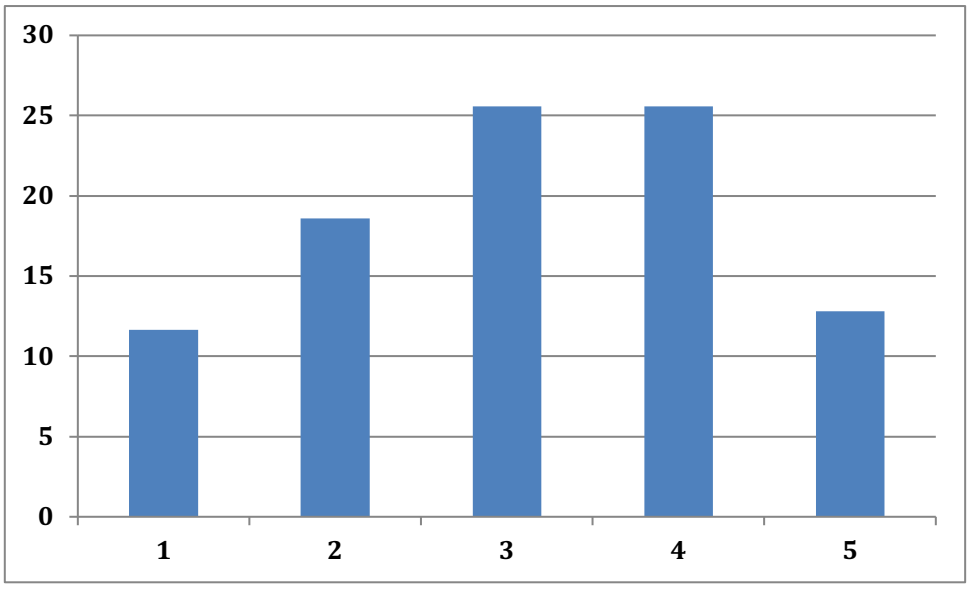
Q30B. An adequate regulatory and legal framework exists in the field of genetic tests (privacy of patients, analysis costs, quality accreditation of genetic laboratories, etc.) in Greece.



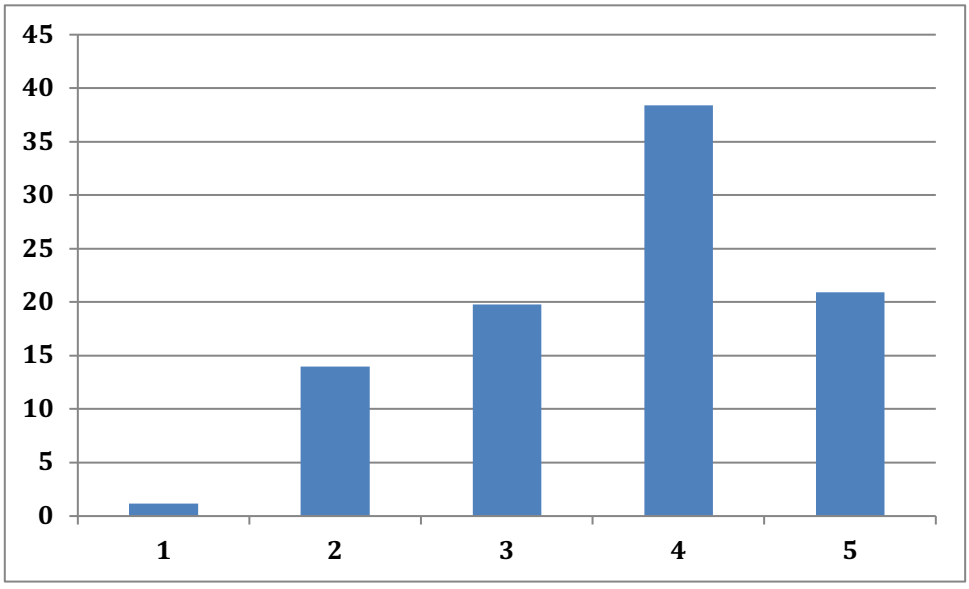
Q31B. Do you believe that pharmacogenomics helps in the reduction of the occurrence, frequency and severity of *drug*-induced *side effects?*



