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"Cost analysis of personalized treatment after genotyping in psychiatric patients"

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«ΟΙΚΟΝΟΜΙΚΑ ΚΑΙ ΔΙΟΙΚΗΣΗ ΤΗΣ ΥΓΕΙΑΣ»

"Ανάλυση κόστους της εξατομικευμένης θεραπείας μετά από γενετικό τεστ σε ψυχιατρικούς ασθενείς"

ΚΟΥΡΕΤΣΗ ΜΙΚΑΕΛΑ ΣΤΑΥΡΟΥΛΑ, Α.Μ.:ΟΔΥ1728

Επιβλέπων: Αθανάσιος Βοζίκης, Αναπληρωτής Καθηγητής, Πανεπιστήμιο Πειραιώς

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Ανάλυση κόστους της εξατομικευμένης θεραπείας μετά από γενετικό τεστ σε ψυχιατρικούς ασθενείς

Περίληψη

Υπόβαθρο: Η οικονομική ανάλυση στη φαρμακογονιδιωματική είναι ένας αναδυόμενος κλάδος για την ανάλυση κόστους-αποτελεσματικότητας σε θεραπεία βασισμένη στο γονιδίωμα των ασθενών. Η παρούσα μελέτη αποτελεί μία μονοκεντρική μελέτη που βασίζεται σε δεδομένα πραγματικών ασθενών με Μείζονα Καταθλιπτική Διαταραχή, οι οποίοι είτε υποβάλλονται στο γενετικό τεστ και λαμβάνουν ανάλογη θεραπεία είτε λαμβάνουν συμβατική θεραπεία, χωρίς τη διεξαγωγή του γενετικού τεστ.

Μέθοδος: Το Εργαστήριο Φαρμακογονιδιωματικής και Εξατομικευμένης Θεραπείας του Πανεπιστημίου Πατρών σε συνεργασία με την Ψυχιατρική Κλινική του Πανεπιστημιακού Νοσοκομείου Πατρών συμπεριέλαβε σε μία πολυκεντρική μελέτη ενήλικες ασθενείς (>18 ετών), διαγνωσμένους με Μείζονα Καταθλιπτική Διαταραχή. Σκοπός της παρούσας μελέτης ήταν η ανάλυση ενός δείγματος της μελέτης που διεξάγεται στην Πάτρα, με τον υπολογισμό του κόστους της συμβατικής και της εξατομικευμένης θεραπείας, τη σύγκριση των εναλλακτικών θεραπειών και την αξιολόγηση του κόστους της ασθένειας και των ανεπιθύμητων ενεργειών που εμφανίστηκαν σε κάθε προσέγγιση.

Αποτελέσματα: Συνολικά 62 ασθενείς συμπεριλήφθηκαν στην παρούσα μελέτη. Η μέση ηλικία των ασθενών στην ομάδα παρέμβασης ήταν 47,96 χρόνια, ο μέσος ΔΜΣ ήταν 26,2 Kg/m^2, 13 ήταν άνδρες και 15 γυναίκες. Στην ομάδα ελέγχου, η μέση ηλικία των ασθενών ήταν 53 έτη, ο μέσος ΔΜΣ ήταν 26,76 Kg/m^2, 8 ασθενείς ήταν άνδρες και 26 ήταν γυναίκες. Η λιανική τιμή του γενετικού τεστ υπολογίστηκε στα €198,46, οι φαρμακευτικές δαπάνες ανά μήνα ήταν €17,66 ανά ασθενή για την ομάδα παρέμβασης και €17,47 για την ομάδα ελέγχου, και άλλα άμεσα μη φαρμακευτικά κόστη περιλάμβαναν το κόστος παρακολούθησης από το θεράποντα ιατρό και το κόστος νοσηλείας, τα οποία ανήλθαν σε €16,35 και €9,80 μηναία για την ομάδα παρέμβασης και την ομάδα ελέγχου, αντίστοιχα. Δεν καταγράφηκαν αξιοσημείωτες διαφορές κόστους, εκτός από τους άνδρες στην ομάδα ελέγχου, των οποίων το κόστος σε φάρμακα ήταν 108,04% μεγαλύτερο σε σύγκριση με τους άνδρες στην ομάδα παρέμβασης. Αντίθετα, το αντίστοιχο κόστος για τις γυναίκες στην ομάδα παρέμβασης ήταν 49,96% μεγαλύτερο σε σύγκριση με τις γυναίκες στην ομάδα ελέγχου. Το 44,92% του συνολικού κόστους για φαρμακευτική αγωγή καταναλώθηκε για βασική θεραπεία

στην ομάδα παρέμβασης έναντι 52,47% στην ομάδα ελέγχου, ενώ τα αντιψυχωσικά αντιπροσώπευαν το υψηλότερο κόστος μεταξύ όλων των θεραπειών για συνοδά νοσήματα. Κανένας από τους ασθενείς και στις δύο ομάδες δεν παρουσίασε μέτριες ή σοβαρές ανεπιθύμητες ενέργειες, καθιστώντας έτσι αδύνατη την αξιολόγηση της αποτελεσματικότητας.

Συμπεράσματα: Η παρούσα μελέτη, αν και δεν κατέστη δυνατό να υπολογιστεί η αποτελεσματικότητα της γενετικά καθοδηγούμενης φαρμακευτικής συνταγογράφησης, λόγω του μικρού αριθμού των περιστατικών που μελετήθηκαν, εν τούτοις αποτελεί την πρώτη προσπάθεια υπολογισμού του κόστους της γενετικά καθοδηγούμενης φαρμακευτικής αγωγής σε ψυχιατρικούς ασθενείς στην Ελλάδα σε σύγκριση με την συμβατική θεραπεία που δίνεται στους ασθενείς με ψυχικά νοσήματα. Η σύγκριση των δύο σκελών μελέτης έδειξε παρόμοιο θεραπευτικό κόστος. Προσδιορίστηκαν όλα τα κόστη και τα αντίστοιχα ποσοστά συμμετοχής τους στο συνολικό κόστος και αναλύθηκαν με βάση διάφορες ομάδες, όπως η ηλικία των ασθενών και τα φάρμακα που συνταγογραφούνται.

Μελέτη μεγαλύτερου αριθμού περιστατικών αναμένεται να επιβεβαιώσει ότι, όπως και στην καρδιολογία και την ογκολογία, η γενετικά καθοδηγούμενη φαρμακευτική αγωγή συμβάλλει στη μείωση των ανεπιθύμητων ενεργειών της φαρμακευτικής αγωγής και του συνοδού κόστους της θεραπείας σε ψυχιατρικούς ασθενείς.

Σημαντικοί όροι: γενετικό τεστ, υγειονομικά κόστη, κόστος ασθένειας, μείζων καταθλιπτική διαταραχή, εξατομικευμένη θεραπεία, φαρμακογενετική, φαρμακογονιδιωματική, φαρμακοοικονομική ανάλυση, μείωση δαπανών υγείας

Cost analysis of personalized treatment after genotyping in psychiatric patients

Abstract

Background: Economic evaluation in genomic medicine is an emerging discipline to assess the cost–effectiveness of genome-guided treatment. This is a single center study using real world data of patients with Major Depressive Disorder who were either genotyped to follow a pharmacogenomic (PGx) guided treatment or received standard therapy without undergoing the genetic test.

Methods: The Laboratory of Pharmacogenomics and Individualized Therapy, of the University of Patras, Department of Pharmacy, in cooperation with the Psychiatric Clinic of the General University Hospital of Patras, recruited adult patients (>18 years old) diagnosed for Major Depressive Disorder (MDD) in a multicenter study. The objective of this study was to analyze a small sample of the study in Patras, with the estimation of the economic impact for standard therapy and pharmacogenetic-guided treatment for MDD, the comparison of the alternative treatments and the evaluation of the cost of illness and ADRs in each approach.

Results: A total of 62 patients were included in this study. The mean age of the patients in the intervention arm was 47,96 years, the mean BMI was 26,2 Kg/m^2, 13 were male and 15 female. In the control arm, the mean age of the patients was 53 years, the mean BMI was 26,76 Kg/m^2 , 8 patients were male and 26 were female. The retail price of genetic testing was calculated at €198,46, the pharmaceutical expenditures per month were €17,66 per patient for the intervention arm and €17,47 for the control arm and other direct non pharmacy costs included the outpatient monitoring and the hospitalization cost, which were translated into €16,35 and €9,80 on monthly average for the intervention and the control arm, respectively. No notable cost differences were reported, except for males in the control arm who consumed 108,04% more depression-related pharmaceutical medications compared with the males in the intervention arm. On the other hand, females in the intervention group consumed 49,96% more pharmaceutical medications compared with the females in the control group. 44,92% of the total cost for pharmaceutical regimen was consumed for baseline therapy in the intervention arm versus 52,47% in the control arm, while antipsychotics represented the higher costs among all comorbid regimens. None of

the patients in both arms had moderate or severe ADRs, precluding the evaluation of effectiveness.

Conclusions: The current study, although it was impossible to evaluate the effectiveness of the genome-guided pharmaceutical treatment due to the small sample examined, is nevertheless the first attempt to calculate the cost of genome-guided treatment in psychiatric patients in Greece compared with the conventional treatment prescribed to patients with mental illnesses. Comparison of the intervention and control arm represented similar treatment costs. All costs and their respective percentage of participation in the total cost were identified and analyzed based on various factors, such as the age of the patients and the drugs prescribed.

A study of a bigger sample examined is expected to confirm that, as in cardiology and oncology, personalized treatment after genotyping helps towards the reduction of ADRs and the relevant health care costs in psychiatric patients.

Keywords: pharmacogenetics, genetic test, major depressive disorder, costs of illness, illness burden, health care expenditures, personalized medicine, cost savings, pharmacoeconomics, psychotropic, cytochrome P450, healthcare cost reduction

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THEORETICAL FRAMEWORK

CHAPTER 1: TYPES OF ECONOMIC EVALUATION IN HEALTHCARE

1.1 Introduction to Efficiency of Health Systems

Enthusiasm for the field of health economics and results research has developed exponentially as governments and different payers think about how to give the most ideal health outcomes at moderate expenses. (Willke and ISPOR 2018) Health economics are not so much being about expenses, but instead about value and understanding utility. Consequently, this part of financial matters is concerned with issues related to efficiency, effectiveness, value and behavior in the production and consumption of health and healthcare. (Wolfe 2008) Rewarding the innovations that create value is the best step towards encouraging the right type of new product innovation. What is meant by value makes this decision critical to determine, especially if we are rewarding it from pooled insurance funds. “Value” in relation to health means, of course, different things to different individuals. Ill patients, in most instances, want improved health, in terms of improved survival or quality of life, or both. From the budget holder point of view, on the other hand, any reduction in the resource costs of treating illness is also valuable. (Louis, Kamal-Bahl and Towse 2017) Through a consideration of value, health economics can help patients and consumers clarify the assumptions that are being made, consider uncertainties, and evaluate trade-offs.

Therefore, health economic evaluations are primarily used to inform decision making. The person who makes the decision about what health care will be provided is generally not the individual receiving the health care. The individual receiving the health care typically does not have a good idea of the potential benefits and harms of a decision. And patients, in general, do not pay out of pocket for the services they receive. Current cost-management initiatives and consideration of future drug coverage initiatives bring a significant focus to methods for evaluating the costs and consequences of competing therapeutic alternatives. This increased attention to balancing costs and outcomes is a response to the limited resources available to face the rising demand for medical services. If new technologies focus on the maximization of health benefits, assessments must be used to enhance our ability to make rational and appropriate health care decisions and to help direct health resources toward their most productive uses. (Berger and Olson 2013)

Health care economics try to gain a better understanding of the value of one health care intervention compared to an alternative approach, taking into consideration all the impacts across patients, providers, and the health care system. This value can be measured in terms of price, a longer life expectancy, improvements in quality of life, health state, resources saved, and so on. The key components of the evaluation are that all relevant factors are included in the analysis and that the same approach is applied to all decisions that are being assessed. (Ofman, et al. 2003) Economists use several different methods to carry out economic evaluations of health care interventions, including cost-minimization analysis, cost-benefit analysis, cost-effectiveness analysis (CEA), and cost-utility analysis (CUA). All these approaches consider the cost of the intervention as well as downstream costs, but they differ in the measurement of the outcome or utility of an intervention.

1.2 Cost Effectiveness Analysis (CEA)

The term cost-effectiveness has become synonymous with health economic evaluation and has been used to depict the extent to which interventions measure up to what can be considered to represent value for money. The term has also been misused in the pharmacoeconomic literature, either to describe the results of a partial economic analysis, such as a comparison of the costs of two treatment alternatives, or to describe the results of a cost-minimization analysis. It is important to make the distinction that CEA compares both the costs and the consequences of competing alternatives whose outcomes are not equal but are measured using common units. Also, the fact that CEA can help inform health care spending, but its value depends on using assumptions that are appropriate to the analysis setting and, thus, practitioners should develop context-specific values reflecting the health care system and local priorities is another way of avoiding the misuse of the “cost-effective” term. (Leech, et al. 2018) CEA is one of the economic evaluation techniques, depending on the nature of the benefits specified. (Phillips and Anderson 2009) Cost-effectiveness analysis is a quantitative framework for evaluating the complex and often conflicting factors involved in the evaluation of health care technologies. (Berger and Olson 2013) CEA has been defined by the National Institute for Health and Clinical Excellence (NICE) as an economic study design in which consequences of different interventions are measured and compared for a management of a disease (EDEJER, et al. 2003), using a single outcome, usually in ‘natural’ units that may be determined objectively via appropriate measurements. (for example, life-years gained, deaths avoided, heart attacks avoided, or cases detected). Alternative/innovative interventions are then

compared with an analytical technique in terms of cost, which is expressed in monetary terms per unit of effectiveness. (Lee, McLaughlin-Miley and Chatterton n.d.) CEA is, therefore, a method of financial evaluation wherein the value of the resources spent on an intervention is compared with the quantity of health gained as a result.

CEA is the most frequently used form of economic evaluation in the health care sector. This approach can help to determine whether the value of the resources spent on the intervention is "value-for-money". (Phillips and Anderson 2009) In other words, CEA is not a method to show which interventions reduce cost. Rather, its aim is to inform which interventions provide the greatest value for the amount of money that is spent. Additionally, CEA is not a method that removes individual or group responsibility for making clinical and financial decisions but, on the other hand, provides information that is incorporated into larger decisions involving additional considerations, such as issues of equity. (Berger and Olson 2013)

Therapeutic interventions, on one hand, normally lessen the impact of the disease, eradicate its symptoms, improve quality of life, and also extend survival where this is feasible. However, society's healthcare needs increase over the years, the related costs are too considerable and the available resources too restricted to fulfill current needs. (Lee, McLaughlin-Miley and Chatterton n.d.) The application of cost-effectiveness analysis allows such a comparison to be made and the limited resources that the health systems can allocate to be used effectively based on optimization behaviors, grounded in the tenets of economics (Canning, et al. 2009). Of course, in order to realize the need for cost-effectiveness analysis, we only have to compare the medical care between the United States and the developing countries. In the first occasion, the medical care is never denied to anyone who can afford it, and there is no limit on how much is spent on health care. General guidelines on which interventions might generally be preferable are then provided to clinicians, policymakers and insurers. This lack of an emphasis on cost-effectiveness could partially explain why the United States spends around twice as much on health care as the next biggest spender but ranks low among developing nations in terms of life expectancy. On the other hand, the need for cost-effectiveness becomes critical in developing nations, where government health budgets may be as low as five dollars per person. (Labonte, et al. 2009)

This tool of analysis serves three primary goals: determination of the price of a technology, definition of the level of insurance compensation, and drafting of guidelines to be used as guides for healthcare professionals when prescribing. (Lee, McLaughlin-

Miley and Chatterton n.d.) (Phillips and Anderson 2009) Therapies are characterized as cost-effective when they have outcomes worth their corresponding costs relative to competing alternatives:

I. Alternatives which are less expensive and at least as effective as other alternatives

2. Alternatives which are more expensive than alternative therapies with an additional benefit worth the additional cost

3. Alternatives which are less expensive and less effective in instances - here the extra benefit provided by the competing therapy is not worth the additional expense.

A distinction must be made between those interventions that are completely independent, that is, where the costs and effects of one intervention are not affected by the introduction or otherwise of other interventions, and those that are mutually exclusive, that is, where implementing one intervention means that another cannot be implemented, or where the implementation of one intervention results in changes to the costs and effects of another. In reality, the likelihood is that decisions will have to be made between different treatment regimens for the same condition, different dosages or treatment versus prophylaxis – that is, mutually exclusive interventions. The crucial question is: what are the additional benefits to be gained from the new therapeutic intervention and at how much greater cost? In order to answer such a question, incremental cost-effectiveness ratios (ICERs) are used, which will be further discussed. (Phillips and Anderson 2009)

1.3 Starting an economic evaluation

A. Definition of the problem- The problem should be stated but the perspective and objectives of the question also should be specified, in a concise and measurable manner. The perspective chosen for a study delineates the viewpoint from which the analysis is performed and points out the types of cost and outcomes data that will need to be collected. Many experts suggest that the perspective of society is best to select because it allows for complete evaluation of the impact of a drug or technology on the system as a whole. However, adopting a narrower perspective allows researchers to assess specific questions using more relevant comparisons for a given setting. Patients and their caregivers are concerned with availability of care and expenses that

will be not covered by third-party payers for which they will be charged. Providers need information that allows them to act as patient advocates in gaining access to beneficial technologies and drugs, whereas third-party payers are concerned with minimizing costs while offering services that allow them to maintain competitiveness in the marketplace. In private industry, a benefits manager may be particularly concerned with the direct medical costs of providing therapy to employees and the productivity of an employee. (Lee, McLaughlin-Miley and Chatterton n.d.)

B. Identification of the treatment alternatives and outcomes. All clinically relevant treatment options and feasible outcomes should be both identified and investigated. Primary clinical outcomes often relate directly to patient morbidity and mortality. Primary clinical outcomes (health outcomes) typically are preferable to intermediate outcomes, but some are not easily measured. Examples of primary clinical outcomes include the cure of acute conditions such as infections or ketoacidosis, control of chronic conditions, such as diabetes mellitus, Parkinson's disease, or hypertension, improved functioning and reduction in disability, and lives saved, or years of life saved. Intermediate outcomes should be identified when primary outcomes cannot be measured and could be described as the changes in the risk of illness a patient faces. (The Golden Helix Foundation; n.d.) Intermediate outcomes are measurable effects of treatment that are thought to be indicative of a specific long-term, primary outcome and they are more easily measured, but, if used in a CEA, they require extrapolation of clinical significance to primary outcomes. (Drummond, et al. 2015) Examples of intermediate and corresponding primary outcomes include reductions of hypertension as measured in mmHg rather than waiting for years to measure the reduction of stroke or death incidents, forced expiratory volume in 1 second as a predictor of acute exacerbations of asthma, and CD4 lymphocyte counts as a predictor of stage of infection with the human immunodeficiency virus. (The Golden Helix Foundation; n.d.) Process measures refer to activities which, it is known or believed, have a direct bearing on the outcomes accomplished by the intervention. For example, it is known that people suffering a heart attack should be given thrombolytic drugs as soon as possible in order to improve their health outcome. Thus, a useful process measure would be the proportion of such patients given the drug. It is assumed that any change in the process measure is correlated with a change in the health problem. (The Golden Helix Foundation; n.d.) Economic are called those outcomes associated with use of health care resources, such as length of hospital stay, length of intensive care unit stays, frequency of physician visits, drug use, and other services or treatments used. Humanistic outcomes are those reported by patients from

their own viewpoint, such as patient satisfaction with health and health-related quality of life. After tracing back to the literature, it is advisable to produce a comprehensive list of important clinical, economic, and humanistic outcomes and then determine which of these parameters are most relevant to include in the analyses. (Gray, et al. 2010)

1.4 Cost-utility analysis (CUA)

Cost-utility analysis (CUA) 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. A common method to measure the effectiveness is the "quality-adjusted life-year" (QALY). QALY has been in use since 1970s and is estimated using a variety of different measures. (The Golden Helix Foundation; n.d.) Quality is frequently 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. The quality of life of a dead man is valued as 0 and the perfect health is rated as 1. 1 QALY is "one year of life for a person in perfect health", or more precisely "the equivalent of one year of life in perfect health". (O'Brien, et al. 2002) A "quality-adjusted life-year" is a one-year-period 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. If a prostate cancer patient, for example, is found to have 75% quality of life, then one year of life with prostate cancer is equivalent to 0.75 years of life with perfect health (0.75 QALYs). If the patient improves after treatment to 90%, then one year of post-treatment life is equivalent to 0.9 years of life in perfect health, and the treatment benefit is 0.15 years of life. (The Golden Helix Foundation n.d.)

Various methodological tools are used to value a patient's health state and quality of life, with those that are specialized for specific diseases, and others that seek to evaluate a patient's general state of health. Some are based on simple indices and some others are more comprehensive but also more difficult to assess. The subjects in such studies are commonly patients but may also be health professionals such as nurses or physicians, or the general population. Quality assessment may be done in a direct or indirect way through the use of certain characteristics of the treatment groups and the creation of empirical utility functions by professional investigators. Some examples of such efforts are the EuroQol EQ-5D, the Health Utility Index, the Quality of Well-Being Scale (QWB), the SF-36 Questionnaire. Because of the importance of

the quality of life, and because this type of analysis will (in theory) facilitate broad comparisons between different medical interventions by reducing them all to a common measure of value (the QALY), CUAs are becoming more and more common, with many organisations such as the UK National Institute of Health and Care Excellence (NICE) encouraging their use.

Disability Adjusted Life Years (DALYs), on the other hand, are according to Anand and Hanson (1998) an inequitable measure of aggregate illness-health and an inequitable criterion for resource allocation. Through age weighting and discounting, a different value on years lived is placed at different ages and at different points in time. DALYs value a year saved more for the able-bodied than the disabled, more for those in middle age-groups than the young ones or the elderly, and more for individuals who are ill today compared with those who will be ill in the future. (D. Canning 2013)

1.5 ICER

The simplest definitions of value tend to refer to a ratio or relationship between costs and health outcomes, with the widely used incremental cost-effectiveness ratio (ICER) being the gold standard for economic evaluation of health care technologies. (Louis, Kamal-Bahl and Towse 2017) According to ICER, the best result is when outcomes improve and costs go down, whereas the worst is when outcomes become worse and costs increase. In health care, most interventions result in higher costs with improved outcomes. (Berger and Olson 2013)

For two different treatments, for example, I (new Intervention) and S (Standard treatment), each associated with a specific effectiveness (E) and cost (C) for the management of a disease, EI, ES, CI, and CS correspond to the mean effectiveness of the new intervention/treatment, the mean benefit of the standard treatment, the mean cost of the new intervention, and the mean cost of the standard treatment, while $\Delta E = EI - ES$ and $\Delta C = CI - CS$ represent the differences in cost and effectiveness, respectively. (The Golden Helix Foundation; n.d.)

Comparative evaluation will give the four possible scenarios as described below (Drummond, et al. 2015):

A) $\Delta E = EI - ES > 0$ and $\Delta C = CI - CS > 0$

This is the most common case, since an increase in mean survival with the innovative intervention, with a corresponding increase in overall cost associated with

its administration is observed. In recent years, new discoveries are being made incessantly, due to the development of new drugs, innovative gene and biological therapies, targeted treatments, new diagnostic methods, or procedures. These procedures have, in general, great expenses as far as their development, purchase and operation is concerned, and those parameters are incorporated in the price of technology, the fraction of the overall cost of the intervention that significantly increases the final cost of services. In order to evaluate the association between the increased cost and the additional effectiveness, a specific criterion should be borne in mind.

B) $\Delta E = EI - ES > 0$ and $\Delta C = CI - CS < 0$

The new treatment dominates in this scenario, because it is not only more effective, but its cost is also lower than the standard treatment. The standard treatment must be, therefore rejected, and the health system must fully adopt the new intervention.

