CHAPTER

16 ECONOMIC EVALUATION OF GENOMIC AND PERSONALIZED MEDICINE INTERVENTIONS: IMPLICATIONS IN PUBLIC HEALTH

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16.1 INTRODUCTION

The term "medical genetics" has been defined as the science of human biological variation as it relates to health and disease; the study of the etiology, pathogenesis, and natural history of diseases and disorders that are at least partially genetic in origin; and the application of genetics to medicine or to medical practice.[1] A milestone in the history of the discipline of genetics is the year of 1953 when James Watson and Francis Crick came up with the double helix model of DNA.[2]

After the double helix structure had been described, researchers spent a considerable amount of effort to find how the information, that is, contained in the DNA is translated into proteins.[3,4] With this knowledge the field of genetics evolved, mainly focusing in explaining the hereditary nature of certain diseases. Yet, genetic information was also proven to be important to guide therapeutics, a field that is also known as pharmacogenomics.[5,6] Initially, the term "pharmacogenetics" was introduced in 1956[7] to describe the relation between hereditary factors and drug metabolizing capacity. Later, the term "pharmacogenomics" was introduced, not only covering pharmacogenetics but also including acquired genomic variants and mRNA expression profiles affecting drug metabolism, while the term "personalized medicine" was introduced,[8] to indicate the combined knowledge of genetics to predict disease susceptibility, disease prognosis, or treatment response of a person to improve the person's health.

It is known that the side effects for the same drug vary from patient to patient and experimental evidence suggests that the variable phenotypic expression of drug treatment efficacy and toxicity is determined by a complex interplay of multiple genetic variants and environmental factors.[9] Pharmacogenomics is referred to as "... the delivery of the right drug to the right patient at the right dose," and several pharmacogenomic testing approaches currently exist to identify the underlying pharmacogenomic biomarkers.[10–12]

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16.2 PHARMACOGENOMICS, PERSONALIZED MEDICINE, AND HEALTH ECONOMICS

Understanding the relative benefits and costs of alternative pharmacogenomics strategies is important in order to ensure that patients receive not only effective but also economically efficient care. The aforementioned progress made in the development of personalized medicine has coincided with health-care systems placing greater emphasis on evidence-based clinical practice,[13–18] particularly as they are operating within an increasingly budget-scarce environment. It is often argued that personalizing treatment will inevitably improve clinical outcomes for patients and help achieve more effective use of health-care resources. Hence, demand is increasing for demonstrable evidence of clinical utility and economic viability to support the use of personalized medicine in health care.[19]

Health economics is a branch of economics concerned with issues related to efficiency, effectiveness, value, and behavior in the production and consumption of health and health care.[20] There are three key features in health economics analyses as currently applied: (1) they are more focused on the benefits received by the health-care system and society as a whole rather than the individual/patient, namely, improvements in quality of life for the majority of patients, on average expansion of life expectancy and resources saved, to name a few; (2) the recipient of the medical intervention is, in the majority of cases, not the most informed medical decision-maker (the so-called "asymmetry of information"[21]) and, as such, does not have a complete picture of the potential benefits and harms of a given medical intervention or decision; and (3) most of the time, the recipients of medical interventions do not directly pay for these treatments; rather, payment is received from a third party that the recipient supports through taxes, medical premiums, or a shared model of employer/employee contributions. As such, health economics aims to better understand the value and costs of a certain medical intervention compared with another by taking into assumption all the factors that impact on patients, health-care providers, health-care system in general, and, ultimately, society.