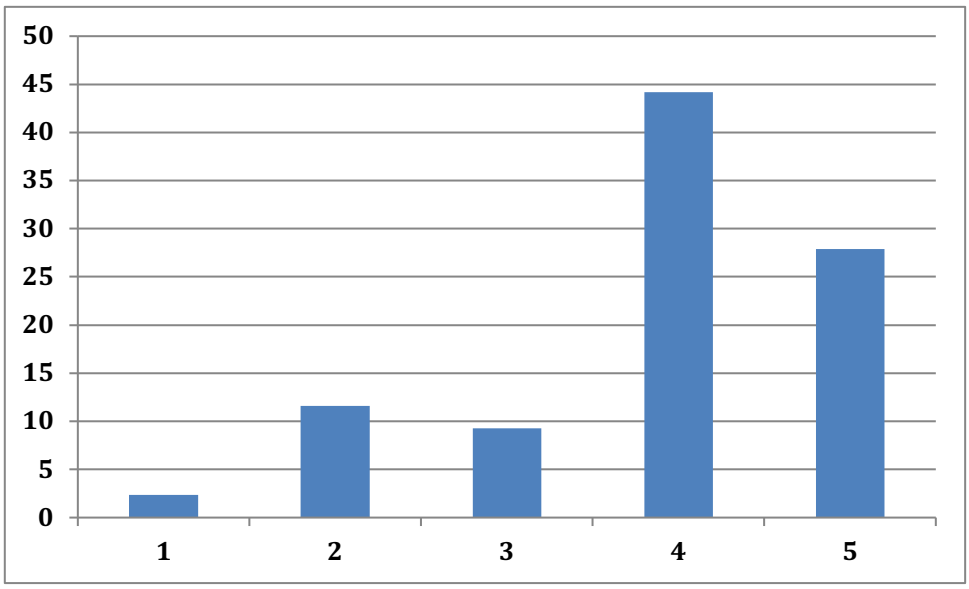
Q32B. Do you believe that pharmacogenomics helps in reducing the cost of developing new drugs ?



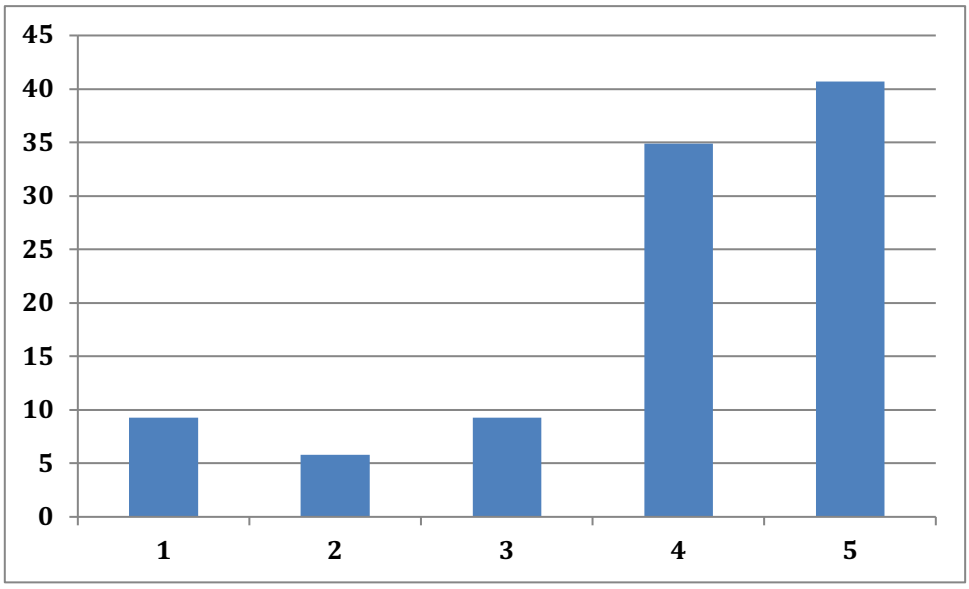
Q33B. Do you believe that pharmacogenomics helps in *reducing health care costs by rationalizing drug dose?*



Q34B. Do you believe that pharmacogenomics could be exploited by employers, insurance companies, *etc* to discriminate certain population groups or patients?