C) $\Delta E = EI - ES < 0$ and $\Delta C = CI - CS > 0$

This unpromising situation for the new intervention consists of expanded cost, even though lower effectiveness from its use compared to the standard treatment. In such a case, the new treatment is dominated by the established one and should be disposed of as it is not to the society's best interest and is anything but a good health investment.

D) $\Delta E = ET - ES < 0$ and $\Delta C = CT - CS < 0$

In this fourth scenario, the effectiveness as a result of a longer survival is over the established standard treatment, despite the fact that the utilization of the new intervention is associated with resource savings. In this situation (as in scenario A), a definitive choice to adopt or dismiss the new treatment will be derived from weighing the savings (which is the desirable outcome) and the diminished effectiveness (which is a negative outcome) when comparing treatments. This criterion might be equivalent to the one in scenario A.

The cases described above are presented graphically in Figure 1.1. (Black 1990).

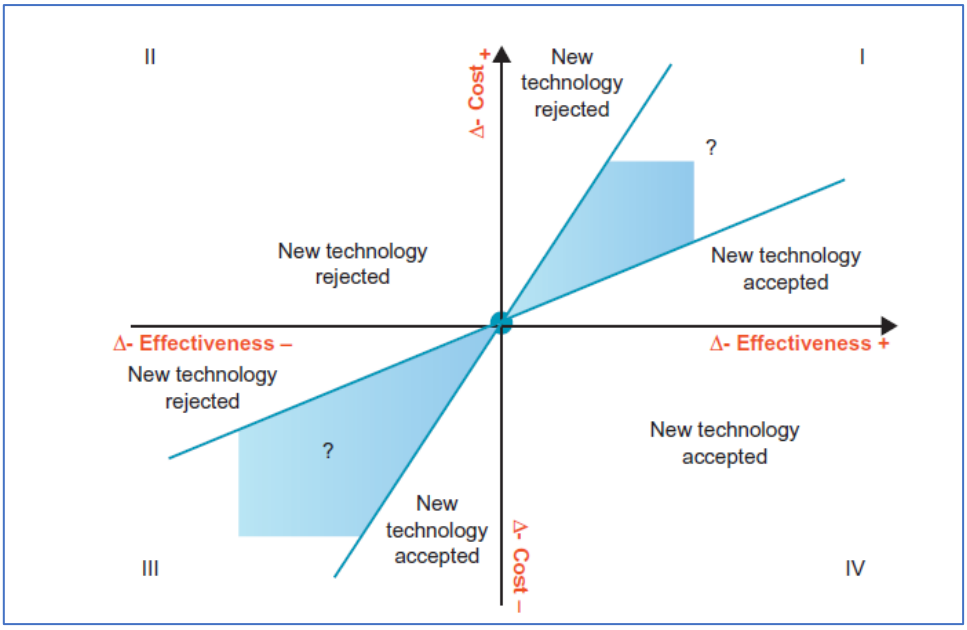

Figure 1.1. The CE plane.

The horizontal axis by convention measures differences in effectiveness and the vertical one measures differences in costs. The axes show the difference between cost and benefit for interventions T and S with the differences indicated with the Greek delta (Δ). Quadrant I represents the first scenario, where the new technology increases survival as well as cost, compared to the standard treatment. If the additional cost is not forbidding then the new technology will be adopted, if the cost is considered excessive, on the other hand, then it will be rejected.

There is also a “grey zone” where the additional benefit is related to higher cost and the result will be undetermined until the expense considered acceptable for one additional year of life is fully quantified. Quadrant IV represents scenario B, where T is cheaper and better, so no additional criteria are needed here, the new treatment should be selected immediately and reimbursement for S should be discontinued. The same argumentation is followed for scenario C, where T is more expensive and less beneficial and should therefore be rejected. Quadrant III represents scenario D, where the resources saved by treatment T are associated with reduced survival and a fully defined quantitative criterion is needed in this case, too, in order to compare treatments. If there is no difference between treatment benefits, then we move along the vertical cost axis and compare only the costs of the interventions. If T is more expensive then we are in the upper area of quadrant I and in quadrant II, in which case the treatment is turned down, otherwise we are located in the lower part of quadrant IV and in quadrant III, in which case we accept the treatment based on the cost-minimization analysis mentioned previously.

Note that, according to the diagram, the angles of the slopes (thresholds) for scenario A and scenario D are identical, which indicates that the additional investment we are eager to make with the aim of obtaining one additional year of life is equal to the savings we will demand for losing one year of life. As a society, however, we are continuously less willing to lose one year of life compared to standard treatment (Morrison 1998) and usually the amount of savings required is quite larger than the amount we would be willing to pay in order to obtain one additional year of life, it can be as high as twice the first in the case of health services (O'Brien, et al. 2002). This case is represented in Figure 1.2.

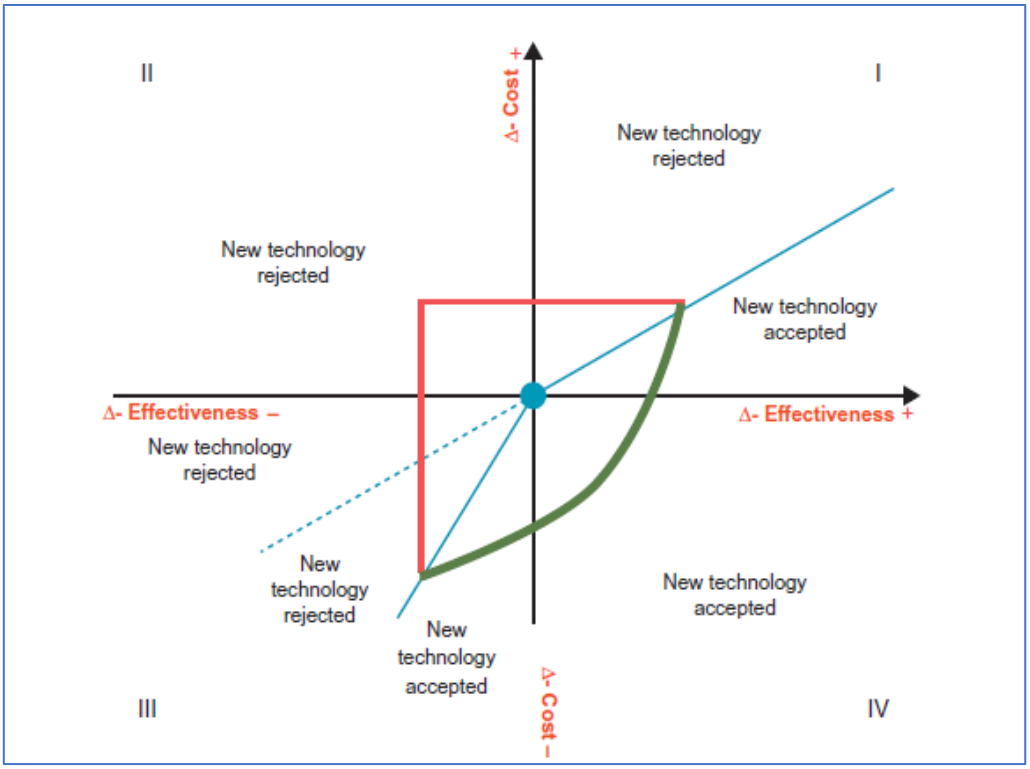

Figure 1.2. The kinked CE plane.

The area of rejection of the new technology is now greater in quadrant III, as the figure reveals, since the indifference angle is smaller than in quadrant I. There is a mathematical formula which quantifies the ratio of differences, it is called incremental cost-effectiveness ratio (ICER) and is described below.

Willingness to pay (WTP) is called the amount a society is willing to pay to obtain one year of life and is represented by the Greek letter lambda (λ) (Pauly 1995), whereas the savings a society demands for losing one year of life, as mentioned previously, are expressed by the willingness to accept (WTA). The λ is the inclination of the line dividing the cost-effectiveness diagram in two and if the ICER is greater than

λ then the new technology will be rejected, whereas if it is smaller than the new technology it is a socially beneficial and called “cost-effective”. If the WPA is greater than the ICER, the formula can be readjusted as follows:

$$\lambda > ICER \text{ ή } \lambda > \frac{\Delta C}{\Delta E} \text{ ή } \lambda \chi \Delta E > \Delta C \text{ or } \lambda \chi \Delta E - \Delta C > 0$$

The increase in effectiveness is greater than the increase in cost for points within the quadrant I, given that λ is by definition a positive number, whereas if ΔE<0 and ΔC<0 then the term $\lambda \chi \Delta E$ is a negative number and the term $-\Delta C$ is a greater positive number, which implies that the cost (savings) is greater than the benefit (obtained by S) and treatment T is again a cost-effective option. (The Golden Helix Foundation; n.d.)

1.6 Applications of CEA and Sensitivity Analysis

The evaluation of cost-effectiveness is a fundamental part in deciding if a treatment is endorsed for reimbursement and for formulary inclusion. Health technology assessment agencies, for example, NICE spot impressive load on the relative cost effectiveness of treatments in making their decisions. NICE requires the utilization of cost–utility investigation, in which the result measure is communicated as a QALY, and which empowers correlations with be made crosswise therapeutic regions – utilizing the QALY as the 'common currency'. In cost–utility investigation the ICER along these lines turns into the cost per QALY picked up and can be contrasted with those of threshold value of what is considered to speak to cost-effectiveness. (Ramsey, et al. 2005) While models will in general report single rundown results, for example, 'the incremental cost per incremental life-year', the translation of those outcomes will to a great extent rely upon the degree of certainty or uncertainty in different components. These might include the strategy that has been utilized in developing the model (that is, the model structure) or could be identified with the genuine values that have been utilized to populate the model. (Taylor and Filby 2009) Cost-effectiveness analysis (or cost–utility analysis) is a long way from being an exact science, and there is regularly impressive vulnerability related with the discoveries and wide variety around the estimate created. For instance, one of the early innovation evaluations attempted by NICE was on interferon beta and glatiramer acetate for the treatment of multiple sclerosis. Appraisals of the cost-effectiveness changed hugely due to varying suspicions identifying with the span of treatment, the number, seriousness and effect on quality of life (QoL) of relapses that happened, and the

degree to which improvement was determined by the mediations. It is in this manner basic that the evaluation of cost-effectiveness ought to be exposed to a sensitivity analysis to empower decision-makers to be completely mindful of the scope of potential scenarios. (Phillips and Anderson 2009)

The requirement for sensitivity analysis emerges as a result of various elements. These include:

- Methodological issues emerging from various methodologies and strategies utilized in the assessment
- Potential variety in the appraisals of costs and effects utilized in the assessment
- Extrapolation from watched occasions after some time or from middle of analysis to conclusive health results
- Transferability of results and the validity of results from different populations/patient groups

ICERs accordingly require some sign of the certainty that can be set in them. Sensitivity analysis tests every one of the assumptions utilized in the model and empowers the effect of changes on the baseline evaluations to be researched, contemplating, for instance, the way that the 'true cost' of one of the treatment methodologies is to some degree higher or lower than the gauge utilized in the examination, or that there are critical changes in the life-years picked up or different parameters utilized. Such an activity would include analyzing the sensitivity of the model to changes in its inputs. (Gold, et al. 1996)

The most straightforward type of sensitivity analysis is to just shift one incentive in the model by a given sum and analyze the effect that the change has on the model's outcomes. This is known as one-way sensitivity analysis, since just a single parameter is changed at one time. The investigation could, obviously, be rehashed on various parameters at various occasions. This type of analysis can be embraced utilizing different various methodologies, every one of which is helpful for various purposes. Assume that a specialist might want to test which parameters have the best effect on a model's outcomes. For this situation, every parameter in the model (or, at any rate, every one of the key parameters) could be changed by a particular sum. For every parameter change, the specialist may record the percentage effect on the model's principle result, which can be appeared as a tornado diagram (Figure 1.3.). (Taylor and Filby 2009)

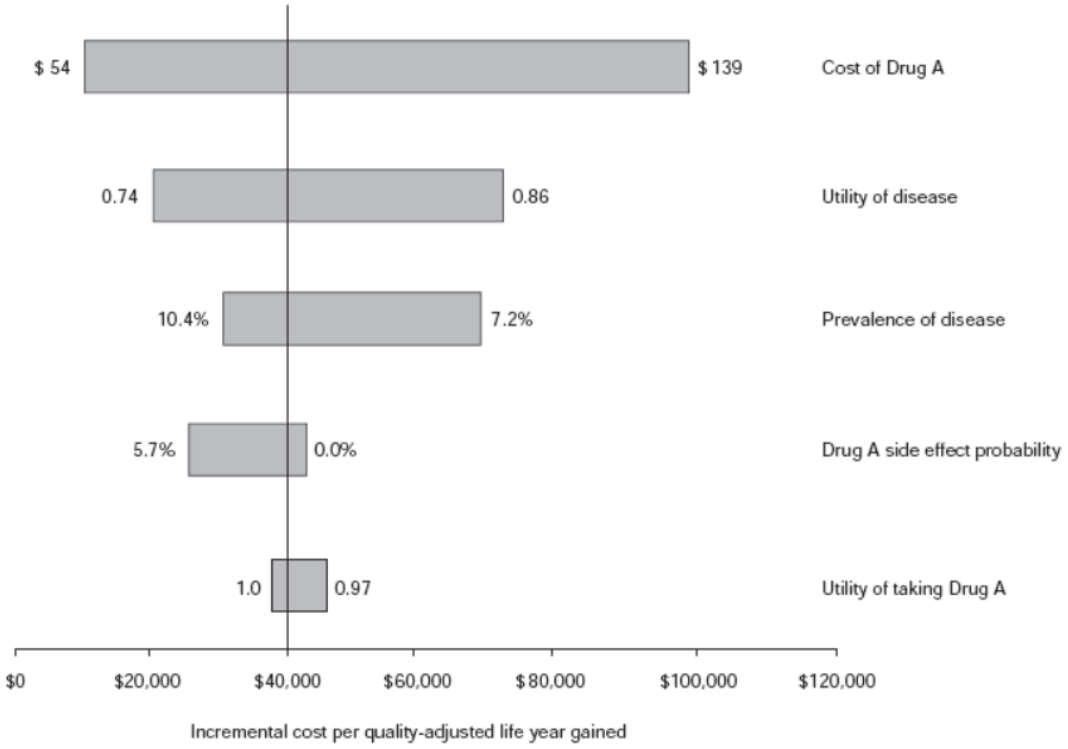

Figure 1.3. The CEA tornado diagram (Kenneth J. Smith, the health science).

Although a tornado diagram is valuable in exhibiting the effect that a fixed change in every parameter has on the primary results, it isn't helpful in speaking to the certainty that a decision maker may have in the model's inputs. For instance, it may be that the level of confidence in one specific parameter is low to the point that it is altogether sensible that the present input might be 'off-base' by as much as 100%. This may be found in situations where no data have been published to help a specific model input. A case of this could be the effect of a medication on a patient's long-term mortality, when no long-term trial data exist, leaving only short-term ones being accessible. On the other hand, a few parameters, (for example, the cost of a mediation) might be sensibly notable and, in that capacity, the user would have a high level of confidence in the value. In this manner, one type of one-way sensitivity analysis is to shift every parameter to the most astounding and least potential qualities. The meaning of potential might differ amongst models, yet it is generally sensible to shift the parameters, if they are known, as per the data confidence intervals. On the other hand, it is sensible to shift the parameter over the entire scope of values that have been seen in the literature.

At long last, an increasingly definite way to deal with this type of sensitivity analysis on one explicit parameter is to evaluate the effect of a scope of qualities on the model's outputs. In such an examination, it is conceivable to create a basic

diagram, plotting the main model result against every conceivable input value. This would show the connection between the input value and the model's outcomes. This sort of investigation can likewise be utilized to pass judgment on the threshold at which the fundamental determinations of a model may change. For instance, Figure 1.4. proposes that the cost-effectiveness of a specific mediation will stay underneath a prespecified edge of £20,000 just if the intercession is valued underneath £270. As the cost of the mediation expands, it appears to be less and less cost-effective.

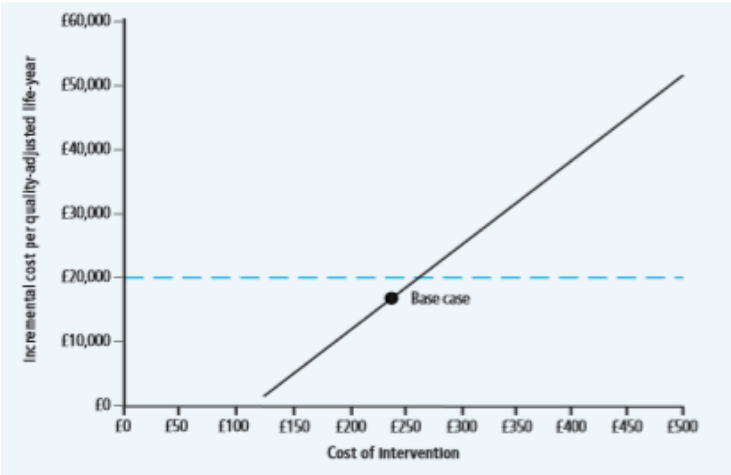

Figure 1.4. Sensitivity analysis diagram.

The examination of the relationship of at least two distinct parameters evolving at the same time might be necessary, although one-way sensitivity analysis is valuable in exhibiting the effect of one parameter shifting in the model. This methodology includes the evolving of, state, two key parameters-for instance, the cost and effectiveness of an intercession- demonstrating the outcomes for every potential blend of qualities inside a given range. It ought to be noted, in any case, that the presentation and elucidation of multiway sensitivity analysis turns out to be progressively difficult and intricate as the quantity of parameters included increments. One technique that is some of the time used to evaluate the confidence around all parameters is to embrace extreme sensitivity analysis, by fluctuating the majority of the parameters in a model to their 'best' and 'most exceedingly terrible' case. The best-and most pessimistic scenario values ought to be chosen considering the point of view of the mediation that is being evaluated. For instance, in one situation the most idealistic values would be picked, while in another, the most moderate figures would be utilized. Once more, the degree to which every parameter ought to be changed will rely on the certainty intervals related with each input.

The use of probabilistic sensitivity analysis is presently perceived as the proper configuration for undertaking and reporting sensitivity analysis. (Taylor and Filby 2009) Probabilistic sensitivity analysis (PSA) manages the critical issue of statistical estimation of amounts and ought to dependably be incorporated into any solid monetary investigation. For instance, single sensitivity analysis isn't suitable in cases of emphatically correlated, dubious variables or for those which follow distributions. The equivalent is valid for information originating from various sources. Practically speaking, the ICER has a probabilistic nature in light of the fact that the kinds of expenses and the benefit from every mediation pursue theoretical or observational distributions (Briggs, Sculpher and Claxton 2007). Moreover, the presentation of another intercession into the health framework involves accepting certain risks, so this sort of investigation is demonstrated for dealing with the vulnerability related with those alternatives. PSA considers the mean value, the standard deviation, and the distribution of every variable, making thousands of results under computer simulation by choosing arbitrary cases dependent on the characterized suppositions. (The Golden Helix Foundation n.d.) Given that all parameters stay viable, probabilities should dependably stay somewhere in the range of zero and one, while expenses can never be negative. The model runs and the software "picks out" one value for every parameter and reports the model's outcomes. In the event that the model is, at that point run an extraordinary number of times (sometimes, more than 100,000 'repetitions'), the outcome and variation in results are recorded each time. (O'Hagan, Stevens and Montmartin 2000) A cost-effectiveness scatter plane is commonly utilized to display the outcomes, where, as the Figure 1.5. shows, every repetition is plotted on a graph appearing the incremental cost and effectiveness of the particular mediation. (Taylor and Filby 2009)

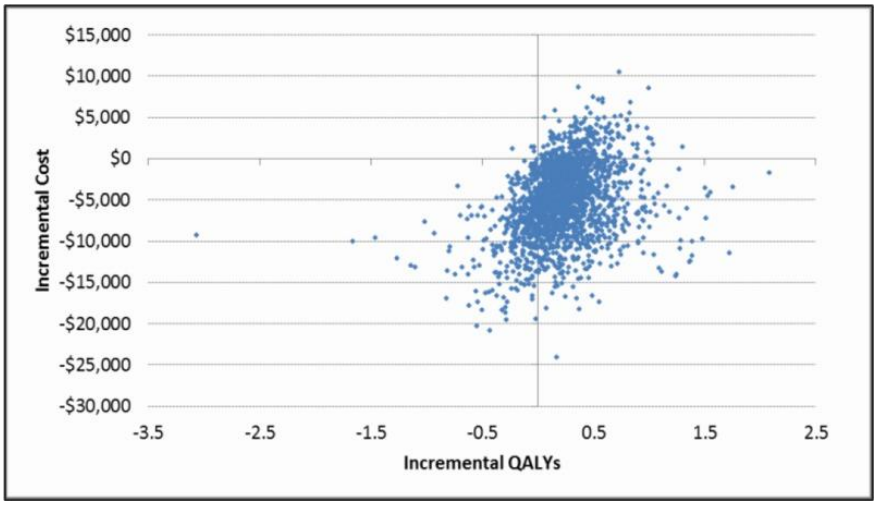

Figure 1.5. Scatter plot.

The cost-effectiveness acceptability curve is then derived from the cost-effectiveness plane and demonstrates the probability that the ICER lies underneath a specific threshold (ceiling), which speaks to a benchmark against which to survey whether the intercession can be viewed as speaking to value for money (Figure 1.6.). There are clearly various issues affecting the utilization of such unequivocal approaches to informing what treatments are made accessible, a large number of which are disagreeable and disputable. (Fenwick, O'Brien and A 2004)

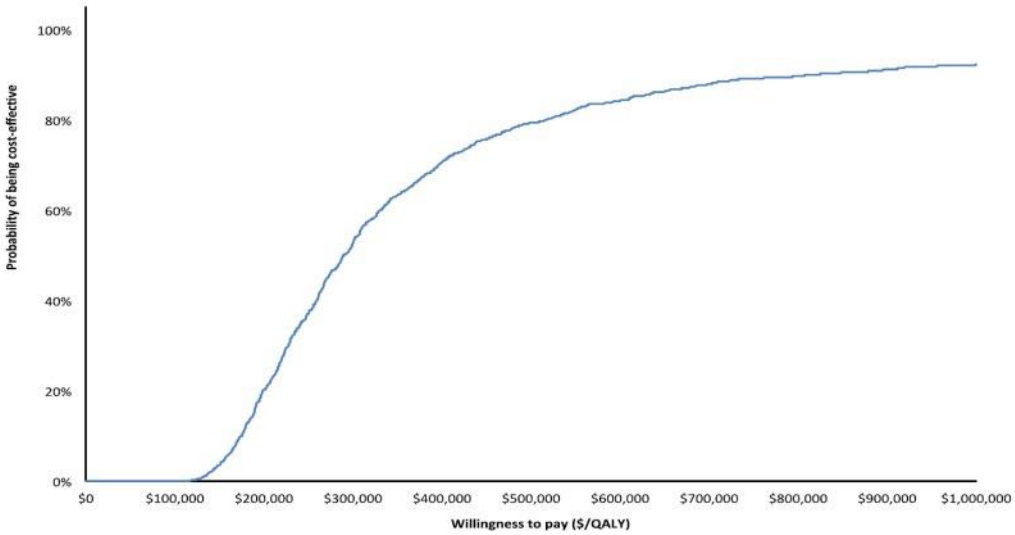

Figure 1.6. CE acceptability curve.