Q35B. Would you be interested in attending conferences or seminars on applications of genetics and pharmacogenomics?



Item 6 – Questionnaire distributed to the various stakeholders that have participated in the study

Question 1: What is the stakeholders' opinion to support the goals of pharmacogenomics and genomic medicine?

Stakeholders	Strong support	Medium support	Non-mobilized	Medium opposition	Strong opposition
Academic and research organizations					
Greek bioethics council					
Private genetic laboratories					
Religious organizations and church					
Consumers and citizens					
Pharmaceutical and biotechnology companies					
Genetics and genomics professional associations					
Ministry of Health					
Payers (Private Health Insurance Industry)					
Payers (Public Health Insurance Funds)					
Other private companies [a]					
Pharmacies					
Physicians (Geneticists)					
Physicians (others)					
Press and Media					
Private providers					
Public providers					
Greek National Medicines Organization					

Question 2: In your opinion, what is the intervention power of each of the following stakeholders to influence the field of pharmacogenomics and genomic medicine?

Stakeholders	Low	Medium	High
Academic and research organizations			
Greek bioethics council			
Private genetic laboratories			
Religious organizations and church			
Consumers and citizens			
Pharmaceutical and biotechnology companies			
Genetics and genomics professional associations			
Ministry of Health			
Payers (Private Health Insurance Industry)			
Payers (Public Health Insurance Funds)			
Other private companies [a]			
Pharmacies			
Physicians (Geneticists)			
Physicians (others)			
Press and Media			
Private providers			
Public providers			
Greek National Medicines Organization			

Question 3: Please indicate with Low (L), Medium (M) and High (H) the level of interest of each of the following stakeholder regarding pharmacogenomics and genomic medicine.

Stakeholders	Type of interest						
	Financial	Political	Personal	Scientific	Union-related	Ethical	Other
Academic and research organizations							
Greek bioethics council							
Private genetic laboratories							
Religious organizations and church							
Consumers and citizens							
Pharmaceutical and biotechnology companies							
Genetics and genomics professional associations							
Ministry of Health							
Payers (Private Health Insurance Industry)							
Payers (Public Health Insurance Funds)							
Other private companies [a]							
Pharmacies							
Physicians (Geneticists)							
Physicians (others)							
Press and Media							
Private providers							
Public providers							
Greek National Medicines Organization							

Supplementary Table 1. Policy Content

Goal	Proposed mechanism
Create an ongoing dialogue among government, physicians, citizens and firms	Create an active and sustained dialogue with society and industry on the socio-economic and ethical implications, benefits, and requirements of Genetics-Genomics.
Prepare for a costly but beneficial revolution in healthcare	1. Ensure that private incentives for developing personalized health therapies are better aligned with the public interest in accessible, effective and safe treatments. 2. Continue actively developing regulatory systems for healthcare products that incorporate pharmacogenomics. 3. Support long term research, using population-based medical databases, into health outcomes. 4. Analyze the long-term impacts of pharmacogenomics and genomic medicine on healthcare, including data confidentiality, new models for healthcare delivery, and new relationships between doctors and patients. 5. Examine the social, ethical and physical consequences of longer life spans.
Prepare the foundation for the long-term development of pharmacogenomics and genomic medicine	Develop regulatory, research, and health record systems which can link prescribing histories, genetic and other information, to support long-term follow-up research into health outcomes.
Promote the integration of pharmacogenomics and genomics research across commercial applications	Although coordinating policies across government ministries has always been a challenge, the benefits from promoting the integration of biotechnology and research should be worth the effort.

Supplementary Table 1 (continued).