As therapeutic, hereditary, and pharmacologic sciences meliorate, our desires for significant treatments (and worries about expanding costs) are increasingly more liable to be figured out. With the assistance of creative thinking and cooperation of payers, health technology assessors, manufacturers, policymakers, patient groups, health economists, and outcomes researchers, empowering advancement which meets critical unmet medical needs, while moderating its large economic weights, might be a realistic objective. (Barton, Briggs and Fenwick 2008)

CHAPTER 2: PHARMACOGENOMICS

2.1 Introduction

Novel treatments are being continuously brought forward, as drug discovery and healthcare get an orientation toward both personalized medical treatment and curative therapies for chronic and genetic diseases. On one hand, these novel treatments have provided more and better options for patients, on the other hand, though, the expenses on a per patient basis are higher, not only for use, but also for development. A negative scenario would be the treat of the sustainability of these innovations caused by potential systemic budgetary pressures. Cost measurement of specialty drugs, for orphan diseases and cancer for example, require the assessment of a host of factors. Complications as far as manufacturing these drugs, distributing them, using unusual resource intensive handling or dispensing procedures, and administering them in complicated dosing regimens are often to appear. Moreover, their minimal generic substitutions available and the smaller patient populations that they refer to, bring high fixed costs of development and manufacturing for fewer patients. They may also require monitoring, additional services, related diagnostics, risk evaluation, increased focused clinical management, mitigation strategies, entail complicated billing with increased prior authorizations, have adherence issues that impact outcomes, and have limited distribution networks. When trying to reconcile these cost measurements with value and near-term affordability ratios, major challenges can be created. (Willke and ISPOR 2018)

With the initiating driver of value being health gain, when considering treatment options, informed patients take into account uncertainty. The use of complementary diagnostics, for example, and especially a genetic test, to reduce uncertainty of diagnosis and target treatment can give patients peace of mind. They may be more willing to receive treatments with side effects under these circumstances. (Louis, Kamal-Bahl and Towse 2017)

2.2 Precision Medicine

The genetic variants that affect health are divided into two categories. The variants occurring frequently in the general population but only with a subtle impact on health belong to the first category and raise the risk of a particular adverse health effect by only a modest amount, which geneticists do not yet know how best to aggregate, in

order to predict overall risk. Whereas these variants tend to have little utility in most clinical settings, those ones that are found rarely in the population but that dramatically increase the risk of a health disorder, belong to the second category. In these cases, the knowledge gained from genomic information can be useful for preventing or treating diseases, using the relatively "blunt tools" of modern medicine, such as bilateral mastectomies, annual colonoscopies, or drugs that can have substantial side effects. Where there is a genetic aetiology behind a patient's disorder, genomic diagnostics' tangible benefits involve giving information to people about their conditions that can be used to guide treatment or prevention measures. Many people are in need of a diagnosis, even if no treatment for a condition is available. Many people are also in need of ending the "diagnostic odyssey", going from physician to physician, trying to find out what is wrong with them and thereby hope to reduce anxiety and save resources. This information can also lead, in some cases, to reproductive decisions and direct preventive strategies for family members who may also be at risk. (Berger and Olson 2013) Nevertheless, the application of whole genome sequencing could be useful in a limited number of cases, such as children with multiple malformations, familial disorders passed among multiple generations, progressive neurological disorders, and patients with unusual presentations, such as cancer at a young age. Most common diseases, though, such as hypertension or diabetes, have multiple causes, including factors such as diet, exercise, smoking, the environment, and the contribution of any one genetic variant is small.

Diseases are also characterized by diversity, in a similar way as individuals are. Therefore, when comparing identical therapies, there is no guarantee that they will have the same therapeutic effect. A significant advantage in preventing, prognosing and treating a disease in a more effective way, is the enriched knowledge regarding the molecular aetiology of a variety of human genetic diseases. According to Hippocrates of Kos (460–370 B.C.E.) "…it is more important to know what kind of person suffers from a disease than to know the disease a person suffers". Hence, if two individuals suffer from the same disease and follow the same treatment, taking the same drug in the same drug dosage, they might present differential effect, with the one fully treated or with the appearance of adverse reactions or even any beneficial effect. These adverse reactions, possible toxicity events or even an ineffective treatment can favour the deterioration of certain patients' diseases, but also lead to increased treatment costs. Hundreds of deaths due to adverse effects or hospitalizations for drug-related side effects, which cost the national health systems billions are caused due to the lack genetic information, by a remarkable percentage. The genetic variation

between individuals has brought increased knowledge in precision medicine that may potentially help towards the appropriate treatment. The limited resources in healthcare systems have made the justification of current spending and future investment in public healthcare system seem of the utmost importance.

According to the Precision Medicine Initiative, precision, or personalized, medicine is "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person.". Clinicians are better equipped to predict which treatment and prevention pathways should be followed by different groups of people in a more accurate way using this approach. On the basis of the genetic characteristics of each individual, modifying protocols that maximize the benefit and minimize the toxicity can be produced with the assistance of personalized medicine. Certain treatments with beneficial effects can be evaluated in terms of improved quality of life and survival extension or measured in terms of a clinical marker.

A fundamental part of precision medicine is Pharmacogenomics, which studies the genetic aetiology resulting to differential drug response among the population. Medicines work differently among individuals and Pharmacogenomics' aim is to increase our understanding in regards to that way, based on genomic contributions to a medicine's safety and efficacy. (Squassina , et al. 2010). Hence, diversified and targeted diagnostics and therapies could come of pharmacogenomics, which, when used together, could yield broader health benefits to society.

Genomic variations have specific effect on drug response, as far as drug metabolism (pharmacokinetics) and drug action (pharmacodynamics) are concerned, which are studied by Pharmacogenetics. In addition, it has been shown that idiosyncratic adverse drug events (ADE) are potentially explained by genetic variants and as a result, pharmacogenetics could be responsible for the administration of the most suitable medicine for a specific clinical occasion when the related patient population has a particular genotype. That field enables the scientific community in modern medicine to manage the observed responses to drug medications, taking into account the fact that the genetic factors are responsible for the account for 20-95% of them. It is worth mentioning, though, that independent of, in conjunction with or in addition to genetic factors, other aspects such as age, food intake, drug interactions and co-morbidity affect an individual's drug response. Pharmacogenomics is a more extensive term meaning to deliberately evaluate the way genomic pathways influence malady vulnerability, pharmacological capacity and drug disposition and response. It

not just intends to recognize genomic biomarkers for infection characterization, organizing and analysis, inside the setting of medication reactions yet additionally to advance medication disclosure with the objective to accomplish an increasingly alluring pharmacological reaction. These days, the expression "pharmacogenomics" is more extensive used to cover the majority of the abovementioned and it impacts both new and existing meds. It is relied upon to majorly affect the interpretation of beginning period ventures into medicinal medications.

Personalized medicine should extend to disease prevention by recognizing genetic predisposition and by appropriate nutritional or other interventions in peoples' lifestyle so as to reduce the need for toxic therapies contributing to the improvement of health in developing and developed countries. As a promising research field, personalized medicine can promote health while simultaneously it can rationalize the costs and congestion of the health system by reducing the time of hospitalization. In addition, personalized medicine can accelerate the approval of new treatments by reducing the duration of clinical trials from 10-12 years to 3-5 years due to target patient recruitment (companion diagnostics).

The sequencing of the human genome and the recognizable proof of connections between explicit hereditary variations and illnesses have prompted huge fervor over the capability of genomics to coordinate patient treatment toward progressively powerful or less hurtful mediations. All things considered, the utilization of entire genome sequencing difficulties the conventional model of medicinal consideration where a test is requested just when there is a reasonable sign for its utilization and a way for downstream clinical activity is known. This has made a strain between specialists who fight that utilizing this data is untimely and the individuals who accept that having such data will engage social insurance suppliers and patients to settle on proactive choices in regard to way of life and treatment choices. Genomic testing may have important implications for people with some diseases, such as familial disorders or progressive neurological diseases and for healthy people, genomic data are unlikely to have much effect on assessing the risk of common diseases. By and by, genomic screening could be utilized to discover the moderately uncommon people in a populace who are at high danger of preventable infection, pre-emptively distinguish genetic variations that impact the effects of medications, give extra data to screening of new-borns, and illuminate an assortment regarding conceptive choices. Genomic testing ought to be seen as another accessible test and possibly utilized when and if the circumstance warrants. Additionally, some stakeholders are concerned that genomic technologies will add costs to the health care

system without providing commensurate benefits, and others think that health care costs could be reduced by identifying unnecessary or ineffective treatments. Financial models are much of the time used to envision the expenses and advantages of new medicinal services advances, approaches, and guidelines. Economic models additionally have been utilized to inspect significantly more explicit issues, for example, looking at the results and cost-effectiveness of two distinctive drug treatments for a similar condition. These sorts of examinations offer something other than forecasts of future human services costs. They give data that is significant when actualizing and utilizing new innovations. Unfortunately, in any case, these financial evaluations are regularly constrained by an absence of information on which to base the examination. This especially influences health economics, which incorporates numerous variables for which current techniques are lacking for surveying, for example, individual utility, social utility, and patient inclination. (Berger and Olson 2013)

Pharmacogenetics (PGx) contemplates the connection between genetic variation and between individual changeability in medication reaction as far as efficacy and wellbeing. Consequently, PGx learning can be utilized to tailor pharmaceutical treatment to the hereditary make-up of the patient. Customizing drug medications through PGx testing could improve their efficacy and security, just as diminish costs. In any case, as health care resources are finite, it is significant that the cost-effectiveness of novel PGx-guided treatment methodologies is surveyed notwithstanding their clinical utility before they are broadly connected. Economic evaluations, which think about expenses and results of in any event two contending intercessions, are a helpful apparatus to educate basic leadership and organize medicinal services spending. With regards to PGx testing, a pharmaco-economic study may balance PGx-guided treatment with standard treatment (ST) with a similar medication, or with an elective medication that does not require genetic testing, or with the two choices. At the point when the PGx procedure is observed to be increasingly viable at a satisfactory extra cost (financially savvy) or progressively viable at a lower (cost-sparing or overwhelming), this gives a solid contention to the execution of PGx testing. The fuse of genomic sequencing into medication will, at that point, depend not simply on the falling expenses of genomic screening yet additionally on the worth that genomic sequencing gives.

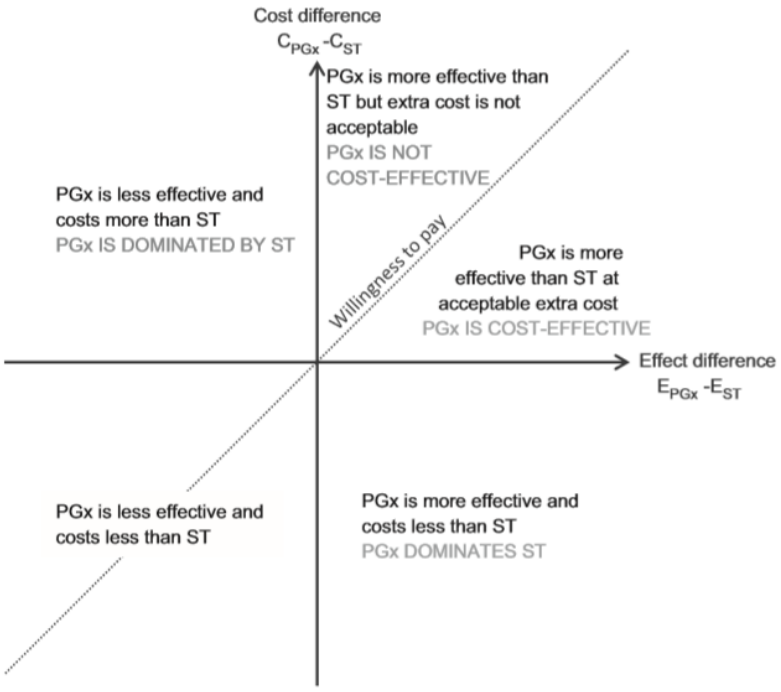

Figure 2.1. Cost-effectiveness plane of pharmaco-economic studies.

The incremental cost-effectiveness ratio (ICER) condenses the distinction in costs and health outcomes between a PGx-guided strategy and ST:

ICER= Cost of PGx -Cost of ST/ Effect of PGx -Effect of ST

On the off chance that the PGx treatment diminishes costs and accomplishes a superior result than the ST, at that point the PGx methodology commands the ST. Conversely, if the PGx alternative costs more yet is less viable than the ST, at that point the PGx treatment is ruled by the ST. When one treatment comes at greater expense but at the same time is more effective than the other, the ICER is contrasted with a willingness-to-pay threshold to decide cost-effectiveness. (For the most part, ICERs up to £20000– £30000 per QALY (or $30000–$50000 per QALY) are viewed cost-effective.) As costs, health outcomes and willingness-to-pay thresholds vary between nations or may contrast as indicated by the suspicions and viewpoints received, economic studies assessing the equivalent PGx test may arrive at various resolutions. (Berger and Olson 2013)

2.3 Challenges of Genomic Medicine

In spite of the fact that the most recent years it has been gained an extraordinary ground towards customized medication in the scientific community, there are as yet different difficulties and snags to defeat so as to apply pharmacogenomics in future medicine and endeavor its advantages for the general public. (Berger and Olson 2013)

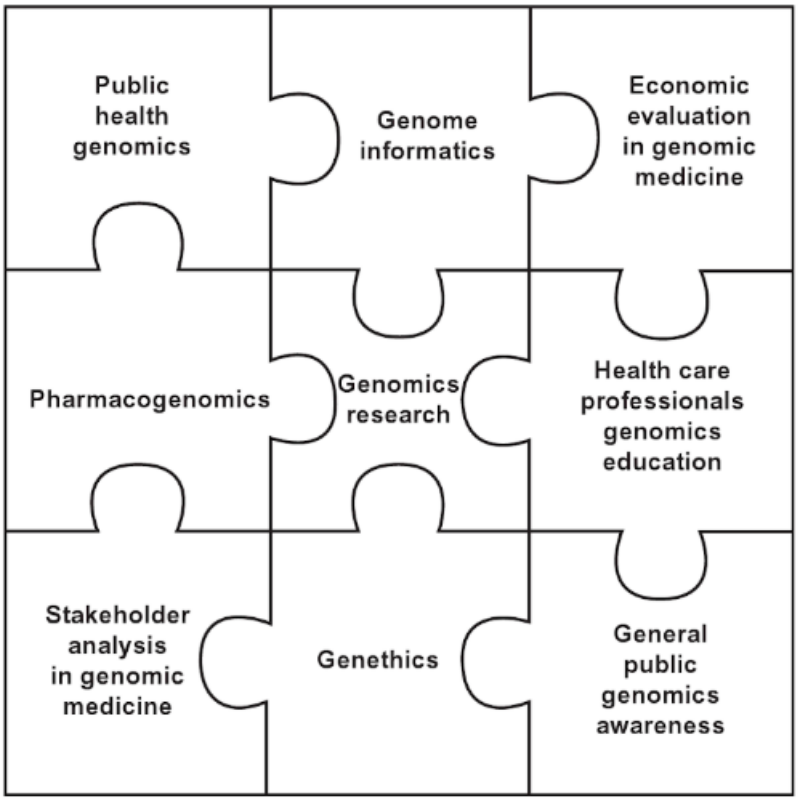

Figure 2.2. The different disciplines that establish the multidisciplinary field of genomic medicine.

2.3.1 Education of health professionals

One of the significant advances that ought to be taken, is the high-level training of health-care professionals associated with the medical specialties that can be productively connected in pharmacogenomics. It is of great importance, to fill the hole between the pharmacogenomics testing as such and the translation and usage of its outcomes in a clinical setting, otherwise called as translation of genomic results into patient care (Patrinos 2010). In this structure, a few worldwide associations have proposed the consolidation of pharmacogenomics and personalized medication

courses in center medical educational module (Gurwitz, Weizman and Rehavi 2003). The educational program of a few medical, pharmacy and health science schools routed to undergrad and postgraduate understudies are dynamically refreshed with such courses. In addition, the dire need to fuse genetic and pharmacogenomics education into medical and pharmacy schools has been inspired by testing the moral ramifications of personalized medicine (Frueh and Gurwitz 2004).

In parallel, public health genomics studies have effectively centered around assessing the point of view of health-care professionals and overall population about pharmacogenomics and genomic medicine. These studies can prompt the foundation of the legal framework in regard to the genetic testing administrations, the security of residents' interests and lastly the forming of the general genomic medication arrangement condition. As indicated by the studies, the general public requires from health care professionals an exhaustive and certain clarification of the genetic test alongside a reasonable understanding of its implications for prescriptions. In any case, the study members outlined the hole between the patients' exclusive requirements and medicinal services experts' knowledge (Mai, Koromila, et al. 2011). Then again, it merits referencing that both stakeholders have an inspirational frame of mind towards genomic medicine. (Mai, Mitropoulou, et al. 2014) In comparable studies led in Japan, the participants (the scholarly world, human services experts, industry and government) communicated similar desires and comparable concerns with respect to the poor genetic open mindfulness and the likelihood of breaching privacy (Tamaoki, Gushima and Tsutani 2007).

2.3.2 Demonstration of clinical utility

So as to actualize another innovation into clinical practice, it ought to have clinical utility. In a straightforward way, in light of vigorous proof the advantages of the new innovation should exceed the dangers. In its tightest sense, clinic utility alludes to the capacity of a screening of diagnostic test to anticipate or improve adverse health effects, for example, mortality, morbidity or disability through the appropriation of useful medications on the state of test outcomes. Otherwise, the lack of guidelines in genomic medicine lead to absence of integration into practice. The absence of proof in the territory of pharmacogenomics has been compensated by the CPIC guidelines. (Holtzman, et al. 1997). The majority of the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) working group has featured the absence of clinical utility proof with respect to genetic testing and subsequently can't suggest in support of the utilization of a given genetic test for a specific characterized reason.

2.3.3 Health care costs

Another rule vital for selection of pharmacogenomic testing in a clinical setting is the cost-effectiveness. Thusly, aside from its clinical utility a pharmacogenomic test ought to likewise be cost-effective (Deverka, Vernon and McLeod 2010). A couple of past reports have appeared certain pharmacogenomic-guided drug treatments identified with psychiatry (Perlis, et al. 2009), malignant growth (Carlson and et al. 2009) and chronic inflammatory diseases (Priest and et al. 2005) demonstrated to be cost-effective. An average precedent is a study of Perlis et al. where the selection of a certain pharmacogenomics test for antidepressant efficacy was useful and cost-effective for a major depressive disorder (Perlis, et al. 2009). By then, it ought to be referenced that the frequencies of the pharmacogenomics markers may considerably fluctuate among various populations and this significant factor ought to be tended to in the various studies.

Besides, the distinctive reimbursement approaches of the different health care systems have diverse consequence of the health care costs identified with genomic medicine (Mette, et al. 2012). For instance, nations with public health and insurance system are increasingly inclined to envision the scattering of pharmacogenomics (Ginsburg and Willard 2009). Then again, in nations like the US, portrayed by strictly private health and insurance sector different groups have the chance to settle on various choices notwithstanding when face with a similar proof. All in all, the results of pharmacogenomics and customized medicine can be a profitable device for health care decision-makers as they can successfully expand the quality of the clinical care and the financial advantages for public wellbeing in spite of the way that pharmacogenomics tests for specific ailments/medications might be more cost-effective than cost-sparing (Deverka, Vernon and McLeod 2010) (Flowers and Veenstra 2004) (Mette, et al. 2012).

2.3.4 Insurance and Privacy issues

Considering the way that pharmacogenomics and genomic medicine emphatically depend on between individual genomic changeability, these orders need to manage various issues identified with genetic stigmatization and discrimination, privacy and potential ramifications for access to life and medical coverage. In the United States, the Genetic Information Nondiscrimination Act of 2008 ensures against

separation in medicinal insurance and in the working environment, however no such securities exist for long haul care, disability or life insurance. Across the board genetic testing represents the risk of allelism—that individuals will be characterized by their genetic sequences and by the characteristics those sequences produce as opposed to by the characteristics that really matter in an individual. Around 20 percent of the human genome has patent cases, which implies that entire genome sequencing has the capability of being translated as violating various licenses. Boundless testing would present security issues on the grounds that genomic data is advanced and would be anything but difficult to convey. Individuals who volunteer for genetic tests can end up feeling upset, for instance, on the off chance that they discover that their genomic data is the property of a privately-owned business.

In an overview directed in 1998 among the individuals from the National Society of Genetic Counselors (NSGC) Special Interest Group (SIG) with respect to malignant growth, half of the members expressed that they are not willing to charge their insurance agencies for genetic testing because of conceivable hereditary separation (Matloff and et al. 2000). Notwithstanding, a later comparable review led in 2007 delineated that the cancer genetics professionals (CPGs) changed recognition after some time and the dread of hereditary segregation is essentially less regular than in 1998.

In spite of the fact that the previously mentioned overviews allude to generally genetic testing, utilization of pharmacogenomics testing can prompt hereditary trashing/separation (Robertson 2001) (Issa 2002) as an individual can be named as great, poor or non-responder to a specific treatment. These names could lead the pharmaceutical organizations to overlook patients with uncommon or complex genetic condition in the purpose of financial advantage. Procedures like this would prompt ensuing hardship of successful treatment for specific subpopulations (Rothstein and Epps 2001).

Additionally, a similarly significant issue that may raise concern, especially in the entire genome sequencing time, is the capacity of genomic data in databases with the innate risk of losing classification or privacy, since a gigantic amount of genotypic, phenotypic and statistic information in regards to people are between related (Vaszar, Cho and Raffin 2003). Along these lines, it is vital the consolation of security insurance and confidentiality.

To this end, assurance for security and confidentiality must be guaranteed, especially in the entire genome sequencing period, in light of the fact that

pharmacogenomic tests can convey a few sorts of auxiliary data that speak to a danger of psychosocial hurt and adverse insurance or employment implications. Additionally, specific subpopulation groups may confront hereditary separation when attempting to get to social or medical coverage (Smart, Martin and Parker 2004). The Health Insurance Portability and Accountability Act Privacy Rule, the Genetic Information Non-separation Act (GINA), and the Genomics and Personalized Medicine Act (GPMA) are for the most part authoritative endeavors in the United States attempting to address these inquiries, despite the fact that they frequently need clearness on basic issues with respect to interpretation of human hereditary variation from the seat to the bedside (Lee and Mudaliar 2009).

Healthy individuals have less to pick up and more to lose from any therapeutic intervention, including genomic tests. Assessing the risk of common infections through entire genome analysis of a healthy individual has gotten the most consideration, yet this attention "is to some degree lost". As of now, evaluation of genetic risk alleles has "rather weak predictive power" in light of the fact that the expanded dangers will in general be little. Moreover, few data recommend that learning of one's genomic status is successful in changing conduct and, regardless of whether it is, genomic information additionally could be a double-edged sword, if people do without solid eating regimens and exercise as a result of an apparent diminished danger of building up an ailment. (Berger and Olson 2013) A conceivable utilization of genetic testing in sound individuals is finding the moderately uncommon people in a populace who are at high danger of preventable diseases, what has been called as "newborn screening of adults." Risk evaluation will dependably be most important when the recognized risks are high.

Another huge test is that the genome cannot be easily predicted, and it isn't really a friendly place. For certain individuals, entire genome sequencing will reveal things they were not searching for and might not have any desire to know. A few people will find that they are at high hazard for untreatable and awful conditions, for example, deadly familial insomnia, Huntington's disease, or early beginning Alzheimer's disease. The potential for returning data when there is no medicinal move that can be made is a significant externality in choosing whether to do whole genome sequencing on everybody. Furthermore, various individuals will settle on these choices in an unexpected way, and these choices are considerably progressively troublesome when parents and kids are included. (Berger and Olson 2013)

2.4 Factors influencing CEA in PGx

Flowers and Veenstra (Flowers and Veenstra 2004) built up a system for components that could impact cost-effectiveness in pharmacogenomic testing. Significant elements incorporate the penetrance and prevalence of the genetic variation, the expense and precision of the test, the prevalence of the infection and the results whenever left untreated, and the effectiveness and cost of treatments.

	Factors to Assess	Features That Favor Cost-Effectiveness
Gene	Prevalence	• Variant allele is relatively common
	Penetrance	• Gene penetrance is high
Test	Sensitivity, specificity, cost	• High specificity and sensitivity • A rapid and relatively inexpensive assay is available
Disease	Prevalence	• High disease prevalence in the population
	Outcomes and economic impacts	• High untreated mortality • Significant impact on quality of life • High costs of disease management using conventional methods
Treatment	Outcomes and economic impacts	• Reduction in adverse effects that significantly impact quality of life or survival • Significant improvement in quality of life or survival due to differential treatment effects • Monitoring of drug response is currently not practiced or difficult • No or limited incremental cost of treatment with pharmacogenomic strategy

SOURCE: David Veenstra, IOM workshop presentation, July 17–18, 2012.