Goal	Proposed mechanism
Reverse the neglect of pharmacogenomics and genomic medicine	1. Boost research in biotechnologies by increasing public research investment, reducing regulatory burdens and encouraging private-public partnerships. 2. Encourage the use of biotechnology to address global health issues by supporting international agreements to create and sustain markets for sustainable biotechnology products.
Turn the potentially disruptive power of pharmacogenomics and genomic medicine to an economic advantage	1. Implement flexible policies that can adapt to and support socially and economically beneficial disruptive technology in pharmacogenomics and genomic medicine. 2. Fund foresight research to identify beneficial disruptive technology in pharmacogenomics and genomic medicine and the types of incentives, infrastructure, regulation, education, and business models that would support their development.

Appendix 3

Curriculum Vitae

Curriculum Vitae

Christina Mitropoulou graduated from the University of Athens, Department of Economics (Athens, Greece) and received an MBA from NIMBAS University School of Business (Utrecht, the Netherlands). She is currently Managing Director of the Golden Helix Foundation, an international organization involved in research and educational activities in the field of Genomic and Personalized Medicine (London, UK; www.goldenhelix.org) and also Principal Investigator and member of the Executive Board of the PREPARE clinical study, as part of the U-PGx project, funded by the European Commission (H20220- 668353).

She is also actively involved in educational activities of the Golden Helix Academy, teaching and evaluating courses in (a) Economic Evaluation in Healthcare Systems (Health Technology Assessment, economic evaluation in Genomic Medicine), (b) Health Economics and Decision Making (Pharmaceutical Price Regulation and Reimbursement, Economics for healthcare professionals, Health Economics, insurance) and also in the organization of international conferences.

Christina has more than 30 peer-reviewed publications and book chapters in high impact international scientific journals and international textbooks and she has co-authored and co-edited two textbooks on Economic Evaluation in Genomic Medicine, published by Elsevier/Academic Press (Economic Evaluation in Genomic Medicine, ISBN 978-0128014974; 2015 and Economic evaluation of Genomic and Precision Medicine, ISBN 9780128133828; 2020). For her research projects, she has received funding from the European Commission and other funding bodies.

Appendix 4

List of Publications

List of publications

A. Scientific articles in peer-reviewed journals

1. Patrinos GP, Pasparakis E, Koiliari E, Pereira AC, Hünemeier T, Pereira LV, **Mitropoulou C.** Roadmap for Establishing Large-Scale Genomic Medicine Initiatives in Low- and Middle-Income Countries. Am J Hum Genet. 2020;107(4):589-595.
2. Siamoglou S, Karamperis K, **Mitropoulou C**, Patrinos GP. Costing Methods as a Means to Measure the Costs of Pharmacogenomics Testing. J Appl Lab Med. 2020;5(5):1005-1016.
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B. Textbooks and book chapters

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Appendix 5

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Propositions

1. The level of public awareness of pharmacogenomics and its impact upon society is often rather low. *This thesis*
2. A large proportion of physicians and pharmacists disagreed with the idea of direct-to-consumer genetic testing. *This thesis*
3. More than half of the ley stakeholders are highly supportive of pharmacogenomics in Greece. *This thesis*
4. Genotype-guided warfarin therapy appears to be cost-effective for elderly patients in Croatia. *This thesis*
5. Genome-guided clopidogrel treatment may represent a cost-saving option for the management of myocardial infarction in Serbian patients. *This thesis*
6. Incremental cost-effectiveness ratio (ICER) is a tool used for cost-effectiveness analysis and is given by the difference in costs between two healthcare programs divided by the difference in outcomes between a new health care program and the existing approach. *Gafni et al. Soc Sci Med. 2006;62:2091-2100.*
7. Cost-minimization analysis is difficult to justify if two alternatives offer the same level of effectiveness. *Briggs and O'Brien. Health Econ. 2001;10:179-184*.
8. Cost–utility analysis uses various indices and tools to measure the quality of the patient's life, in order to adjust the result according to patient quality of life. *Torrance GW. J Health Econ. 1986;5:1-30*
9. The desired value for the willingness-to-pay indicator is approximately three times the average per capita income of the country. *Eichler et al. Value Health. 2004;7:518-528.*
10. Abacavir was among the very first cases for the application of economic analysis of genome-guided treatment interventions. *Hughes et al. Pharmacogenetics. 2004;14:335-342.*
11. "Not everything that counts can be counted, and not everything that can be counted, counts" Albert Einstein