Table 1.1. Elements that impact the Cost-Effectiveness of Genomic Testing Strategies

2.5 Discussion on what has to be done

The financial aspects of genomic sequencing shift by application and by setting. A noteworthy inquiry is in this way how to outline and break down the financial issues. Values and costs can be estimated in various ways, and these strategies impact choices about the utilization of advances. Specifically, improved strategies are required for evaluating value, individual utility, and patient inclinations. A related confusion is that general wellbeing, clinical care, and academic medicine have diverse monetary evaluation models. These models must be adjusted such that has a different

effect to patients. Additionally, specific models will be pretty much helpful in the right now advancing health care environment. The infrastructure should be created to gauge results identified with economic factors alongside standard wellbeing results, for genomics as well as over the health care system. For instance, better and faster methodologies are required for performing monetary assessments of genetic and genomic tests and the results of examining specific genetic variations. Arranging tests and variations into classes that can be surveyed is one conceivable method for maintaining a strategic distance from the assessment of tests and variations one by one. The mix of economic investigations into ongoing entire genome sequencing clinical examinations is being considered in some showing tasks, however it could be a piece of all clinical studies. The economic motivations for test and proof development under the present arrangement of reimbursement versus a value based pricing approach that joins the intellectual cost of elucidation should be additionally investigated. On the off chance that health care resources are level or declining, and a conceivably inventive innovation is accessible, the topic of subsidizing genomic intercessions could be addressed considering the way that we ought not be paying for pricey, not especially efficacious things in lieu of certain things in genomics that really are efficacious and not excessively costly. If responsible care organizations give a model to delivering increasingly effective human services utilizing genomic advancements is along these lines to be replied. Health systems will require new techniques and a more grounded foundation, including informatics, to follow and investigate the downstream results of giving sequence data. As far as when ought to genomic sequencing be done during the life expectancy of an individual is concerned, potential outcomes run from having the total sequence available at childbirth to directing targeted sequencing at the time of diagnosis. If genomic results that are as of now accessible are bound to be utilized than results that should be acquired after the patient presents themselves, this brings up the issue of thresholds for the utilization and generation of proof. Knowledge picked up from new innovations may not be appropriate to all populations on the grounds that not all populaces are spoken to in research which could increase disparities in health care. Efforts ought to be put resources into deciding how new advancements could compound or enhance existing differences. In any case, recollect that this issue isn't explicit to genomics. (Berger and Olson 2013)

CHAPTER 3: COST ESTIMATION

3.1 Health Care Costs

In production, research, retail, and accounting, a cost is the value of money that has been used up to produce something or deliver a service, and hence is not available for use anymore. More generalized in the field of economics, cost is a metric that is totaling up as a result of a process or as a differential for the result of a decision. Hence cost is the metric used in the standard modelling paradigm applied to economic processes. (Stephen and Stuart 2007) It is important to stress at the start that cost, in monetary terms, isn't just concerned with the money related objectives. The expense of utilizing an asset in a specific service or treatment is, subsequently, not (necessarily) the price that is paid for that asset, yet the benefit foregone (the opportunity lost) by not choosing the alternative.

The market, in financial terms, involves a demand side – in light of purchasers' needs and wants, bolstered by a capacity to pay for the specific commodity, and a supply side – in view of producers' aim to create profit, and the interaction between them. Markets work as per price signals, that is, if costs change, demand and supply will acclimate to a position where producers will most likely sell all that they need at that cost, and consumers will almost certainly buy all that they need at that specific cost. Thus, if levels of demand and additionally supply modify, the cost will acclimate to reflect such changes and move to a position where demand and supply are again equivalent. Defenders of the market framework accept that its 'invisible hand' will bring about an allocation of resources that will maximize the benefits to society, known as Pareto-efficiency. While the goal of trying to maximize the benefits to society, given the degree of resources accessible, shows up from the start sight to be impeccably substantial and praiseworthy, there are various different issues that encroach on the quest for such a target. The discipline of economics is established on the reason that there will never be sufficient assets to totally fulfil human wants, alluded to by business analysts as scarcity. This idea is major to everything else in economics.

The social welfare function has two individual segments, efficiency and equity. The term efficiency is utilized by financial analysts to consider the degree to which decisions identifying with the allocation of limited resources maximizes the benefits for society and has been characterized as 'maximizing well-being at the least cost to society'. (Mitton and Donaldson 2004) The idea of efficiency grasps inputs (costs) and

outputs as well as outcomes (benefits) and the connection between them, with a society being judged in efficiency terms by the degree to which it augments the advantages for its populace, given the assets at its disposal. (C. Phillips 2005)

Health care costs are the genuine expenses of providing administrations related to the delivery of health care, including the expenses of procedures, treatments, and medications. The term is separated from health expenditures, which alludes to the measure of money paid for the services, and from fees, which alludes to the amount charged, regardless of cost. It has frequently been expressed, inaccurately, that health economics is tied in with setting aside money and lessening expenditure, supporting the idea that cost is only concerned about budgetary goals. All things considered, health market analysts would not be evaluating mediations and medicines that prolong life, or those that try to avert death, as far as their relative cost-effectiveness, as they would be just worried about spending less and concentrating on projects and strategies that improve monetary spending plans instead of targeting to the wellbeing of patients. In absolutely monetary terms, the least expensive patient is a dead patient, but in reality, the expense of a specific service or treatment is not really the value that is paid for that asset, however the opportunity lost by not picking the alternative. (C. Phillips 2005)

The measurement and comparison of costs and health outcomes is essential in a pharmacoeconomic study. (Phillips and Anderson 2009) Since costs are seen differently from different points of view, in economics the notion of cost is based on the value that would be gained from using resources elsewhere – referred to as the opportunity cost. Resources used in one programme, in other words, are not available for use in other options, and, as a result, the benefits that would have been derived have been sacrificed. In practice, it is usual to assume that the price paid reflects the opportunity cost, and to adopt a pragmatic approach to costing and use market prices wherever possible. The primary requirement for conducting a CEA is that the alternatives studied must have primary, measurable effects on one clear clinical outcome parameter, as treatment outcome is expressed in terms of achieving this primary outcome. In general, cost-effectiveness depends on the value placed on a health outcome relative to its cost. (Phillips and Anderson 2009) This requirement restricts the use of CEA compared to cost-benefit analysis because in cost-benefit analysis treatment outcomes for disparate programs are quantified purely in monetary terms.

Whereas costs are naturally expressed in monetary units, a healthcare intervention's effect can be expressed in different ways. Unlike cost-benefit analysis, cost-effectiveness analysis does not place a dollar value on human life or health. CEA includes valuation of life in nonmonetary terms, in the form of units of effectiveness. CEAs evaluate the effect of an intervention in terms of a disease or treatment specific measure, for example the number of adverse events avoided, the lives saved, the decreases in blood pressure, the change in score on a depression rating scale or time taken to remission. Results of CEA are afterwards expressed as a cost-effectiveness ratio, such as cost per case cured, cost per life saved, or cost per infection avoided. Cost-effectiveness as a term implies value for money, meaning neither the most effective therapy, nor the drug having the lowest acquisition cost necessarily the most cost effective. Rather, the relative costs and consequences of each alternative must be examined together when determining the most cost-effective option.

Cost-utility analysis (CUA) is a special form of CEA, where the scope of effectiveness is broadened by assessing the impact of an intervention on patients' functional status, health status, or health-related quality of life by including a utility in the analysis. Health outcomes are assessed, in CUAs, as quality-adjusted life years (QALYs), which measure the expected number of post-treatment years of life accounting for the quality of life. QALYs allow comparisons of treatment strategies across therapeutic areas and populations, though, they are an abstract concept ('quality' is hard to define) and their validity has been questioned. As with all economic evaluation techniques, the aim of cost effectiveness analysis is the maximization of the level of benefits – health effects – relative to the level of resources available. (Lee, McLaughlin-Miley and Chatterton n.d.) Moreover, the perspective of a pharmaco-economic study determines which costs and benefits are taken into account. These can be limited to costs to the public health-care system or private insurers, for instance, staff salaries, drugs and equipment costs, or may include broader costs such as productivity losses and informal care. Commonly used perspectives are the third-party payer and societal perspective, whereas some studies take a hospital or patient one. (Verbelen, Weale and Lewis 2017)

There are basically three stages involved in the process of costing health care services and interventions:

1. identification of costs,
2. measurement of identified costs and

3. their translation into a monetary amount, bearing in mind that money may not always be the most representative indicator of opportunity cost.

3.2 Cost Determination-Study Perspective

The study perspective is a key factor when determining the cost categories that will ultimately be involved in the analysis and each perspective refers to the institution for which any economic consequences from the alternative therapeutic interventions are valued (Muenning 2008). A distinction between the direct and indirect costs or productivity costs, as well as the definition and inclusion of what are termed intangibles, is conventional when conducting a CEA. The intangibles may be difficult to quantify but are often consequences of the intervention and should be included in the cost profile. Attention must be paid in the specification of the costs included in a cost-effectiveness analysis, so as to ensure that the findings are not subject to misinterpretation. (The Golden Helix Foundation; n.d.)

The costs are divided in the following categories (Phillips and Anderson 2009):

• The direct costs, which depict the actual cost consumed for the intervention and health care process and can be subdivided into:

- The direct health care costs which health care suppliers cause and include the total expenditures for monitoring, treatment, diagnostic tests, medication, etc., that come as a result from the treatment.
- The direct non-health care costs, that is the 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.).

• The indirect costs, namely the financial losses due to the presence of the disease, without considering the costs for providing treatment. If the patient had not become sick, he/she could have been engaged in normal daily activities and could have produced an accountable value of goods, which are the indirect ones. The loss of productivity because of the disease, either because of work absenteeism or because of reduced productivity (presentism) or even due to premature death, the free time, time expended by relatives providing assistance, and other time lost are all examples of indirect costs.

• Intangible/invisible costs describe difficult-to-measure consequences of the disease and its treatment and appear due to the pain, discomfort, anxiety, reduced quality of life (QOL), or other social or moral consequences of the disease, or its treatment.

In economic evaluation, the cost of an intervention refers to the “total resources” expended to treat the disease, from the concerned institution’s perspective, and is not limited to the cost of a specific technology (e.g., the price of the drug) being valued against an alternative. As we move to broader analyses of the consequences of the disease, this cost can increase considerably. When talking about treatments in oncology and cardiology, for instance, which 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, a misleading solution is a simple comparison of the price of two drugs. This method does not take into account the effect their administration has on the overall burden to the system through utilization of all the relevant resources, such as hospitalization days and medication given to treat toxicities. Disputes come up when selecting the cost variables that should be included in economic evaluation, since possible variability in the cost categories will result in incomparability between different economic evaluation studies. Hence, various guidelines have been developed, after discussing about costs, with the aim of achieving consistency. (The Golden Helix Foundation n.d.)

3.3 Costs in Genomic Medicine

The costs of each medical intervention comprise the foundation of every monetary assessment. As opposed to cost information utilized in classic economic evaluation, in genomic medicine there is frequently vulnerability with respect to which expenses ought to be gathered, the time that they ought to be gathered, and how expenses shift between various research centers and health care systems. (The Golden Helix Foundation n.d.)

There is an assortment of variables that lead to this issue. For instance, in the United States, reimbursement for genetic tests has been founded on a "stack" of system-based codes (e.g., DNA extraction and purification, amplification, sequencing and so on). Different laboratories could utilize various strategies to produce results, implying that the equivalent genetic test can have particularly various costs and reimbursement because of the particular strategy that was utilized.

Another issue is that a germline genetic test outcome does not change through the span of an individual's lifetime and in this way could be utilized on numerous occasions for consideration choices. A case of this is the pharmacogene CYP2D6, which is assessed to be engaged with the oxidative metabolism of 25% of the medications utilized in patient care (Samer, et al. 2013). How might one play out a CEA for CYP2D6 if the skyline is the patient's life expectancy?

In genomic medicine, there are direct and indirect costs that ought to be mulled over for financially assessing a genomics-related intervention, with the direct and indirect costs of the genetic test including:

- Patient recruitment, test accumulation (blood, saliva, buccal swabs and so on)
- Nucleic acid isolation
- Genetic testing, including amplification and purification
- Nature of genomic variation tried (germline versus somatic)
- Data examination, including data storage and investigation, utilizing informatics solutions and genomic databases
- Frequency of data analysis (based on novel genomics research findings)
- Accreditation, Quality Control of genetic testing stages and measures
- Genetic advising and results correspondence (with doctors and patients)
- Post-testing activities (counting treatment alternatives, follow-up testing, observing, and so forth.)
- Training of work force, health care professionals
- Infrastructure obtaining and support

When conducting a cost estimation for a genomic related intervention, direct costs include:

- Hospitalization
- Medications received by the patient
- Management of the adverse events
- Laboratory tests
- Operations
- Genetic test

what's more, the indirect costs of a genomic related intervention include:

- Patient’s productivity loss

- Family costs (travel, settlement, efficiency misfortune) (David, et al. 2015) (Faulkner et al 2012)

Those expenses ought to be likewise joined by the costs gathered by the medical interventions directed by the genetic test outcomes, for example, expenses of treatment (from which the expenses from the adverse medication reactions and follow-up tests avoided because of the genetic testing ought to be deducted). The last expenses can be critical. For instance, a focused-on resequencing or a microarray-based methodology, the two of which are really costly tests on an independent premise, to recognize the genetic premise of an uncommon mental disorder could be cost-effective if the expenses for follow-up testing can be kept away from. In the instance of chronic hepatitis C, even a little augmentation of progress due to a genomic intervention can be cost-effective, if the results of treatment disappointment (end-stage liver sickness hepatocellular carcinoma) are all around exorbitant (Bock et al. 2014). Another significant cost thing includes drug response and/or disease progression monitoring. On account of warfarin treatment in which observing, for instance, CYP2C9 genotyping, is moderately modest (Veenstra, Higashi and Phillips 2000), genomic interventions to individualize treatment may not be cost-effective. Now, it must be noticed that this probably won't be the situation in developing nations, where genotyping and follow-up treatment expenses may fluctuate (Mitropoulou C., et al. 2014). All things considered, genomic tests that are bound to be cost-effective are those for conditions for which observing is costly and awkward (Veenstra, Higashi and Phillips 2000) or when adverse effects and treatment failures that could be counteracted by the utilization of genomic testing are over the top expensive (Bock et al. 2014)

Unfortunately, there are not yet settled rules and reimbursement rates for genomic-based mediations and testing in light of the fact that the genomic innovations either are unreasonably new for repayment rates to have been set up, for example, whole-genome sequencing, or are incorporated as a feature of a cost thing for a whole treatment methodology, in which case expenses may fluctuate significantly relying upon the genetic testing research center cost strategy (Deverka, Vernon and McLeod 2010). The last contrasts might be the consequence of the utilization of either laboratory-developed assays versus commercially available accessible and quality-guaranteed genotyping packs or the variable costs among various nations. In the last case, it is significant that genome-guided warfarin treatment might be cost-effective in developing nations (C. Mitropoulou, et al. 2015) that don't have committed

anticoagulation monitoring centers yet not cost-effective in developed nations, which makes it troublesome if not difficult to sum up economic assessment results between various health care systems.

The nature of the genomic variation being tried is additionally a significant parameter that ought to be thought about in financial assessment studies relating to genomic medicine. Genomic variations might be either germline, in which case genomic testing should just be performed once during a patient's lifetime (de Leon, et al. 2009), or obtained/somatic, which now and again requires intermittent genetic examinations, as on account of chronic lymphocytic leukemia. Moreover, for new advances, for example, cutting edge sequencing, data analysis with its orderly expenses may should be rehashed more than once on the grounds that genomic information translation is every now and again refreshed with new genomics research results, taking into account novel genotype-phenotype relationships on data re-assessment.

Aside from the direct costs demonstrated already, there are additionally indirect costs, for example, the profitability costs (e.g., time lost from work) or the expenses for a patient to look for the best possible treatment, which mirrors the time that will be lost from work. To come back to the warfarin cost-adequacy precedent, despite the fact that the cost-effectiveness might be minor, as substantiated by (Meckley, et al. 2010), from the patient point of view having a few less INR estimations speaks to a noteworthy decrease in life interruption that, whenever measured, could affect the cost-effectiveness conclusion. Another precedent would be the utilization of a gene expression panel to stratify danger of repeat in endocrine receptor-positive, hub negative breast cancer patients to figure out which patients are less inclined to profit by subordinate chemotherapy dependent on a low repeat chance. These patients could forego chemotherapy with its attendant morbidity with an unassuming effect on cancer related results, supporting this as a cost-effective (or potentially even cost-sparing) intervention.

At last, education and training expenses are extra cost things in genomic medication financial assessment studies, in spite of the fact that these expenses might be hard to figure as well as model precisely as a result of the intricacy of genetic tests performed in a solitary instrument (e.g., real-time PCR or sequencer) or the economy of scale (various instruments working in parallel) that would contribute in decreasing the general analysis costs. (The Golden Helix Foundation n.d.)

3.4 Cost Analysis in Genomic Medicine

As indicated by the couple of accessible economic assessment studies in genomic medicine, it appears that no brilliant principle is as of now accessible, as opposed to most of financial assessments of traditional medical interventions that contemplate the immediate effect of a therapeutic intercession on the health care system and general wellbeing (Mette, et al. 2012). The data given by genomic investigation, especially entire genome sequencing performed very early throughout life, can have long haul effects that are not mulled over with traditional financial assessments. Consider distinguishing an α-synuclein gene variant prompting Parkinson disease in youthful asymptomatic patients. For this situation, old style studies neglect to gauge the long-haul combined expenses and impacts for such a patient. Additionally, the planning of an economic assessment study might be a similarly significant parameter on the grounds that the genetic testing expenses are quickly diminishing, while their explicitness and precision are consistently expanding. This reality may prompt patient subgroup stratification with direct effect on individualized medications, or the fuse in the clinical routine with regards to microarray-based genetic screening tests.

Cost-effectiveness of a particular genomic innovation as well as a genome-based mediation must be evaluated with regards to a particular clinical application including a specific patient subpopulation. In that capacity, when performing economic assessment for such an innovation or mediation, it is of most extreme significance to painstakingly recognize and choose the comparators. For instance, one ought to evaluate independently hereditary and non-hereditary testing notwithstanding surveying hereditary related to non-hereditary testing. In the last case, joining a shabby customary screening approach with a costly hereditary test may demonstrate to be cost-effective, as on account of consolidating immunohistochemistry with DNA sequencing, individually, for the recognizable proof of patients with Lynch disorder among recently determined patients to have colorectal malignancy (M. Mvundura, et al. 2010). On account of warfarin, the effect of non-genetic patient factors has at any rate as incredible an effect on warfarin dose as does the pharmacogenomics variations and, in that capacity, they are incorporated into warfarin dosing calculations. An investigation of warfarin dosing dependent on genomic factors alone contrasted with clinical factors alone would not be regarded safe, which is the reason all warfarin pharmacogenomic studies have contrasted a conventional dosing calculation and a conventional in addition to genomic calculation.

It is critical to painstakingly assess the suitable point of view from which the economic examination is performed, on the grounds that the outcomes will change contingent upon the stakeholder viewpoint that is picked. Albeit most cost-effectiveness studies are done from the societal point of view, the utility of the outcomes for a given partner viewpoint might be restricted dependent on the health care environment of the stakeholder. (The Golden Helix Foundation n.d.)

3.5 Cost Analysis in other studies

- A pharmacoeconomic model was developed to evaluate whether pharmacogenomic (PGx) guided warfarin treatment of elderly ischemic stroke patients with atrial fibrillation in Croatia is cost-effective contrasted with non-PGx therapy (C. Mitropoulou, et al. 2015). The time frame of the model was set at 1 year. Only direct healthcare provider costs reimbursed by the payers were considered, in particular costs which are related straightforwardly with the care of patients and mirror every one of the assets expensed in conveying the medications under investigation and dealing with any unfavourable occasions inside the health care system of Croatia.

The pharmacoeconomic model was a decision tree (Figure 3.1.) constructed in a TreeAge Pro Suite 2013 and was populated with cost data from Croatia public tariff lists, in accordance with current treatment rules on patient administration, results and monetary outcomes. Contrasts related uniquely to the expense of the assets 'expended' at each comparing node of the model and the corresponding transition probabilities, for instance, in the event of significant bleeding costs incorporated extra days in hospital, CT scan, extra tests for INR, frozen plasma and vitamin K, drug medications, endoscopic interventions in the event of gastrointestinal bleeding.

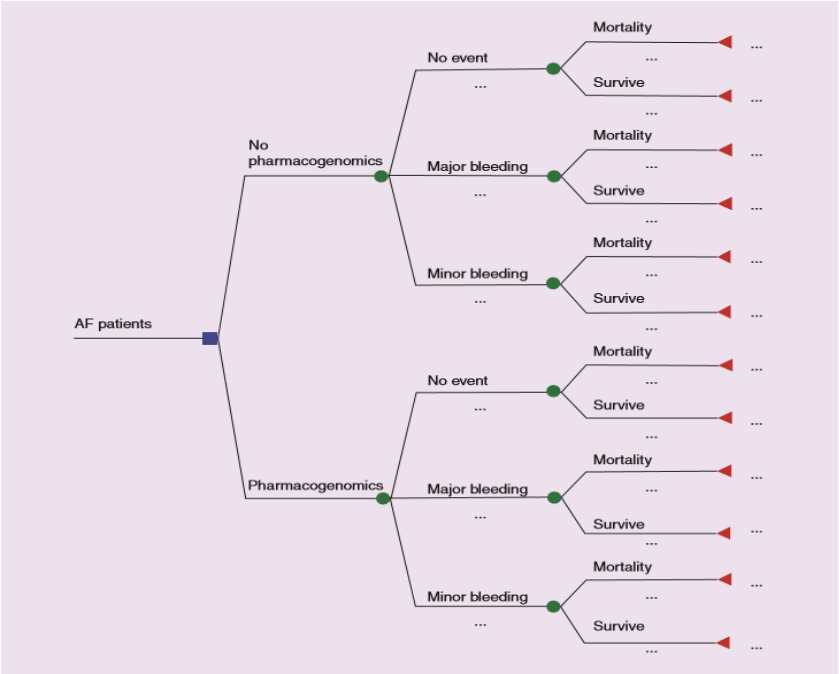

Figure 3.1. Decision tree (C. Mitropoulou, et al. 2015).

The model simulated the progression of patients from the moment they began treatment, to different states dependent on indicated probabilities which were gathered from the investigation and from the literature. The probability of moving between various states was affected by the effectiveness of every treatment and consequently the expense and quality-adjusted years of life. As represented in Figure 3.1., patients could change from the initial state to three distinct states including ‘no event,’ ‘major bleeding’ and ‘minor bleeding.’ From these states each patient could ‘survive’ or ‘die’ inside a 1-year time horizon. Singular patient information was bootstrapped 5000-times to get the mean of the bootstrapped mean and its SDs and Cis, as costs information are regularly slanted or do not follow normal distribution. The primary thing driving all out treatment expenses was the expense of PGx testing in the PGx group, representing around 75% of the absolute expenses in this arm.

Deterministic outcomes showed that PGx arm was related with greater expense per patient and higher all out quality-adjusted life-years (QALYs) contrary to the N-PGx arm. The outcomes from the Probabilistic Sensitivity Analysis were outlined by plotting the distribution of contrasts in expenses and impacts in the cost–effectiveness plane. All the recreation investigations felt into the North East quadrant demonstrating that the PGx arm was marginally increasingly costly however, simultaneously, more effective than N-PGx. The cost–effectiveness acceptability curve

was then plotted to exhibit the likelihood (on the y-axis) that PGx might be cost-effective contrasted with the N-PGx for a range (on the x-axis) of maximum monetary values that a decision-maker might be eager to pay per QALY. Information demonstrated that the likelihood of PGx being savvy expanded essentially at a willingness-to-pay threshold in the range of €40,000 to €50,000 per QALY, utilized in numerous purviews, outstandingly, at €60,000 per QALY its likelihood of cost–effectiveness was higher than 80%.

- A cost-effectiveness analysis for genotyping before allopurinol treatment to avert extreme cutaneous adverse drug reactions was published in 2017, with the development of a decision-tree model in TreeAge Pro 2014 software. (Ke, et al. 2017) Allopurinol is the most likely drug to induce severe cutaneous adverse reactions (SCAR) and a solid relationship between possession of the HLA-B*58:01 allele and danger of allopurinol-incited SCAR has been seen in the general Asian population. The study assessed the cost-effectiveness of HLA-B*58:01 screening contrasted with utilizing other accessible urate-lowering agents (ULA) (benzbromarone, febuxostat, and allopurinol) without earlier genotyping in treating new patients with the accompanying options: (1) genetic screening pursued by allopurinol prescribing for noncarriers of HLA-B*58:01, (2) prescribing benzbromarone without screening, (3) prescribing febuxostat without screening, and (4) prescribing allopurinol without screening. The occurrence of allopurinol-related SCAR and the related health services expenses were examined, including lifetime saved and quality-adjusted life-years (QALYs) gained. A 1-year time horizon and third-party payer perspective were modeled. All costs for outpatient care, emergency visits, and inpatient medical care are paid by a single third-party payer National Health Insurance program in Taiwan. The monetary point of view for the study, along these lines, incorporated all related healthcare costs. The burden of adverse drug reaction–related visits to the healthcare system was evaluated among patients receiving healthcare services for allopurinol-associated adverse reactions. The total cost incorporated all relating outpatient and emergency visits and any hospitalizations. Mean annual expenses of allopurinol-related SCAR, direct medical cost per SCAR occurrence, and overall medical costs between 2001 and 2011 were examined.

A decision tree model was constructed (Figure 3.2.) to appraise the cost-effectiveness of HLA-B*58:01 genotyping for adult patients with recently diagnosed

hyperuricemia or gout in Taiwan for whom allopurinol, benzbromarone, or febuxostat were viewed as appropriate as first-line monotherapy.

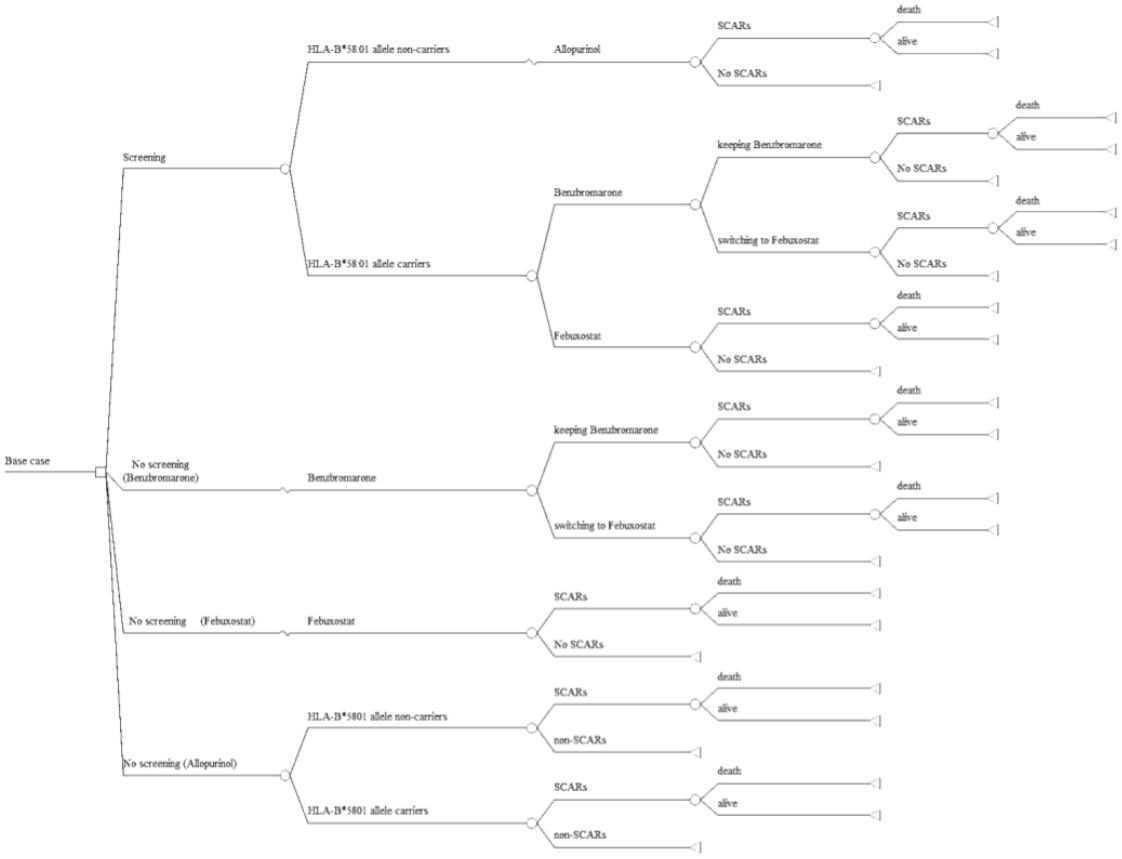

Figure 3.2. Decision tree (Ke, et al. 2017).

The possible outcomes of the decision tree were: (1) cure after allopurinol-induced SCAR, (2) death due to allopurinol-induced SCAR, and (3) no allopurinol-induced SCAR. The prevalence of the HLA-B* 58:01 allele in the Taiwanese population, the connection between the HLA-B*58:01 allele and allopurinol-related SCAR, the incidence of SCAR related to ULA alternatives, the PPV (positive predictive value) and NPV (negative predictive value) of the HLA-B*58:01 genetic test were examined in a deterministic analysis with a Tornado diagram. Costs that were analyzed, included the HLA-B 58:01 screening, the annual cost of urate-lowering agents, considering the probability and duration of ULA switching and the total medical costs of treating patients with SCAR and the ones associated with dying from SCAR. In order to evaluate cost-effectiveness acceptability curves at different maximum willingness to pay (WTP) thresholds, a probabilistic sensitivity analysis (PSA) was developed. The indication was that HLA-B*58:01 screening prevented potential life-

threatening SCAR and proved to be beneficial for many lives, especially in high-risk groups. The ICER found to be lower than the WHO (World Health Organization) Willingness to Pay threshold and genetic screening before ULA initiation was considered to be more cost-effective with a lifelong time frame than same alternative treatment strategies without prior screening in Taiwan.

- A population-based testing program for Lynch syndrome from the US health care system perspective was the subject of a cost-effectiveness analysis of genetic testing strategies for Lynch syndrome among newly diagnosed patients with colorectal cancer (CRC). (Mvundura, et al. 2010) A decision model was developed to estimate the cost-effectiveness and direct costs of screening, diagnosis, and health care associated with CRC were calculated. A germline mismatch repair (MMR) gene mutation is responsible for Lynch syndrome, which can lead to colorectal cancer or other malignancies. In order to prevent them and detect premature death, an age-targeted testing is performed, so that an asymptomatic individual is identified.

Among the Four Lynch syndrome testing strategies that were modeled for CRC cases aged under 50 years, the first two began with offering immunohistochemistry (IHC) testing and their difference depended on a different protein mutation testing. Strategy 3 used microsatellite instability (MSI) testing, which did not examine which MMR gene was not functioning, in comparison with the first 2 strategies. In strategy 4, a sequencing/rearrangement testing was offered to all patients.

QALYs and discounted life-years (LYs) saved were used as a measure of effectiveness and the perspective which was followed was that of the national health care system. The costs included the discussion and offering of a MSI or IHC testing to newly diagnosed patients with CRC, with the reflection of an expert opinion, the performance of the genetic testing and the genetic counseling. Those costs were related to detecting cases of Lynch syndrome from newly diagnosed patients with CRC. Also, first-degree relatives of a proband with Lynch syndrome were offered to take a test, after the family mutation had been identified. Their locating and offering testing were calculated from the published literature, alongside with the costs of genetic counseling and the costs of testing for the family mutation. Additional costs of surveillance for CRC among relatives with Lynch syndrome, the costs of treating complications associated with colonoscopies, the treatment costs of CRC that relative developed during their lifetime were also extracted for the published literature. The model estimated total costs for the US health care system as a whole and ICERs were estimated.

Due to difficulty in obtaining the costs of Lynch syndrome testing, for the first-baseline cost scenario that was estimated, as far as the laboratory test was concerned, the main source data for the economic inputs was EGAPP Supplementary Evidence Review, whereas three commercial laboratories were used to obtain list prices for the second scenario. The second scenario for genetic testing did not appear to be so cost-effective since the prices used were undiscounted. All costs were expressed in 2007 US dollars. Universal testing was substantially more expensive than age-targeted testing of CRC patients not older than 50 years, namely total program costs were 72% to 82% higher in the first case.

IHC as a preliminary test was more cost-effective, about 40% smaller than MSI testing. ICERs ranged from $12,332 to $49,272 per LY saved for using IHC or MSI as preliminary tests for universal genetic testing strategies compared with no testing for Lynch syndrome, whereas ICERs for universal genetic testing ranged from $18,778 to $85,391 per LY saved compared with age-targeted testing, after taking into account the scenarios mentioned above. Important factors in favor of a smaller ICER were the increase in the first-degree relatives that agreed to take the genetic test and to be under surveillance afterwards. Important factors against a small ICER were the increase of the costs of MSI and IHC tests and gene sequencing. Denmark's health care system highly recommends IHC testing to all newly diagnosed patients with CRC.

- A cost-effectiveness analysis was conducted in Serbian patients with myocardial infarction (MI). (C. Mitropoulou, et al. 2016) After receiving primary percutaneous coronary intervention, the patients were either genotyped, in order to take pharmacogenomic (PGx)-guided clopidogrel treatment or took conventional clopidogrel treatment without prior genotyping. CYP2C19 enzyme activates the antiplatelet agent clopidogrel and so as to form the most suitable therapeutic scheme, genetic testing is recommended by regulatory agencies. Carriers of CYP2C19*2 and CYP2C19*3 alleles have lost CYP2C19 enzyme function and, therefore, may require increased clopidogrel doses, in order to avoid thrombotic events, whereas CYP2C19 homozygous wild-type (*1/*1) patients are extensive metabolizers. The CEA included genetic testing costs, namely for 121 patients that were genotyped, hospitalization costs, restenosed percutaneous coronary intervention (RePCI), vascular operation, rehabilitation, all direct costs, reimbursed by the Serbian health insurance fund.

A decision tree was constructed as an economic model (Figure 3.3.), which depicted strategy A, according to which, a random patient would be treated without taking the genetic test and strategy B, according to which, all patients received the

right treatment. Comparing the alternative strategies, in strategy A no genetic testing costs were involved, whereas in strategy B, every patient had to bear the genetic testing costs. On the other hand, though, as far as strategy A was concerned, CYP2C19*2 hetero- and homozygous patients could not receive the safest treatment in accordance with their genetic profile.

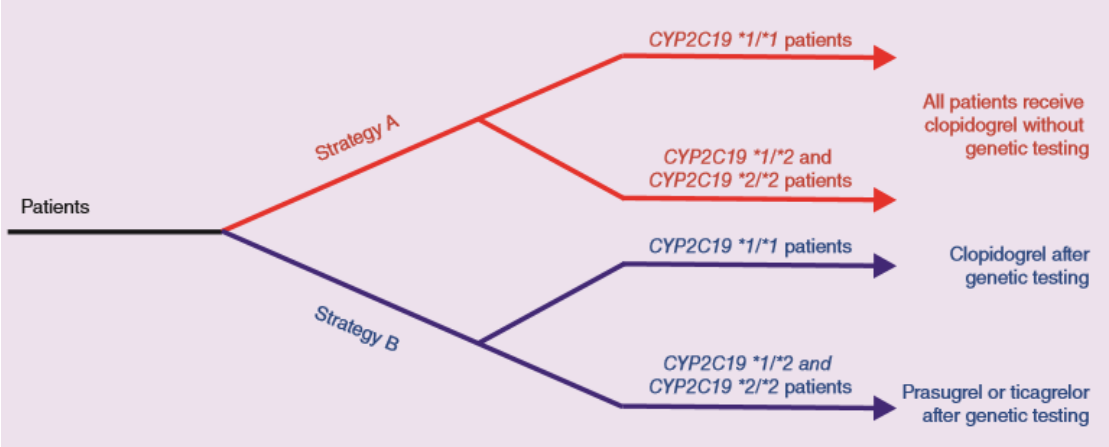

Figure 3.3. Decision tree (C. Mitropoulou, et al. 2016).

Major were the hospitalization costs for the extensive metabolizers and the CYP2C19*1/*2 and CYP2C19*2/*2 patient group (79.2% on average of the total cost). Cost of rehabilitation was the second main cost factor (11.2% for the 1st group and 11.6% for the 2nd one, respectively). Cost of genetic testing attributed to 2.4% of the total cost in the case of extensive metabolizers. Strategies A and B equalized, from a cost perspective point of view, after conducting a break-even analysis, when CYP2C19*1/*1 patients reached 75% of the total population. In higher percentages, Strategy A, namely not performing a genetic test represented a cost-effective option, as CYP2C19*1/*2 or CYP2C19*2/*2 genotype were less likely to appear and clopidogrel would not increase the risk of thrombotic events. In lower percentages, which depicted the base case analysis, Strategy B saved €13 per person on average and proved that PGx-guided clopidogrel treatment may be cost-effective compared to alternative strategies.

• Gene-expression analysis in early breast cancer was compared to adjuvant systemic treatment after completing the software program Adjuvant! Online (AOL), in order to figure out the most cost-effective therapeutic strategy. (Tsoi, et al. 2010) According to the National Surgical and Adjuvant Breast and Bowel Project (NSABP) trial, 15% of patients with node-negative HR-positive disease who were treated with tamoxifen after curative resection of primary tumor developed recurrence in 10 years. The irrational and excessive treatment of adjuvant chemotherapy and hormonal

therapy together against early breast cancer may lead to overtreatment, increasing the cost and the risk of morbidity. AOL uses clinicopathological features to predict the disease evolution, but frequently overestimates the need and the benefit of chemotherapy. On the other hand, Oncotype DX, developed by Genomic Health Inc., uses the expression of 21 genes to generate a recurrence score (RS) for each individual tumor and, depended on that score, responsiveness to treatment is defined and patients are ranked at risk groups.

For the comparison of lifetime cost and utility of RS-guided treatment using genomic advances or treatment dependent on AOL, a Markov model was constructed with the use of TreeAge Pro 2008 Suite (TreeAge, Williamson, MA) and two strategies were examined. The base case was a 50-year-old woman with node-negative HR-positive HER-2–negative early-stage breast cancer. Strategy A included classification of patients at risk groups for distant recurrence according to AOL and reclassification afterwards according to RS, which determined the treatment decision, whereas Strategy B included only AOL performance. If a woman was classified as high risk, she entered a treatment period of 6 months receiving chemotherapy and then, tamoxifen. Chemotherapy could induce no, minor, major, or severe toxicity or complications leading to death. If a woman was classified as low risk, she entered a treatment period receiving only tamoxifen. A health care payer's perspective was obtained, and the remaining lifetime of patients identified the time horizon.

Considering the costs collection, the 21-gene assay had a suggested retail price from its manufacturer and the costs of drugs, both chemotherapy, namely chemotherapeutic agents, and supportive ones, namely antiemetics, laboratory evaluation, HR utilization per cycle of chemotherapy and minor toxicity, were provided by the Cancer Center pharmacy in Ontario. In case of major toxicity, costs included handling febrile neutropenic complications and growth factor support. If a woman died after septicemia treatment, the cost of it related to chemotherapy (Ontario Case Costing Initiative). For a period of 5 years, either uninterrupted by distant recurrence or death or not, tamoxifen's cost was applied to all patients. Additional costs were obtained from literature, such as the treatment without recurrence for the next 12 months, but with distant recurrence after 21 months, also the treatment if breast cancer reappeared or if the woman's situation lead to death and required terminal medical care for the last 3 months of life. As far as the RS-guided strategy is concerned, the cost of 21-gene assay figured 22% of the total cost of the strategy, and thus, the estimation of the relatively acceptable ICER of $61,800 per QALY, from a health care perspective in the context of a willingness to pay thresholds of $50,000 – $100,000 per

QALY, was mainly driven by that fact. Treatment for lymph node– negative HR-positive HER-2–negative breast cancer after 21-gene assay proved to be more effective and more costly than after completing AOL. The connection between the increased cost of 21-gene assay, ICER and an increasing age of patients was positive. The cost-effectiveness of RS-guided treatment in the older population would increase, if the willingness to pay threshold was increased, or if the cost of 21-gene assay dropped. Cost-effectiveness increased also in younger women, as sensitivity analyses showed that, although the incremental cost of 21-gene assay remained the same in any age, QALYs gained were higher in younger women due to RS strategy (0.099 QALY in 30-year-olds vs. 0.021 QALY in 70-year-olds).

RESEARCH FRAMEWORK

CHAPTER 4: COST ANALYSIS AND EVALUATION OF EFFECTIVENESS

4.1 Aim of the study

Depression is a chronic psychiatric disorder, in which a person's daily life is disturbed by severe sadness, melancholy, or despair. Depression is associated with high prevalence and low treatment response rates, and it fundamentally burdens the patient, the medical provider, and society. (Maciel, et al. 2018) It reduces the quality of life and increases the risk of cardiovascular disease, by constituting a risk factor for coronary artery disease and sudden cardiac death and all-cause mortality. According to studies, depression can reduce life expectancy by 7–11 years, like lifetime smokers. The severity of the disease varies. Emerging episodes range from mild to moderate to severe, according to WHO's International Classification of Diseases (ICD-10). The Institute of Health Metrics and Evaluation (IHME) disaggregates the types of the disorder to mild, persistent depression (dysthymia) and major depressive disorder (severe).

Globally, the share of the depressed population is mainly between 2% and 6%, as illustrated in Figure 4.1.1. Older people (70 years and older) around the world today have a higher risk of depression than other age groups. (Ritchie and Roser 2018)

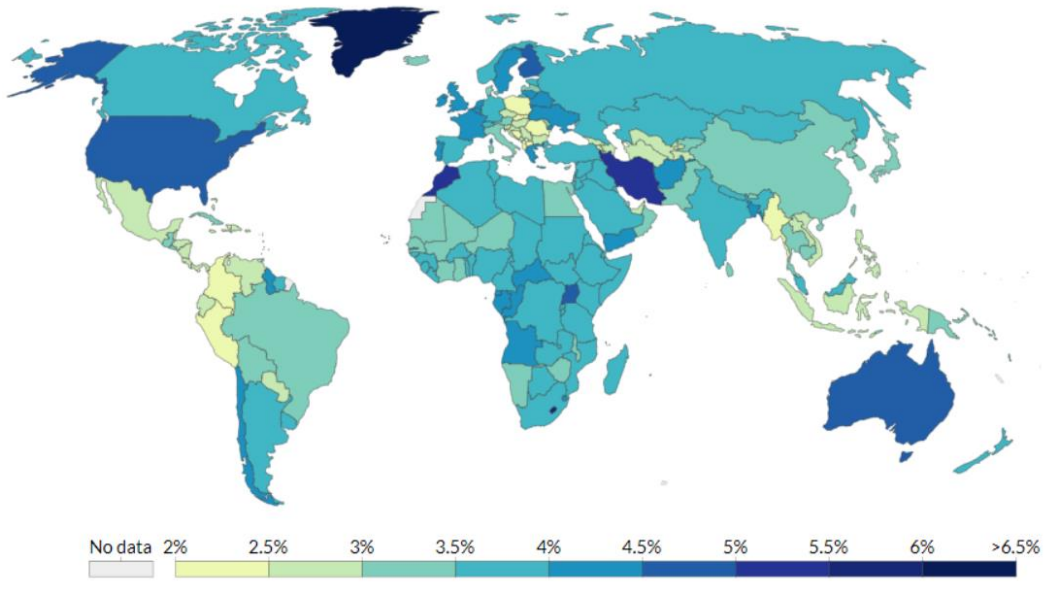

Figure 4.1.1. Prevalence of depressive disorders (Ritchie and Roser 2018).

In 2017, 264 million people in the world were estimated to experience depression, with 4,19% of the Greek population being depressive patients. The Hellenic Statistical Authority revealed an 80% increase in the Greeks suffering from depression between 2009 (2,6%) and 2014 (4,7%). Among these patients, 67% were females and 33% were males. As far as the young Greek people are concerned, 1,6% of the population aged between 15-29 years old and 2,3% of the Greeks aged between 30-34 years old suffered at 2014 from depression. (Hellenic Statistical Authority 2014) Women, young adults, American Indians and Alaska Natives cope more often with major depression, as shown in Figure 4.1.2.

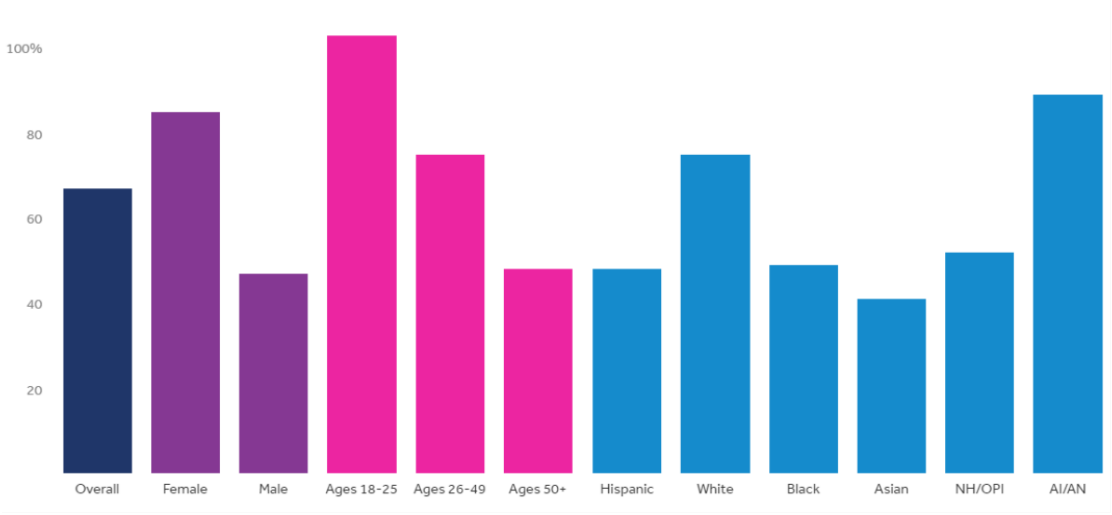

Figure 4.1.2. 12-month prevalence of major depressive episode among adults aged 18+ by gender, age and race/ethnicity (Kamal 2017).

Untreated, severe depression is associated with an increased hazard of suicide, psychiatric hospitalizations, and to a significant loss of productivity due to prolonged absence from work. (Maniadakis, et al. 2013) Epidemiological studies show a consistent correlation between depression and loss of productivity. People with depression are 5 times more likely to be absent from work due to illness and 4.78 times more likely to have a disability.

Figure 4.1.3. shows the burden of depression on health as measured by DALYs (Disability Adjusted Life Years) per 100,000. Considering the fact that DALYs are used to measure total burden of disease and that one DALY equals one lost year of healthy life, Greece's rate is 644.08 DALYs. Greenland's rate is estimated at 1026.94 DALYs and Morocco's at 958.37 DALYs.

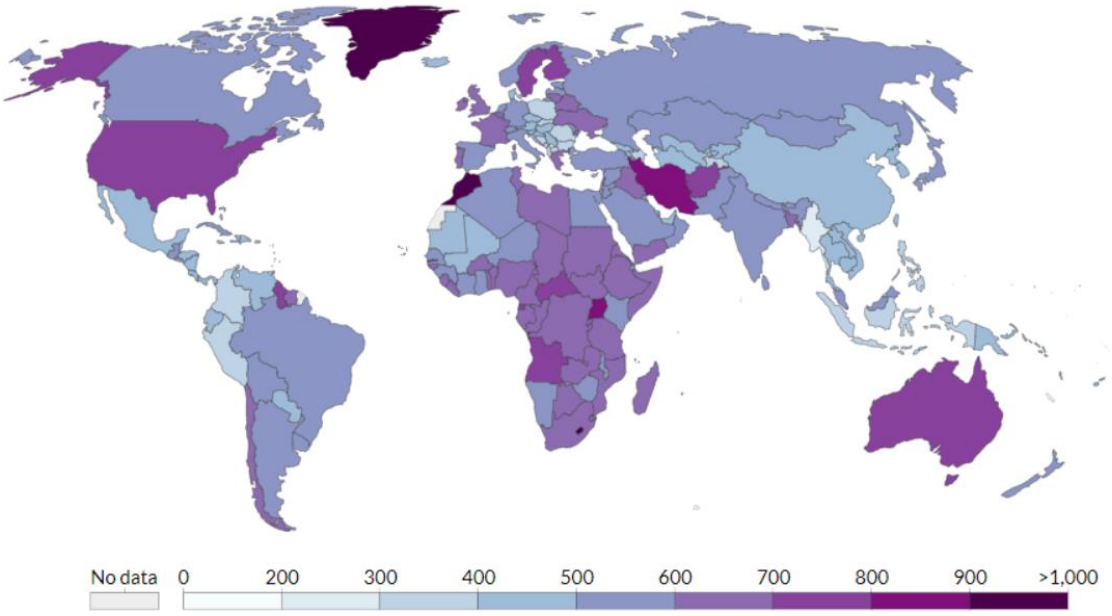

Figure 4.1.3. Burden of depression on health as measured by DALYs per 100,000. (Ritchie and Roser 2018).

These numbers make depression the leading cause of disability in the USA, accumulating approximately 400 million days of disability annually. Depression is also linked to a 50% - 75% increase in healthcare use, costing more than USD $98 billion in 2010. When it comes to the cost of indirect services and lost productivity, the financial burden on people with depression amounts to USD $210.5 billion annually.

The direct costs of treatment for mental illnesses far exceed those for diabetes and hypertension and fall behind only on cardiovascular disease, traumatic injuries, and cancer. The indirect cost of treatment for mental illness is impressive, with major depressive disorder (MDD) responsible for the highest costs of disability in all major illnesses. The National Institute of Mental Health reports that direct and indirect cost of depression is $200 billion annually, of which treatment-resistant depression includes $64 billion. Annual $30.3 billion worth of medication costs is spent on psychiatric drugs. Depression related services are largely outpatient treatment, pharmaceutical medication, or a combination of both, as illustrated in Figure 4.1.4. One in four adults suffers from a mental illness in any given year. (Winner, et al. 2015)

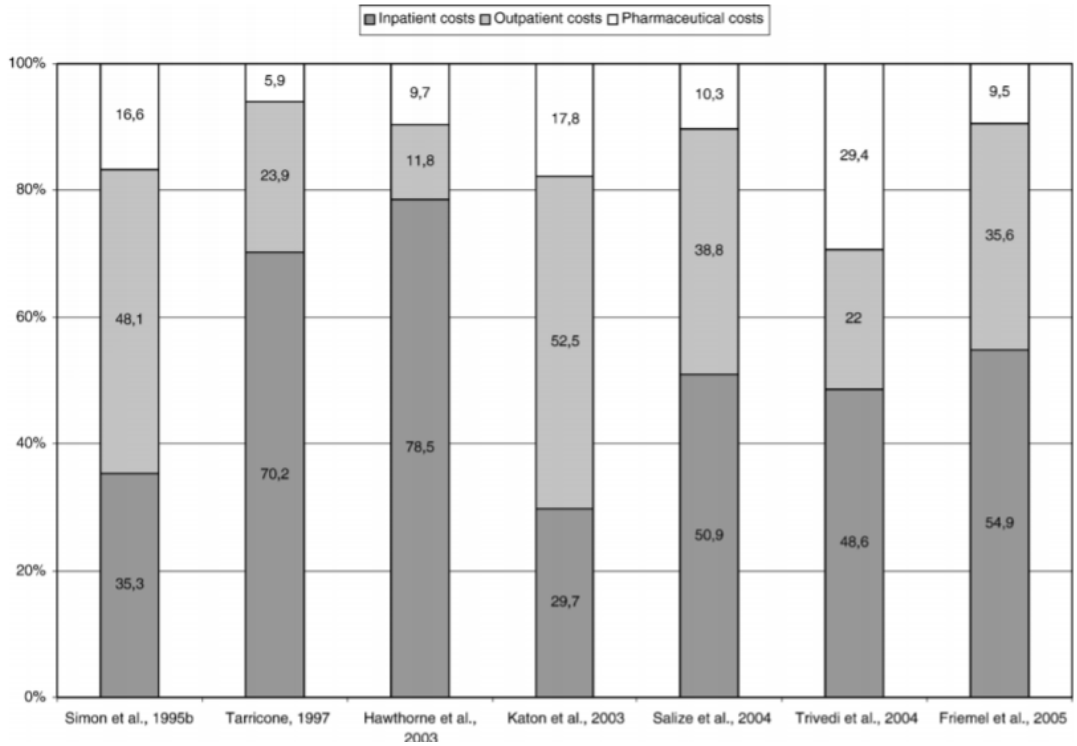

Figure 4.1.4. Depression related inpatient, outpatient and pharmaceutical expenditures.

Among these illnesses, Major Depressive Disorder (MDD) is the most common condition, affecting 6.8% of the US population and is a source of significant financial burden, with an immediate cost of $98.9 billion annually. Psychiatric drugs alone cost $30.3 billion a year, and the cost of antidepressants is up 10% annually.

Depression is projected to contrast only HIV/AIDS and heart disease as a major cause of disease burden by 2030. It is estimated that mental illnesses have disabled 11% of life expectancy, causing at least 15 million disability-adjusted life years a year. Many individuals who suffer from MDD or other mental illnesses avoid seeking treatment due to social stigma, financial costs and limited access to mental health care, which adds to reduced work productivity and increased burden on health care.

A 400% increase in the use of antidepressants over the last 20 years has ranked antidepressants the third most commonly prescribed drug type in all adults because of the availability of new medications. The wide range of antidepressants used includes the class of selective serotonin reuptake inhibitors (SSRIs), the class of selective norepinephrine reuptake inhibitors (SNRIs), the class of tricyclic antidepressants (TCAs), non-TCAs, and the class of monoamine oxidase inhibitors (MAOIs). With antidepressants being among the most widely prescribed medications and with the choice of multiple dosing possibilities, healthcare providers are currently

relying on trial and error methods for drug selection and management. As a result, only 35-45% of patients who follow this approach achieve remission after an initial antidepressant trial. The rest of the patients experience a journey- a pharmacological odyssey- of many failed medication trials due to this lack of efficacy of medication with the hope to eventually find a therapy with a favorable risk/benefit balance, with inevitable side effects. This type of patients are considered therefore resistant to treatment.

Any additional treatment failure for these users reduces the likelihood of remission and increases the likelihood of relapse. In addition, treatment resistant patients are disproportionately burdened by adverse reactions compared to patients who achieve remission, while almost 90% of people with severe adverse reactions cannot achieve remission. The financial burden of treatment failures on the annual direct cost, which is estimated to be 70% higher than that of patients responding to treatment, disability claims, reduced productivity, and lost work may, in part, stem from a mismatch between optimal and actual prescribed medications. (Maciel, et al. 2018) The relative early age of onset, MDD's chronicity, and the inadequate therapeutic outcomes are key factors for both the economic and the societal costs of MDD.

The adoption of new technologies that improve the therapeutic outcomes in a variety of clinical settings could alleviate the high costs and challenges of depression management. Not only the incidence of treatment resistance, but also the excessive use of health care due to failed medication trials could be reduced by adopting an objective method according to which the appropriate medications could be identified.

Some clinical practitioners who seek to change this trajectory positively and bring improved outcomes for patients who suffer from mental illness have lately incorporated Pharmacogenomics-guided (PGx) therapy into practice. Pharmacogenomics (PGx) is a gene-based method, according to which a person's genetic background is used to identify the right drug at the right dose with the aim to maximize efficacy and minimize the occurrence of adverse reactions (ADRs). About 20% to 95% of the variability in response to the medication is due to the patient's genetic background. To date, the US Food and Drug Administration (FDA) has approved more than 260 medicines that contain PGx information on their label. With psychiatric pharmacogenetics, the precision in the prescription of psychotropic drugs is improved, since genetic differences - polymorphisms - in pharmacokinetic (PK) genes involved in the drug absorption, distribution, metabolism and elimination and in pharmacodynamic (PD) genes that affect the mechanism of action of medications and

the response to antidepressants and antipsychotics, are analyzed. PD genes are used to predict drug response and ADRs, and PK genes, with metabolism enzymes included, are used to predict medication exposure and appropriate dosage. However, given the lack of genetic education, the numerous genomic variants, and their huge range of interactions with medications, it is difficult for clinical practitioners to use PGx in practice.

In Psychiatry, considering that antipsychotics and antidepressants can have different effects on patients who experience the same symptoms and diagnosis, PGx-guided prescription can prove to be critical. The side effects of psychiatric medications are usually mild in severity but can significantly reduce the quality of life of patients. Clinical validity and utility play a crucial role when it comes to PGx trials, which means that the genes involved in a PGx trial are predictive of drug responsiveness and that HCPs can afterwards utilize the results in favor of the decisions determining the patient's treatment.

Regarding the metabolism of antidepressants, the pharmacokinetic genes that mostly participate, are those of cytochrome P450. More specifically CYP2D6 is responsible for the metabolism of amitriptyline, paroxetine, sertraline, venlafaxine, clomipramine, doxepine, and imipramine, whereas CYP2C19 participates in the metabolism of citalopram and escitalopram.

The primary objective of the study is to estimate the economic impact for standard therapy and pharmacogenetic-guided treatment for MDD, by calculating the direct costs, namely the cost of medications, the cost of the lab test, the operation and the hospitalization cost, in order to identify the cost of illness of MDD, compare the alternative treatments and evaluate the effectiveness and ADRs of each approach.

4.2 Materials and methods

This is a single center study that was carried out in co-operation with the Laboratory of Pharmacogenomics and Individualized Therapy, of the University of Patras, Department of Pharmacy and the General University Hospital of Patras, using real-world data of patients with Major Depressive Disorder in Greece. Adult patients (>18 years old) diagnosed and treated with the standard therapy for Major Depressive Disorder (MDD) were recruited in the study. Diagnostic Criteria for MDD and Depressive Episodes according to the Diagnostic and Statistical Manual of Mental Disorders, DSM (published by the American Psychiatric Association-APA), include:

- Depressed mood or a loss of interest or pleasure in daily activities for more than two weeks.
- Mood represents a change from the person's baseline.
- Impaired function: social, occupational, educational.
- Specific symptoms, at least 5 of these 9, present nearly every day:

1. Depressed mood or irritable most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful).

2. Decreased interest or pleasure in most activities, most of each day

3. Significant weight change (5%) or change in appetite

4. Change in sleep: Insomnia or hypersomnia

5. Change in activity: Psychomotor agitation or retardation

6. Fatigue or loss of energy

7. Guilt/worthlessness: Feelings of worthlessness or excessive or inappropriate guilt

8. Concentration: diminished ability to think or concentrate, or more indecisiveness

9. Suicidality: Thoughts of death or suicide, or has suicide plan

As far as the functional domain is concerned, patients are categorized as moderately and severely impaired according to the following factors in Table 2.1.

Functional Domain	Moderately Impaired	Severely Impaired
Family Relationships	Quiet, negative and oppositional	Withdrawn, won't talk, brusque, angry, aggressive
School & Academics / Work	Grades/work performance deteriorating, missing/cutting class or work, decreased effort, moderate academic or work stress	Failing performance, missing school or work, doesn't care about work, oppositional, argumentative, high academic or work stress
Peer Relationships	Decreased socializing or extracurricular activities , more time on computer	Isolated, discontinued extracurricular activities, excessive computer time
Stress Level, Anxiety	Minimizes or denies issues, projects onto others or blames others	Withholds feelings, won't talk
Suicidal Ideation	Vague/occasional	Frequently considered, has a plan, or prior attempt
Other Self Harm	Occasional thoughts but no attempts	Cutting, other self injury

Table 2.1. Moderately and Severely Impaired depressive patients according to functional domain.

The data used for this study come from patients -depressive cases already identified by the health system- who were recruited at the Laboratory of Pharmacogenomics and Individualized Therapy and sequenced, as far as the intervention group is concerned. The collected data included demographical data (age, sex, BMI), disease related data (stage of depression), therapy characteristics (index drugs, subsequent drugs, concomitant medications, duration of the treatments) and a registry of the toxicities caused by the treatments (ADRs, Tests due to ADRs, Cost of Tests, Hospitalization due to ADRs and Cost of Hospitalization).

For the economic evaluation of the treatment only medical direct costs, in insurance prices, were included. The non-medical direct, the indirect and the intangible costs were not included as the study was carried out from the perspective of the decision makers managing health care expenditures. The number of utilized resources was combined with the corresponding unit cost, obtained from Government Gazette or the drug price bulletins issued by the Greek Ministry of Health. As for the medication cost, the mean daily drug dose was combined with the relevant drug prices (calculated as the cost per mg). Monthly pharmaceutical costs per patient were calculated and the statistical results of the model are represented in section 4.5. Additionally, the percentage distribution in cost per drug category was calculated depending on the baseline treatment versus the concomitant medications. The management of a moderate adverse event was assumed to require minimal medical intervention/therapy – Grade 2 characterization – and a severe adverse event was assumed to require a laboratory test due to the ADR or a hospitalization – Grade 3 characterization. In the absence of these consequences, the Adverse Event was characterized as mild (Grade 1) and it did not affect the effectiveness of the treatment. The effectiveness was assessed on the basis of mortality, the presence and the severity of ADRs, and the alterations in quality of life they resulted in. The current study combines data from panel expert opinion, published clinical trial results, published longitudinal data on costs and utilities in depression and available bibliography.

4.3 Patients and Treatment

A total of 62 patients were included in this study. Patients were separated at the beginning of the study of the University of Patras in 2 arms randomly, the intervention group and the control group. All patients, regardless of the arm they joined, were prescribed an initial medication from a specialist at the day of recruitment according to their medical history and clinical picture. Depending on the group patients

joined, either their DNA was analyzed after they were asked to give a blood sample (if they were inpatients) or a saliva sample (if they were outpatients), or they did not follow the genotyping process. The physician prescribed standard treatment for the control arm and an initial dose of standard treatment for the intervention arm, until the results of the genetic test were released.

Within an average of seven days, the released results were examined by the physician and based on the genetic profile of each patient, the personalized prescription included either an adjustment of the initial dose, or a switch to an alternative index drug. In case of no significant effect on the plasma concentration of the standard treatment, the tolerance or the response, no changes at the initial standard medication scheme were required.

The purpose of the genetic test was to find out whether the personalization of medication based on the patients' DNA would reduce the likelihood of side effects. Another goal was to find out if personalized treatment improved the quality of life and/or reduced the cost of health care. In addition, the information collected would be used by scientists to learn about the genetic changes in genes that affect the metabolism of drugs.

All patients continued receiving their concomitant medications or were prescribed additional co-meds throughout their participation in the research. Within the first 7 days, any adjustments at the initial pharmaceutical scheme of the intervention group were due to the genetic testing. The first visit at the University of Patras for the monitoring of patients by the physician was held at the 15^{th} day from the day of the recruitment, but the increase or decrease of the initial dose, or the addition of a subsequent drug was due to the overall clinical picture of the patient and was not related to the patient's genetic profile. Two visits at the physician of the General University Hospital of Patras for monitoring were conducted by each patient during the first month, one visit per month for the next 5 months and 1 visit every 3 months for the rest of the participation in the study.

For this study, data from 28 patients of the intervention arm (I arm) and 34 patients of the control arm (arm C) were analyzed. From the 62 patients, 21 (33.9%) were male and 41 (66.1%) were female. From the intervention group, 13 (46,4%) patients were male and 15 (53,6%) patients were female. The mean age at enrollment was 47,93 for the female in the intervention group and 48 years old for the male. The average BMI of the female was 25,55 Kg/m^2 and of the male was 26,96 Kg/m^2 . Demographic data of the intervention group are represented in Table 3.1.

Table 3.1. Demographics Intervention Arm			
Patient	**Age**	**Sex**	**BMI**
1	60	F	34,7
2	53	F	29,4
3	62	F	20,3
4	18	F	17,6
5	63	F	30,8
6	43	M	26,1
7	38	F	29,1
8	47	M	25,5
9	39	M	23,1
10	56	M	33,1
11	69	F	28,4
12	55	F	25
13	72	F	29,4
14	42	M	20,7
15	30	M	24,4
16	55	F	23,1
17	23	F	26
18	26	F	22,8
19	21	F	21,4
20	24	M	24,7
21	47	M	25,3
22	45	M	30
23	59	M	29,9
24	82	M	23,2
25	49	M	32,9
26	57	F	22,8
27	61	M	31,6
28	47	F	22,4

Table 3.1. Demographics Intervention Arm.

In the control arm, 26 (76,47%) patients were female and 8 (23,53%) patients were male. The mean age of the female in the control arm was 53,19 and of the male was 52,38 years old. The average BMI of the female was 25,98 Kg/m^2 and of the male was 29,21 Kg/m^2. Demographic data of the control arm are presented in Table 3.2. A greater proportion of MDD patients were female in both arms compared with the male ones (53,6% in the I arm and 76,47% in the C arm versus 46,4% in the I arm and 23,53% in the C arm respectively), males were slightly older than females at enrollment in the I arm (48 versus 47,93 years old respectively) whereas females in the C arm who were slightly older than males (53,19 versus 52,38 years old) and males' BMI were higher on average in both arms compared to the females' BMI (26,96 Kg/m^2 in the I arm and 29,21 Kg/m^2 in the C arm versus 25,55 Kg/m^2 in the I arm and 25,98 Kg/m^2 in the C arm respectively). Sample characteristics are summarized in Table 3.3.

Table 3.2. Demographics Control Arm			
Patient	**Age**	**Sex**	**BMI**
29	56	F	*
30	58	F	29
31	69	F	31,2
32	46	F	19,9
33	51	F	29,4
34	38	F	22
35	41	M	25,2
36	68	F	26,3
37	50	M	28,1
38	48	M	27,8
39	57	M	33,7
40	41	F	25,4
41	65	M	30,9
42	63	M	32
43	49	F	32,9
44	62	F	25,3
45	58	M	31,8
46	50	F	25,7
47	37	M	24,2
48	47	F	21,9
49	51	F	27,9
50	54	F	24,8
51	84	F	21,8
52	58	F	28,7
53	39	F	20,1
54	44	F	27,2
55	28	F	20,3
56	48	F	40,4
57	75	F	20,4
58	48	F	28,7
59	58	F	24,6
60	47	F	23
61	67	F	26,8
62	47	F	25,8
*Data not available for all subjects. Missing value			

Table 3.2. Demographics Control Arm.

Table 3.3. Sample characteristics.		
	Intervention group	**Control group**
Number of patients, n (%)		
All	28 (100)	34 (100)
Male	13 (46,4)	8 (23,53)
Female	15 (53,6)	26 (76,47)
Age, mean ± SD (years)		
All	47,96 ± 16.32	53 ± 11,70
Male	48 ± 14,62	52,38 ± 10,11
Female	47,93 ± 18,18	53,19 ± 12,33
BMI, mean ± SD (Kg/m^2)		
All	26,2 ± 4,36	26,76 ± 4,57
Male	26,96 ± 4,06	29,21 ± 3,42
Female	25,55 ± 4,64	25,98 ± 4,67

Table 3.3. Sample characteristics.

4.4 Cost of Genotyping and Non-Pharmaceutical Unit Costs

The following steps were conducted in the frame of the experimental procedure of the genetic test for MDD:

i. For the DNA isolation from one sample, the kit “NucleoSpin Blood” was used and the procedure lasted 25-30 minutes. The analysis was processed for 8 samples, in order to save time and reduce costs. (Mackerey-Nagel 2016)
ii. Nanodrop spectrophotometer was used to quantify and assess the purity of the samples. The absorbance and the concentration of nucleic acids and purified proteins was quickly and easily quantified, in 5 minutes. (Nanodrop Quawell)
iii. Polymerase chain reaction (PCR) was conducted to make copies of the specific DNA samples. For the preparation of the DNA segments and their amplification into the thermocycler, 2.30 hours were required. (Kyratec 2011)
iv. The genotyping step was performed with the aid of a specific restriction enzyme, which is selected based on the location of the genome intended to analyze and acts by heating in the Thermoblock.
v. Electrophoresis was used to separate the charged DNA molecules according to size, so as to identify which samples contained the pathogenic mutations that led to depression.

The metabolic enzymes of antidepressants are CYP2D6, which is responsible for the metabolism of amitriptyline, paroxetine, sertraline, venlafaxine, clomipramine, doxepine and imipramine, and CYP2C19, which participates in the metabolism of citalopram and escitalopram. The cost of genetic testing for the above two metabolic enzymes related to the metabolism of antidepressants was therefore calculated based on the cost of genotyping for 47 biomarkers in 13 genes that is conducted in the Laboratory of Pharmacogenomics and Individualized Therapy at the University of Patras at the retail price of €500. An additional retail price of €160 for a relevant metabolic enzyme from a research and development company which offers diagnostic pharmacogenetic DNA tests in Alexandroupoli, Greece was taken into account. The non-pharmaceutical unit costs per item used in the study are illustrated in Table 4.1.

Table 4.1. Non-pharmaceutical Unit Costs.	
Item	**Cost (€)**
Cost of genetic testing	198,46
Cost of hospitalization per day	40
Cost of medical monitoring per visit	10

Table 4.1. Non-pharmaceutical Unit Costs.

Arm I was tested genetically and received a standard treatment for the period until the announcement of the results. Based on the results of the genotyping procedure and within the first 7 days, the patients could either switch to a personalized prescription with an alternative index drug, the increase or the decrease in the initial dose of the index drug, or the continuation of the initial standard treatment if no action was needed for their gene-drug interaction. Index drugs were called the antidepressants that consisted the baseline therapy and these were the active substances citalopram, escitalopram, sertraline, venlafaxine, clomipramine. The guidelines according to which the dose of the index drug was altered, or a subsequent drug was added to the therapeutic scheme are shown in tables 5.1., 5.2., 5.3., 5.4., 5.5.

Table 5.1. Guidelines Citalopram			
Allele/ Genotype/ Phenotype	**Drug**	**Description**	**Recommendation**
CYP2C19 UM	Citalopram	-	NO action is needed for this gene-drug interaction. The gene variation increases conversion of citalopram to a weakly active metabolite. However, there is no significant effect on the plasma concentration of citalopram, the tolerance or the response.
CYP2C19 IM	Citalopram	The risk of QT prolongation and torsades de pointes is theoretically increased because the gene variation leads to an increased citalopram plasma concentration. If you follow the dose recommendation below, the increased plasma concentration and the theoretically increased risk of QT prolongation will be offset.	Do not exceed the following daily doses: 1. Adults up to 65 years: 30mg as tablets or 22mg as drops, 2. Adults 65 years or older: 15mg as tablets or 10mg as drops
CYP2C19 PM	Citalopram	The risk of QT prolongation and therefore also the theoretical risk of torsades de pointes is increased as the gene variation leads to an increased citalopram plasma concentration. If you follow the dose recommendation below, the increased plasma concentration and the increased risk of QT prolongation will be offset.	Do not exceed the following daily doses (50% of the standard maximum dose): 1. adults up to 65 years: 20mg as tablets or 16mg as drops, 2. Adults 65 years or older: 10mg as tablets or 8mg as drops
UM: Ultrarapid Metabolizer, IM: Intermediate Metabolizer, PM: Poor Metabolizer			

Table 5.1. Guidelines Citalopram.

Table 5.2. Guidelines Escitalopram			
Allele/ Genotype/ Phenotype	**Drug**	**Description**	**Recommendation**
CYP2C19 UM	Escitalopram	The risk of conversion to another antidepressant is increased as the gene variation leads to a reduction in the escitalopram plasma concentration.	Avoid escitalopram. Antidepressants that are not metabolised or that are metabolised to a lesser extent by CYP2C19 are, for example, paroxetine or fluvoxamine.
CYP2C19 IM	Escitalopram	The risk of QT prolongation and torsades de pointes is theoretically increased because the gene variation leads to an increased escitalopram plasma concentration. If you follow the dose recommendation below, the increased plasma concentration and the theoretically increased risk of QT prolongation will be offset.	Do not exceed the following doses (75% of the standard maximum dose): adults < 65 years 15 mg/day, =65 years 7.5 mg/day
CYP2C19 PM	Escitalopram	The risk of conversion to another antidepressant is increased. In addition, the risk of QT prolongation and torsades de pointes is theoretically increased because the gene variation leads to an increased escitalopram plasma concentration. If you follow the dose recommendation below, the increased plasma concentration, the theoretically increased risk of QT prolongation and the increased risk of conversion to another antidepressant will be offset.	Do not exceed the following doses (50% of the standard maximum dose): adults < 65 years 10 mg/day, =65 years 5 mg/day
UM: Ultrarapid Metabolizer, IM: Intermediate Metabolizer, PM: Poor Metabolizer			

Table 5.2. Guidelines Escitalopram.

Table 5.3. Guidelines Sertraline			
Allele/ Genotype/ Phenotype	**Drug**	**Description**	**Recommendation**
CYP2C19 UM	Sertraline	NO action is needed for this gene-drug interaction.	The gene variation has a negligible effect on the plasma concentration of sertraline. Moreover, no significant effect on response and side effects has been found.
CYP2C19 IM	Sertraline	NO action is needed for this gene-drug interaction.	The gene variation has a minor effect on the sertraline plasma concentration. No effect on side effects was found.
CYP2C19 PM	Sertraline	The risk of side effects is increased. The gene variation leads to increased plasma concentrations of sertraline.	Do not give doses exceeding 75 mg/day. Guide the dose by response and side effects and/or sertraline plasma concentration.
UM: Ultrarapid Metabolizer, IM: Intermediate Metabolizer, PM: Poor Metabolizer			

Table 5.3. Guidelines Sertraline.

Table 5.4. Guidelines Venlafaxine

Allele/ Genotype/ Phenotype	Drug	Description	Recommendation
CYP2D6 UM	Venlafaxine	It may be difficult to adjust the dose for patients due to altered metabolism between venlafaxine and the active metabolite O-desmethylvenlafaxine. The gene variation increases the conversion of venlafaxine to O-desmethylvenlafaxine and reduces the sum of venlafaxine plus O-desmethylvenlafaxine.	1. be alert to a possible decrease in the sum of the plasma concentrations of venlafaxine and the active metabolite O- desmethylvenlafaxine 2. if necessary, increase the dose to 150% of the standard dose 3. if dose adjustment does not result in efficacy without unacceptable side effects or if dose adjustment based on therapeutic drug monitoring is not possible, then venlafaxine should be avoided. Antidepressants that are not metabolised by CYP2D6 - or to a lesser extent - include, for example, duloxetine, mirtazapine, citalopram and sertraline.
CYP2D6 IM	Venlafaxine	There are indications of an increased risk of side effects and a reduced chance of efficacy. The gene variation reduces the conversion of venlafaxine to the active metabolite O-desmethylvenlafaxine, whilst an association between high O-desmethylvenlafaxine/venlafaxine ratios and response without side effects was found.	It is not possible to offer adequately substantiated advice for dose reduction based on the literature. - avoid venlafaxine. Antidepressants that are not metabolised by CYP2D6 - or to a lesser extent - include, for example, duloxetine, mirtazapine, citalopram and sertraline. - if it is not possible to avoid venlafaxine and side effects occur: 1. reduce the dose 2. monitor the effect and side effects or check the plasma concentrations of venlafaxine and O-desmethylvenlafaxine. It is not known whether it is possible to reduce the dose to such an extent that the side effects disappear, while the effectiveness is maintained. In general, it is assumed that the effectiveness is determined by the sum of the plasma concentrations of venlafaxine and O-desmethylvenlafaxine. However, the side effects do not appear to be related to this sum.
CYP2D6 PM	Venlafaxine	There are indications of an increased risk of side effects and a reduced chance of efficacy. The gene variation reduces the conversion of venlafaxine to the active metabolite O-desmethylvenlafaxine, whilst an association between high O-desmethylvenlafaxine/venlafaxine ratios and response without side effects was found.	It is not possible to offer adequately substantiated advice for dose reduction based on the literature. - avoid venlafaxine. Antidepressants that are not metabolised by CYP2D6 - or to a lesser extent - include, for example, duloxetine, mirtazapine, citalopram and sertraline. - If it is not possible to avoid venlafaxine and side effects occur: 1. reduce the dose 2. monitor the effect and side effects or check the plasma concentrations of venlafaxine and O-desmethylvenlafaxine. It is not known whether it is possible to reduce the dose to such an extent that the side effects disappear, while the effectiveness is maintained. In general, it is assumed that the effectiveness is determined by the sum of the plasma concentrations of venlafaxine and O-desmethylvenlafaxine. However, the side effects do not appear to be related to this sum. Furthermore, a reduced effectiveness of venlafaxine has been observed in depression patients with this gene variation.

UM: Ultrarapid Metabolizer, IM: Intermediate Metabolizer, PM: Poor Metabolizer

Table 5.4. Guidelines Venlafaxine.

Table 5.5. Guidelines Clomipramine			
Allele/ Genotype/ Phenotype	**Drug**	**Description**	**Recommendation**
CYP2D6 UM	Clomipramine	Increased metabolism of TCAs to less active compounds compared to normal metabolizers. Lower plasma concentrations of active drug will increase probability of pharmacotherapy failure.	Avoid tricyclic use due to potential lack of efficacy. Consider alternative drug not metabolized by CYP2D6. If a TCA is warranted, consider titrating to a higher target dose (compared to normal metabolizers). Utilize therapeutic drug monitoring to guide dose adjustments.
CYP2D6 IM	Clomipramine	Reduced metabolism of TCAs to less active compounds when compared to normal metabolizers. Higher plasma concentrations of active drug will increase the probability of side effects.	Consider 25% reduction of recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments.
CYP2D6 PM	Clomipramine	Greatly reduced metabolism of TCAs to less active compounds compared to normal metabolizers. Higher plasma concentrations of active drug will increase the probability of side effects.	Avoid tricyclic use due to potential for side effects. Consider alternative drug not metabolized by CYP2D6. If a TCA is warranted, consider 50% reduction of recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments.
UM: Ultrarapid Metabolizer, IM: Intermediate Metabolizer, PM: Poor Metabolizer			

Table 5.5. Guidelines Clomipramine.

In 2 cases (patients no. 1, 3) the initial dose was increased within the first 7 days after the genetic testing. Patient no. 1, as an intermediate metabolizer of citalopram received an increased dose of 20mg per day, instead of 10mg per day which she received for the initial 6 days after the recruitment in the study. The dose of escitalopram of patient no. 3 increased from 10mg per day to 15mg per day at the 7th day after her recruitment for the same reason. Neither of these two patients received concomitant medications during their time being in the study as well as none of them suffered from any adverse reaction or was in need of hospitalization due to ADRs.

4.5 Direct treatment costs and evaluation of effectiveness

In the frame of the cost estimation for MDD, only direct health care costs were calculated since the majority of the funding bodies in Greece consider the health care perspective as the reference case. The direct cost of healthcare consists of all of the patient care resources consumed during a depressive episode or remission. Specifically, the costs of hospitalizations, the outpatient visits to the health care professionals for monitoring and medical advice, medication costs, laboratory testing, and adverse event management were examined. An expert panel provided the data for resource utilization during the examination period.

In the case of antidepressants as baseline therapy for MDD, the health care providers are charged with 100% of the reimbursed price of the drug since patients'

participation is 0% of the reimbursed price. As far as the concomitant medications are concerned, such as sedatives, antipsychotics, antiepileptics or other drugs that the patients in the study received, the health care providers are charged with 75% or 90% of their reimbursed price depending on the clinical picture and the diagnosis of the patient. The active substances of each pharmaceutical category that the patients received (original drugs), along with their brand names, the reimbursed prices during the exact period that the patients were enrolled in the study and each price/mg are illustrated in tables 6.1., 6.2., 6.3., 6.4., 6.5. (Greek Ministry of Health 07/2017, 09/2017, 11/2017, 12/2017, 02/2018, 08/2018, 07/2019).

Table 6.1. Prices of Antidepressants

Antidepressant (AS)	Brand name	C (mg)	Count	R. Price 07/2017	R. Price 09/2017	Price/mg 07-09/2017	R. Price 11/2017	Price/mg 11/2017	R. Price 12/2017	Price/mg 12/2017	R. Price 02/2018	Price/mg 02/2018	R. Price 08/2018	Price/mg 08/2018	R. Price 07/2019	Price/mg 07/2019
Citalopram	Seropram	20	28	6,29	6,29	0,011	6,34	0,011	6,34	0,011	6,17	0,011	6,13	0,011	6,20	0,011
Escitalopram	Cipralex	10	14	3,34	3,34	0,024	3,34	0,024	3,34	0,024	3,28	0,023	3,23	0,023	3,27	0,023
Escitalopram	Cipralex	20	14	6,29	6,29	0,022	6,34	0,023	6,34	0,023	6,17	0,022	6,13	0,022	6,20	0,022
Venlafaxine	Efexor	75	28						6	0,003	5,40	0,003	4,85	0,002	4,85	0,002
Venlafaxine	Efexor	150	28	7,7	7,7	0,002	7,7	0,002	7,7	0,002	7,62	0,002	7,62	0,002	7,61	0,002
Sertraline	Zoloft	50	14	3,33	3,34	0,005	3,34	0,005	3,34	0,005	3,28	0,005	3,23	0,005	3,27	0,005
Sertraline	Zoloft	100	14	5,39	5,39	0,004	5,39	0,004	5,39	0,004	4,86	0,003	4,37	0,003	4,37	0,003
Clomipramine	Anafranil	75	20						4,7	0,003	4,70	0,003	4,70	0,003	4,70	0,003
Paroxetine	Seroxat	20	30						6,47	0,011	6,61	0,011	6,44	0,011	6,44	0,011
Paroxetine	Seroxat	30	30						8,67	0,010	8,28	0,009	8,28	0,009	8,28	0,009
Trazodone	Trittico	50	30	1,41	1,41	0,001	1,41	0,001	1,41	0,001	1,38	0,001	1,36	0,001	1,35	0,001
Mirtazapine	Remeron	30	30						7,89	0,009	7,81	0,009	7,81	0,009	7,81	0,009
Fluoxetine	Ladose	20	28						7,1	0,013			7,10	0,013	7,10	0,013
Vortioxetine	Brintellix	10	28						30,9	0,110			28,65	0,102	28,54	0,102

Table 6.2. Prices of Sedatives

Sedative (AS)	Brand name	C (mg)	Count	R. Price 07/2017	R. Price 09/2017	Price/mg 07-09/2017	R. Price 11/2017	Price/mg 11/2017	R. Price 12/2017	Price/mg 12/2017	R. Price 02/2018	Price/mg 02/2018	R. Price 08/2018	Price/mg 08/2018	R. Price 07/2019	Price/mg 07/2019
Buspirone	Bespar	10	20	4,02	4,02	0,015	4,02	0,015	4,02	0,015	4,02	0,015	4,02	0,015	4,02	0,015
Alprazolam	Xanax	0,25	30				0,68	0,068	0,68	0,068	0,68	0,068	0,62	0,062	0,65	0,065
Alprazolam	Xanax	0,5	30	1,36	1,36	0,068	1,36	0,068	1,36	0,068	1,36	0,068	1,24	0,062	1,3	0,065
Alprazolam	Xanax	1	30	2,52	2,52	0,063	2,52	0,063	2,73	0,068	2,52	0,063	2,48	0,062	2,48	0,062
Alprazolam	Xanax	2	30						5,46	0,068	5,45	0,068	4,97	0,062	5,2	0,065
Lorazepam	Tavor	1	18	0,65	0,65	0,027	0,65	0,027	0,65	0,027	0,65	0,027	0,6	0,025	0,62	0,026
Lorazepam	Tavor	2,5	18	1,3	1,3	0,022	1,3	0,022	1,3	0,022	1,3	0,022	1,18	0,020	1,19	0,020
Clonazepam	Clonotril	2	30		2,22	0,028	2,22	0,028	2,22	0,028	2,22	0,028	2,22	0,028	3,06	0,038
Diazepam	Stedon	10	30						1,46	0,004	1,46	0,004	1,46	0,004	1,46	0,004
Hydroxyzine	Atarax	25	25						1,08	0,001			1,08	0,001	1,08	0,001
Trihexyfenidyl	Artane	2	50		5,93	0,044	5,93	0,044	5,93	0,044	5,93	0,044	5,93	0,044	5,93	0,044
Bromazepam	Lexotanil	1,5	30						0,41	0,007			0,37	0,006	0,39	0,007
Bromazepam	Lexotanil	3	30						0,82	0,007			0,75	0,006	0,78	0,007

Table 6.3. Prices of Antipsychotics

Antipsychotic (AS)	Brand name	C (mg)	Count	R. Price 07/2017	R. Price 09/2017	Price/mg 07-09/2017	R. Price 11/2017	Price/mg 11/2017	R. Price 12/2017	Price/mg 12/2017	R. Price 02/2018	Price/mg 02/2018	R. Price 08/2018	Price/mg 08/2018	R. Price 07/2019	Price/mg 07/2019
Quetiapine	Seroquel	25	60								5,02	0,003	5,04	0,003	5,11	0,003
Quetiapine	Seroquel	100	60								19,88	0,002	19,88	0,002	19,88	0,002
Quetiapine	Seroquel	200	60	32,74	32,74	0,002	32,74	0,002	32,74	0,010	32,74	0,002	32,74	0,002	32,74	0,002
Quetiapine	Seroquel	300	30								24,49	0,002	24,63	0,002	24,58	0,002
Olanzapine	Zyprexa	5	28								15,99	0,086	15,73	0,084	15,73	0,084
Olanzapine	Zyprexa	20	28										68,45	0,092	68,47	0,092
Olanzapine	Zypadhera	405	1												277,4	
Aripiprazole	Abilify	30	28										37,96	0,034	38,2	0,034
Haloperidol	Aloperidin	10	20										2,7	0,010	2,7	0,010
Paliperidone	Invega	6	28										93,19	0,416	92,8	0,414

Table 6.3. Prices of Antipsychotics.

Table 6.4. Prices of Antiepileptics

Antiepileptic (AS)	Brand name	C (mg)	Count	R. Price 07/2017	R. Price 09/2017	Price/mg 07-09/2017	R. Price 11/2017	Price/mg 11/2017	R. Price 12/2017	Price/mg 12/2017	R. Price 02/2018	Price/mg 02/2018	R. Price 08/2018	Price/mg 08/2018	R. Price 07/2019	Price/mg 07/2019
Lamotrigine	Lamictal	200	30	12,94	12,94	0,002	12,94	0,002	12,94	0,002	12,94	0,002	12,94	0,002	12,94	0,002
Carbamazepine	Tegretol	200	50								3,59	0,0003	3,57	0,0003	3,57	0,0003
Carbamazepine	Tegretol	400	30								4,28	0,0003	4,26	0,0003	4,26	0,0003
Valproate acid	Depakin	1000	30								7,81	0,0002	7,71	0,0002	7,65	0,0002

Table 6.4. Prices of Antiepileptics.

Table 6.5. Prices of other comeds

Other comeds (AS)	Brand name	C (mg)	Count	R. Price 12/2017	Price/mg 12/2017	R. Price 02/2018	Price/mg 02/2018	R. Price 08/2018	Price/mg 08/2018	R. Price 07/2019	Price/mg 07/2019
Sumatriptan	Imigran	100	2	4,01	0,015	3,61	0,014	3,31	0,012	3,31	0,012
Biperiden	Akineton	4	50	3,77	0,014			6,05	0,023	6,05	0,023

Table 6.5. Prices of other comedications.

Based on the raw data with the active substances each patient received – baseline and comorbid medication – at a specific dose per day for a specific period of time enrolled, combined with the positive drug reimbursement lists for the corresponding time periods, total costs per patient, daily costs, monthly costs and mean monthly cost per patient were calculated for both arms and are summarized in table 7.1. On average, the total medication costs were €17,66 per patient per month and €17,47, respectively, for I arm versus C arm, yielding similar pharmaceutical expenditures for both arms per month enrolled. Males in the control arm consumed 108,04% more depression-related pharmaceutical medications, compared with the

males in the intervention arm. On the other hand, females in the intervention group consumed 49,96% more pharmaceutical medications compared with the females in the control group.

Table 7.1. Statistical results of the model [monthly costs (€) per patient group].		
Statistics	**Intervention group**	**Control group**
Mean	**17,66**	**17,47**
SD	**25,23**	**26,29**
Minimum	**3,51**	**3,30**
LCI	**8,32**	**8,63**
Median	**9,13**	**10,69**
UCI	**27,01**	**26,31**
Maximum	**129,18**	**149,44**
Variance	**636,39**	**691,23**
Number of Sample	**28**	**34**
Mean Male	**13,67**	**28,44**
SD Male	**11,81**	**49,28**
Mean Female	**21,13**	**14,09**
SD Female	**32,87**	**13,49**

Table 7.1. Statistical results of the model [monthly costs (€) per patient group].

Patients aged 18-39 years in the control arm consumed 24,62% more on drugs compared to the same Age-Group of patients in the intervention arm, patients aged 40-61 years had similar pharmaceutical expenditures in both arms, with the intervention arm consuming only 1,09% more than the control one and comparing the oldest Age-Group, aged 62-84 years, higher relevant costs were generated by the control arm, namely 4,72%, versus the intervention arm. These statistical results are summarized in Table 7.2.

Table 7.2. Statistical results according to Age-Group [monthly costs (€) per patient group].			
Arm	**18-39 years old**	**40-61 years old**	**62-84 years old**
Mean Intervention arm	16,61 (N=8)	17,66 (N=15)	15,34 (N=5)
SD Intervention arm	29,90	25,23	26,25
Mean Control arm	20,7 (N=4)	17,47 (N=22)	18,08 (N=8)
SD Control arm	32,32	26,29	27,49

Table 7.2. Statistical results according to Age-Group [monthly costs (€) per patient group].

In the stratum of normal weight patients, control arm yielded 2,18% higher medication costs compared with the intervention arm. Overweight patients in the control arm consumed 15,96% more on drug medication than overweight patients in the intervention arm and pharmaceutical costs of obese patients in the control arm were 4,78% higher than the relevant costs in the intervention arm. Statistical results according to BMI are illustrated in Table 7.3.

Table 7.3. Statistical results according to BMI [monthly costs (€) per patient group].				
Arm	**Underweight (<18,5 kg/m^2)**	**Normal weight (18,5-24,9 kg/m^2)**	**Overweight (25-29,9 kg/m^2)**	**Obese (≥30 kg/m^2)**
Mean Intervention arm	13,17 (N=1)	18,37 (N=11)	15,29 (N=10)	17,98 (N=6)
SD Intervention arm	0	26,07	26,26	25,65
Mean Control arm	0 (N=0)	18,77 (N=11)	17,73 (N=15)	18,84 (N=7)
SD Control arm	-	28,31	26,66	29,98

Table 7.3. Statistical results according to BMI [monthly costs (€) per patient group].

When examined according to specific drug category, despite the smaller size of the sample, more patients in the intervention arm received sedative and antipsychotic comorbid medication than patients in the control arm, who received more

antidepressant comedication versus the I arm. The intervention arm consumed 14,26%, on monthly average, more for antipsychotic drugs as comedication, 79,24% more for sedative drugs as comorbid therapy, 458% more on antiepileptic comorbid therapy and almost 22 times more on other comedications versus the C arm. On the other hand, C arm yielded 22% higher pharmaceutical expenditures per month across the index drug category and 215% higher costs across the antidepressant comorbid category than the I arm. Both arms consumed almost the same amount of money monthly on average for subsequent baseline therapy. Figures 4.2.1. and 4.2.2. detail the number of patients that consumed each drug category and the mean pharmaceutical expenditures per patient per month for each drug category, respectively.

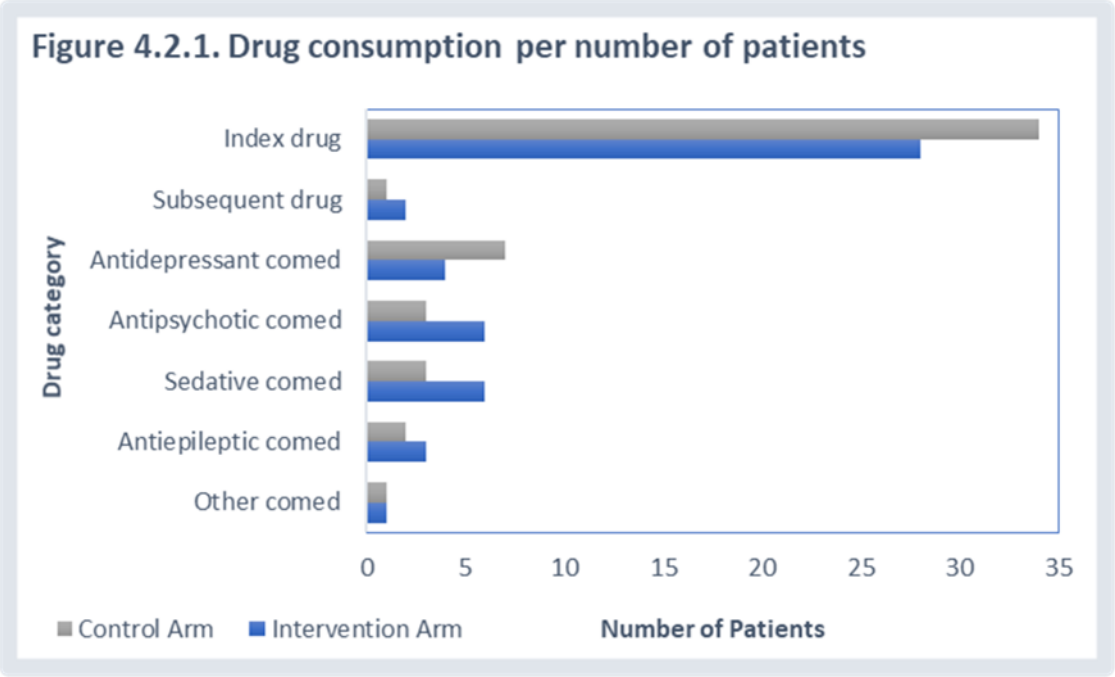

Figure 4.2.1. Drug consumption per number of patients.

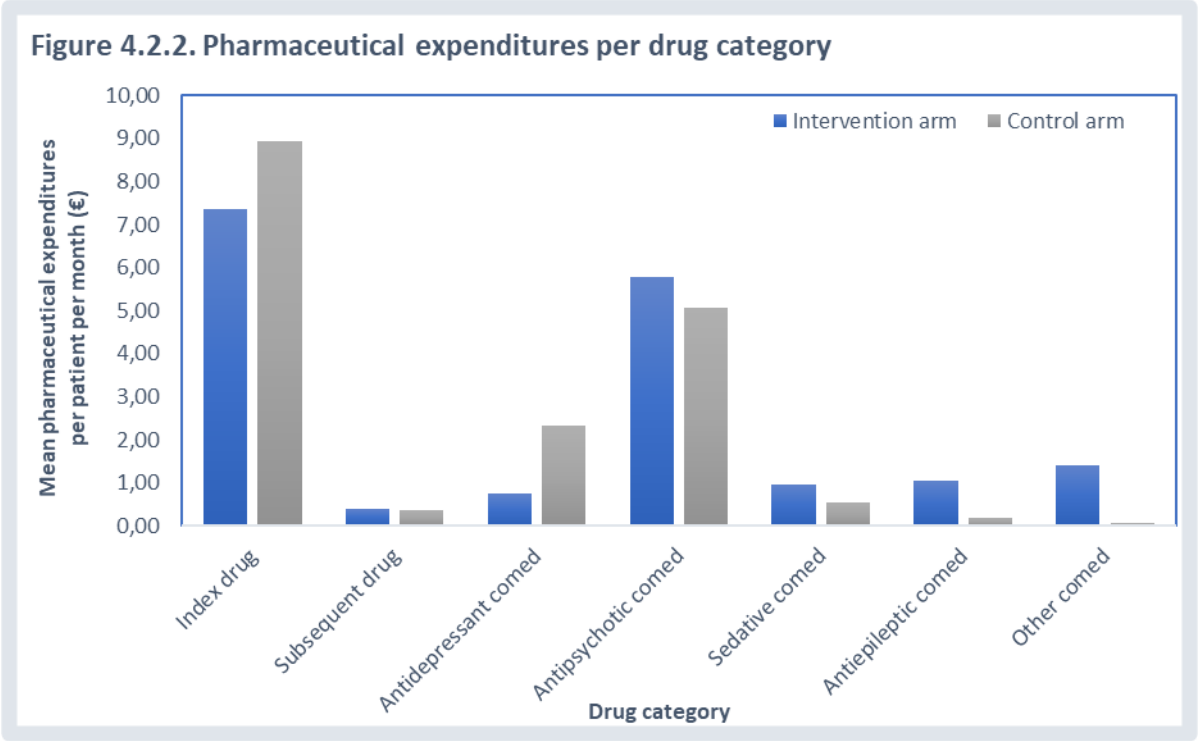

Figure 4.2.2. Pharmaceutical expenditures per drug category.

In the stratum of patients enrolled in the intervention arm, 44,92% of the total cost for pharmaceutical regimen was consumed for the baseline therapy, i.e. index and subsequent drugs, whereas the 55,08% of total costs was dedicated for comorbid medication. Out of 55,08% for concomitant therapies, antipsychotics had higher costs across all categories. Figure 4.3.1. summarizes cost percentages consumed per drug category in total by the intervention arm.

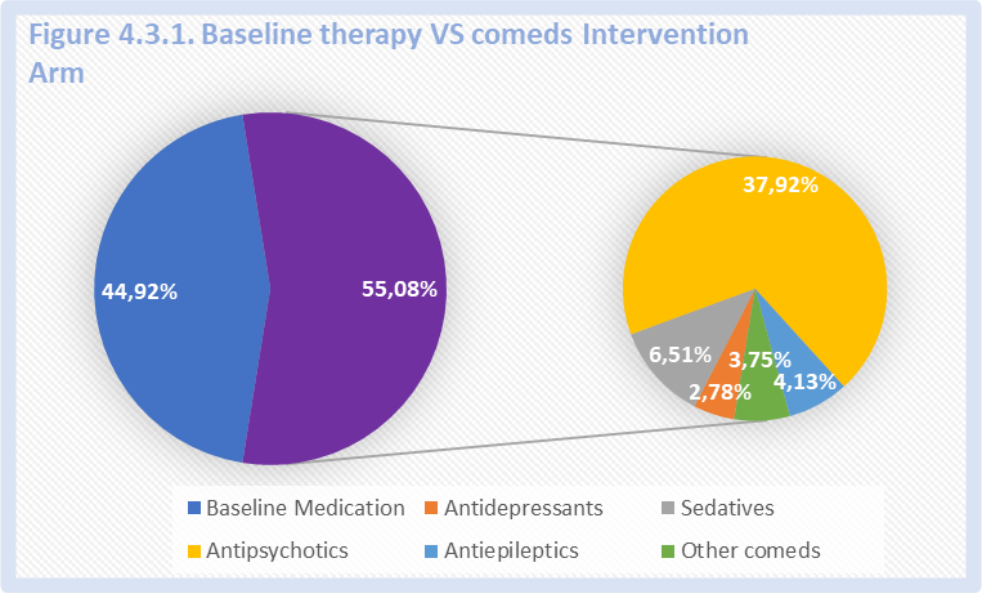

Figure 4.3.1. Baseline therapy VS comedications, Intervention Arm.

Considering the control arm, 52,47% of total costs for pharmaceutical medications was consumed for baseline therapy versus the concomitant medications, for which 47,53% of the total cost was consumed. Out of the latter percentage, once again antipsychotics represented the higher costs among all comorbid regimens. Figure 4.3.2. lists cost percentages consumed per drug category in total by the control arm.

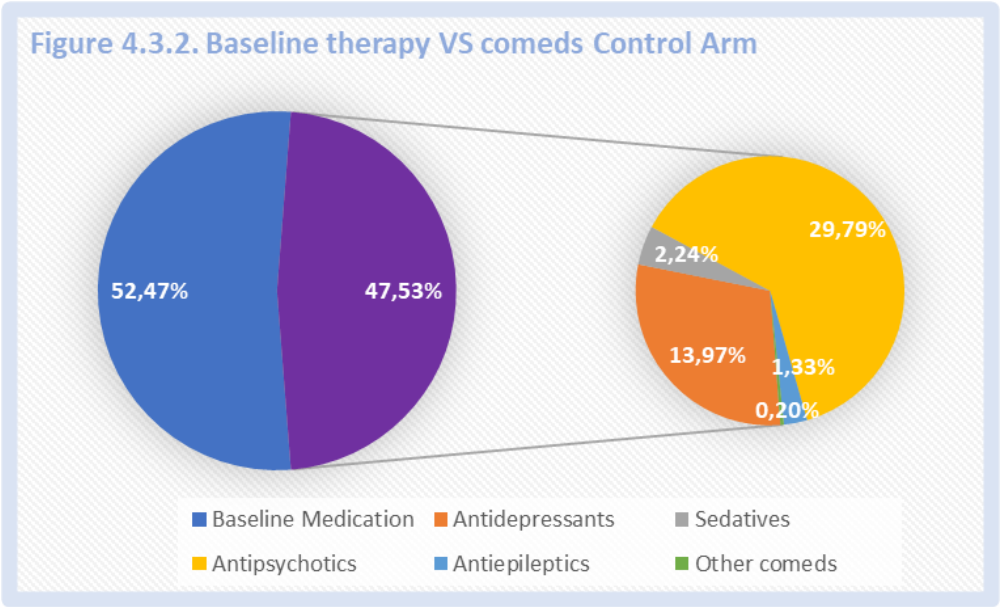

Figure 4.3.2. Baseline therapy VS comedications, Control Arm.

Apart from the pharmacy costs, outpatient costs were also examined, with a specialist being responsible for the frequent monitoring of patients, which increased the direct treatment costs of the patients and the cost of illness for MDD. As far as the inpatient costs were concerned, only patient no. 24 was hospitalized for 31 days since his recruitment day in the intervention arm due to illness and not due to medication's ADRs. His hospitalization cost for these 31 days was €1240 because of the daily hospitalization cost for the psychiatric domain (Greek Ministry of Health 2011). Table 7.4. illustrates the direct non pharmacy costs of MDD, with the intervention arm consuming 66,83% more than the control arm, because of the case of hospitalization.

Table 7.4. Outpatient monitoring & Hospitalization Cost [monthly costs (€) per patient group].

Intervention arm	Control Arm
16,35	9,80

It is now well established that MDD is significantly associated with a wide variety of chronic physical disorders, including arthritis, asthma, cancer, cardiovascular disease, diabetes, hypertension, chronic respiratory disorders, and a variety of chronic pain conditions. Although most of the data documenting these associations comes from clinical samples in the United States, similar data also exist from community epidemiologic surveys carried out throughout the world. These associations have considerable individual and public health significance and can be thought of as representing costs of depression in at least 2 ways. First, to the extent that MDD is a causal risk factor, it leads to an increased prevalence of these physical disorders, with all their associated financial costs, impairments, and increased mortality risk. MDD is a consistent predictor of the subsequent first onset of coronary artery disease, stroke, diabetes, heart attacks, and certain types of cancer. Second, even if depression is more a consequence than a cause of chronic physical disorders, as it seems to be for some disorders based on stronger prospective associations of depression onset subsequent to, rather than before, onset of the physical disorder, comorbid depression is often associated with a worse course of the physical disorder. A number of reasons could be involved here, but one of the most consistently documented is that depression

is often associated with nonadherence to treatment regimens. Based on these considerations, it should not be surprising that MDD is associated with a significantly elevated risk of early death. This is true partly because people with MDD have a high suicide risk, but also because depression is associated with elevated risk of the many types of disorders noted. MDD is also associated with elevated mortality risk among people with certain kinds of disorders as part of a larger pattern of associations of MDD with disorder severity. (The Costs of Depression Ronald C. Kessler, PhD)

The event endpoints of the current model as far as the evaluation of the effectiveness was concerned, included toxicity derived from the baseline or concomitant medication, the medical management of moderate/severe ADRs, persistent social and vocational disability, increased risk of suicide and greater medical morbidity and mortality. The management of a moderate/severe adverse event (Grade 2,3) was assumed to require a physician visit with results in drug prescription or immediate medical attention with the relevant medical and hospitalization costs. The management of a mild adverse event (Grade 1) did not require medical attention and, as a result, health care utilization costs. The classification of the ADRs of the index drugs according to which the cost of illness would be enlarged, is summarized in Table 8.1.

Table 8.1. ADRs of Index Drugs					
ADRs	**Citalopram**	**Escitalopram**	**Venlafaxine**	**Sertraline**	**Clomipramine**
Mild (Grade 1)	Problems with memory or concentration, headache, drowsiness, dry mouth, increased sweating, numbness or tingling, increased appetite, nausea, diarrhea, gas, feeling shaky, sleep problems (insomnia), feeling tired, cold symptoms such as stuffy nose, sneezing, sore throat, changes in weight, difficulty having an orgasm	Constipation, decreased interest in sexual intercourse or loss in sexual ability, diarrhea, dry mouth, ejaculation delay, gas in the stomach, heartburn, inability to have or keep an erection, sleepiness or unusual drowsiness, trouble	Nausea, vomiting, diarrhea, changes in appetite or weight, dry mouth, yawning, dizziness, headache, anxiety, feeling nervous, fast heartbeats, tremors or shaking, sleep problems (insomnia), strange dreams, tired feeling, vision changes, increased sweating, decreased sexual interest, impotence, or difficulty having an orgasm	Drowsiness or tiredness, insomnia or agitation, indigestion, nausea, diarrhea, loss of appetite, sweating, tremors or shaking, sleep problems (insomnia) decreased sexual interest, impotence, difficulty having an orgasm	Blistering, crusting, irritation, itching, change in taste, cracked, dry, or scaly skin, redness of the face, neck, arms, and occasionally, upper chest, shakiness in the legs, arms, hands, or feet, heartburn, inability to have or keep an erection, joint pain or swelling, pimples, constipation, diarrhea, stomach discomfort, upset or pain, swelling, trembling or shaking of the hands or feet, change in interest in sexual intercourse
Moderate (Grade 2) and Severe (Grade 3)	Skin rash or hives, difficulty breathing, swelling of your face, lips, tongue, or throat, mood or behavior changes, anxiety, panic attacks, feeling impulsive, irritable, hostile, aggressive, restless, hyperactive (mentally or physically), more depressed, or having thoughts about suicide or hurting yourself, a light-headed feeling, blurred/ tunnel vision, eye pain, seeing halos around lights, headache with chest pain and severe dizziness, severe nervous system reaction or high levels of serotonin in the body or low levels of sodium in the body--very stiff (rigid) muscles, high fever, sweating, confusion, fast or uneven heartbeats, tremors,agitation, hallucinations, fever, overactive reflexes, nausea, vomiting, diarrhea, loss of coordination, fainting, severe headache/weakness, slurred speech	Coma, confusion, convulsions, decreased urine output, dizziness, fast or irregular heartbeat, headache, increased thirst, muscle pain or cramps, nausea or vomiting, shortness of breath, swelling of the face, ankles, or hands, unusual tiredness or weakness	Skin rash or hives, swelling of your face, lips, tongue, or throat, blurred vision, tunnel vision, eye pain, seeing halos around lights, easy bruising or bleeding (nosebleeds, bleeding gums), blood in your urine or stools, coughing up blood, cough, chest tightness, a seizure (convulsions), low levels of sodium in the body or severe nervous system reaction- headache, confusion, slurred speech, severe weakness, severe vomiting, hallucinations, feeling unsteady, difficulty breathing, very stiff (rigid) muscles, high fever, sweating, fast or uneven heartbeats, tremors, agitation, fever, sweating, shivering, fast heart rate, twitching, loss of coordination, severe nausea, severe vomiting, severe diarrhea	Skin rash or hives, difficulty breathing, swelling of your face, lips, tongue, or throat, agitation, hallucinations, fever, consistent sweating, shivering, fast heart rate, muscle stiffness, twitching, loss of coordination, consistent nausea, consistent vomiting, consistent diarrhea	Bladder pain, bloody or cloudy urine, difficult, burning or painful urination, dizziness, faintness, or lightheadedness when getting up suddenly from a lying or sitting position,blurred vision, body aches or pain, burning, crawling, consistent itching, numbness, prickling, "pins and needles", or tingling feelings, excessive muscle tone, lower back or side pain, muscle stiffness, tension, or tightness, tightness of the chest, trouble breathing, unusual tiredness or weakness, confusion, fear or nervousness, feeling sad or empty, fever, hearing or voice changes, hives or welts, skin rash, irritability, poor concentration, sneezing

Table 8.1. ADRs of Index Drugs.

The source of the data used for this aspect of the study was the panel expert opinion, with the specialist responsible for the monitoring of patients recording the presence of mild or moderate/severe ADRs and their management through medical tests or hospitalization, if necessary. From the intervention arm, 46,4% of patients appeared mild ADRs, the management of which required no medical attention, and therefore, no tests due to ADRs or health care utilization costs. From the control arm, 8,8% of patients experienced mild ADRs due to the therapy they followed, but none of them had moderate/severe ADRs, leading to increased medical costs. Table 8.2. illustrates the presence of ADRs in both arms and their economic consequences.

Table 8.2. ADRs Intervention & Control Arm.					
Arm	ADR presence	Tests due to ADR	Cost of tests (€)	Hospitalization due to ADR	Cost of hospitalization (€)
Intervention	46,40%	0%	0,00	0%	0,00
Control	8,80%	0%	0,00	0%	0,00

Table 8.2. ADRs Intervention & Control Arm.

Since no differences in overall survival, toxicity, suicides, morbidity or quality of life were recorded, the evaluation of effectiveness of personalized medication could not be conducted at this point, leaving the aim of this study being only the economic burden of MDD.

After the evaluation of the effectiveness and calculation of ICER, a sensitivity analysis would be conducted to find out which factor most affects the result and to cover the uncertainty in an effort to figure out how close our sample is to the population. It is undoubtedly meaningful for the decision makers to be mindful of the scope of potential scenarios that a sensitivity analysis tests. Since effectiveness of personalized treatment after genotyping has not been examined and since none of the factors examined has significantly affected the cost of treating MDD, sensitivity analysis has not been performed.

CHAPTER 5: CONCLUSIONS

The current study analyzes a small sample of the clinical study conducted by the Laboratory of Pharmacogenomics and Individualized Therapy of the University of Patras and the Psychiatric Clinic of the General University Hospital of Patras. The current study's incentive was to estimate the total per-patient economic burden of MDD, both for standard therapy and pharmacogenetic-guided treatment from the perspective of decision makers managing health care expenditures.

If the intervention arm's results showed that patients were receiving lower doses of drugs compared with the control arm, which of course would translate into fewer adverse event reactions, this would be a sign of cost reduction for both the health system and on the part of patients, but it would also mean better quality of life for individuals.

The cost of genetic testing for CYP2D6 and CYP2C19, the metabolic enzymes related to the metabolism of antidepressants, was calculated to have a retail price of €198,46, the cost of monitoring had a retail price for patients of €10 and the cost for patients of hospitalization was €40 per day.

Both arms yielded similar pharmaceutical expenditures per month enrolled, namely, €17,66 per patient for the intervention arm versus €17,47 for the control arm, respectively. The biggest difference in costs found in the study was the male consumption of drugs in the control arm, 108,04% greater than the relevant male consumption in the intervention arm. Equally important was the drug consumption difference in the stratum of the females enrolled, as the intervention arm consumed 49,96% more than the control group. Only the Age-Group of 18-39 years exhibited notable cost difference, with the control arm having consumed 24,62% more than the intervention arm. Considerably higher was the pharmaceutical expenditures of the overweight patients in the control arm, who consumed 15,96% more than overweight patients in the intervention arm.

44,92% of the total cost for pharmaceutical regimen was consumed for baseline therapy in the intervention arm versus 52,47% in the control arm, while antipsychotics represented the higher costs among all comorbid regimens. Across the comorbid medications, the intervention arm consumed 79,24% more on sedative drugs, 458% more on antiepileptic drugs and almost 22 times more on other

comedications versus the C arm, whereas the control arm yielded 215% higher costs across the antidepressant comorbid category than the intervention arm.

2 patients from the intervention arm changed into personalized treatment within the first 7 days after the genetic testing, neither of whom received concomitant medications or suffered from any adverse drug reaction during the enrollment in the study. Other direct non pharmacy costs included the outpatient monitoring and the hospitalization cost, which were translated into €16,35 and €9,80 on monthly average for the intervention and the control arm, respectively. This striking difference appeared due to the hospitalization cost generated for one case from the intervention arm, which was €1240 but it was caused from the illness and not due to ADRs.

46,4% of patients in the intervention arm appeared mild ADRs versus 8,8% of patients in the control arm. None of the patients in both arms had moderate or severe ADRs, which would have led to increased medical costs.

Other studies have shown that some of the economic healthcare burden for psychiatric patients may be predicted by multi-gene, pharmacogenomic approaches. (Winner , et al. 2013) conducted a retrospective study with the use of a genotype interpretive report, termed GeneSight, based on which, patients' medication status was identified to be either in the "use with caution and more frequent monitoring" (red bin) category, "use with caution" (yellow bin) category and "use as directed" (green bin) category. Subjects receiving medication from the red bin category had 69% more healthcare visits, 67% more nonpsychiatric medical visits, over 4 times the average number of disability claims per person during the 1 year retrospective chart review, more medical absence days and greater healthcare utilization costs in comparison with the green or yellow binned patients. Prospective trial (J. Winner, J. Carhart , et al. 2015) with the implementation of GeneSight in 2168 subjects who failed initial therapy for their psychiatric condition and typically represent about half of all treated depression patients, reported annual savings over $1000 in direct costs, along with reduced incidence of ADRs and greater effectiveness of antidepressant medication regimens since patients' exposure to polypharmacy was decreased in comparison with 10,880 patients who received untested standard of care.

A growing body of literature shows that the appropriate treatment of mental illness improves outcomes of comorbid non-CNS medical conditions and lowers cost for their treatment. This pattern was found by (J. Winner, J. Carhart , et al. 2015), where significant annual savings for diabetes ($286.95), oncology ($640.01), and cardiovascular ($168.17) medications were obtained in the PGx congruent subgroup

suggesting that non-CNS pharmacy spend savings might be a consequence of improvement in patients' psychiatric conditions or a consequence of cost efficient changes to non-CNS medications by the clinicians in light of the pharmacogenomic information.

More findings by (Brandley, et al. 2018), who enrolled 685 patients diagnosed with depression and/or anxiety in the scope of a randomized, multicenter, double-blind clinical trial showed significantly higher response rates through medication management guided by NeuroIDgenetix, which uses a genetic variant panel of 10 genes, along with concomitant medications, compared with patients receiving standard of care (73% vs 36%, P=0.001). In addition to this, higher remission rates were recorded for the experimental group compared to control (35% vs 13%, P=0.02) and a potential annual cost savings of USD$3,962 per patient tested with NeuroIDgenetix.

These average annual increases in direct and indirect medical utilizations that the chart reviews demonstrated for subjects on more problematic medications propose that keeping patients off of these drugs might cause a reduction in healthcare utilization, while concomitantly offer the possibility of improved efficacy and quality of life.

Our analysis pursued is characterized by specific drawbacks and limitations. First of all, the results have to be considered in the strict Greek setting and on the basis of the present time resource and drug prices. If any of the underlying parameters change, so may the results and the conclusions of the analysis. The Greek health care system is a mixed system, combining Social Health Insurance (SHI) and central financing of the National Health System (NHS). Considerable structural and efficiency-oriented reforms have been initiated since 2010, many in response to the country's Economic Adjustment Programme (EAP). In a major reform, the National Organisation for the Provision of Health Services (known as EOPYY) was created in 2011 by merging the health branches of the major (occupation-based) social security funds, and it now acts as the main purchaser of health services. However, plans to transfer more powers to regional health authorities have had less impact and the health sector remains highly centralized.

The goal of our analysis identifies with the goal of pharmacogenomic-based personalized medicine, which is to provide information that can better define treatments for individual patients and increase the rate or amount of their therapeutic improvement. In addition to, and possibly as a result of these clinical benefits, pharmacogenomic testing also has the potential to decrease direct and indirect

medical costs. Nevertheless, our study does not incorporate Quality of Life or Willingness to Pay Thresholds. Future studies could develop cost-effectiveness models with varying time horizons and cost perspectives (payer, patient) to better approximate the costs and savings associated with pharmacogenetic testing. Future research should also analyze further comorbid conditions, which account for a large portion of the growing economic burden of MDD, as well as the relative importance of factors contributing to that growing burden. These include population growth, increase in MDD prevalence, increase in treatment cost per individual with MDD, changes in employment and treatment rates, as well as changes in the composition and quality of MDD treatment services.

Models such as Markov or Discrete Event Simulation would allow for sensitivity analyses to assess the robustness of the model results and provide more reliable data. Another limitation of the present study is the lack of therapeutic outcome information. This study was limited to cost savings analysis, and it is thus unknown if cost savings and medication response are directly related. However, previous clinical trials found that patients were more likely to respond and had better outcomes when treatment was guided with the combinatorial PGx test results versus TAU (Treatment as Usual).

At this point, it should be noticed that the results of such a pharmacoeconomic study should be considered in conjunction with a list of other factors to make a decision on antidepressant treatment. Based on a recently published review by (Himmerich and Wranik 2012), the potential determinants of antidepressant treatment choice are classified into seven categories, including illness and treatment characteristics, patient and physician characteristics, treatment setting characteristics, decision supports and pharmacoeconomic aspects.

Since genomic medicine has the potential to shift the emphasis in medicine from clinical/therapeutic intervention to prevention, foster the selection of optimal therapies, reduce trial-and-error prescribing and aid in containing the overall cost of health care in the medium to long term, it also requires several important factors such as universal access, affordability, acceptability, fairness, solidarity and appropriateness, demonstration of proven cost-effectiveness and appropriate knowledge and education (for clinicians and patients) available. Patients rely traditionally on their doctors' professional opinion and generally follow their advice. In recent decades, the clinician-patient relationship has evolved into a partnership model. For these patients, it is crucial to have easy access to reliable information about their own disease/condition, and treatment options in clear and nontechnical language. This

applies in particular to the complex field of genomic medicine. Last but not least, political engagement and willingness to change existing health care, while Allowing Space for Innovation Necessary to Move the Field Forward, are required, along with appropriate policy and legislation. If payers are unwilling to reimburse the costs of genomic testing services, progress towards incorporation and implementation will be stalled. Reimbursement decisions in relation to genomic testing are complicated, and although genomic testing has been performed for more than 20 years, the respective decision-making process is still evolving.

In Greece, short-term investment in infrastructure and equipment is indeed needed to make the pharmacogenomic approach on a large scale, and in the midst of the Greek crisis, this does not seem feasible to the health care system. However, those in charge need to realize that in the long run the approach can save health systems from substantially additional costs. And at the same time, patients will end up being much happier and much healthier.

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