16.3 ECONOMIC EVALUATION: TERMINOLOGY AND CONCEPT

Economic evaluation of health services is a branch of health economics that deals with the "systematic evaluation of the benefits and costs arising from the comparison of different health technologies." It represents a way of thinking and problem solving rather than a simple set of terms or methods used by health economists. The term "evaluation" refers to a process of comparing various choices to rank them, based on certain economic and clinical criteria, by order of attractiveness. The definition of economic evaluation includes also the word "systematic." It must be mentioned that analyses based on simplistic criteria of cost comparison between treatments (such as the price of one product compared with another), which include neither the entire financial burden nor the associated benefit for each treatment, are not systematic. When performing an economic evaluation, we seek an accurate comparison of the alternatives to judge their attractiveness to help the decision makers evaluate them. Therefore economic evaluation is useful to policymakers, who can so be informed about the available options (and the consequences of adopting them for the population's

health and the country's budget). In the United States and elsewhere, this combination is referred to as "value."[22–25] Value can be thought of as a relationship between outcomes and cost, and this relationship is emerging as a central dogma for health-care reform.

Economic evaluation is utilized concurrently with evidence-based medicine (EBM). As mentioned earlier, EBM is usually synonymous with the search for knowledge (regarding effectiveness) through systematic review of the literature to identify and propose optimal practices for a health system. Its purpose is to inform the people doing clinical work about these practices and to change current practices if they are suboptimal.

In many cases, however, the distinction between "good clinical practice" and "available economic resources" is controversial and often provides results opposite to those initially expected. For example, the adoption of practices that offer little additional therapeutic benefit but considerable burden may undercut the overall ability of the health system to treat patients in the future, not to mention the next generation. In other cases, society elects—through its health-care system—to transfer resources to those less fortunate, regardless of whether this transfer will achieve a small increase in overall social welfare. Such social groups are usually unable to "obtain welfare" as easily as wealthier population groups. In this sense, help for such groups is not a behavior that leads to efficiency maximization; however, society might choose to uphold the concept of equity at the cost of maximizing efficiency, a fact that may not be taken into account by EBM. In this framework, economic evaluation attempts to link EBM, to the wishes of society, patients, and the state to better achieve multiple goals such as viability, societal fairness, and improved efficiency in the health system. In conclusion, economic evaluation combines objective data (prices of production factors, medical technology, etc.) with preference data to rule on which of the available options maximize the welfare of the society in general or of specific patient groups.

It should be also stated that economic evaluation is a very technical subject which at present is still at the stage of developing new quantitative approaches, whether these are entirely new or borrowed from other related fields such as statistics, mathematics, or econometrics. Of course, we have to bear in mind that despite the attractive veneer of objectivity given by the concise and elegant mathematical nomenclature, the actual subject of financial resource management is in practice fundamentally a political issue and the translation of "knowledge" into "political decision" involves other factors that are mostly outside the province of the academic community.[26] Nonetheless, scientists and technology-driven academic communities might play valuable roles in shaping the knowledge trajectories from lab to innovation-in society through greater transparency and a sociological read of the scientific laboratory and practices.

16.4 METHODS USED IN ECONOMIC EVALUATION

From a technical point of view, economic evaluation uses various tools to evaluate medical interventions, which will be briefly discussed next. The two more commonly used approaches in the field are cost-effectiveness analysis (CEA) and, most importantly, cost–utility analysis (CUA) (Table 16.1).

Table 16.1 Types of Economic Evaluation Analyses

Type of Analysis	Costs	Consequences	Result
CMA	Monetary units	Identical in all respects	Least cost alternative
CEA	Monetary units	Different magnitude of a common *measure*, e.g., LY gained and blood pressure reduction	Cost per unit of consequence, e.g., cost per LY gained
CUA	Monetary units	Single of multiple effects not necessarily common, *valued* as utility, e.g., QALY	Cost per unit of consequence, e.g., cost per QALY
CBA	Monetary units	As for CUA but *valued* in monetary units	Net cost:benefit ratio

CMA, Cost-minimization analysis; CFA, cost-effectiveness analysis; CUA, cost−utility analysis; CBA, cost−benefit analysis; QALY, quality-adjusted life-year; LY, life years.

16.4.1 COST-MINIMIZATION ANALYSIS

A cost-minimization analysis (CMA) can only be used to compare two or more health technologies that have proven to be fully equivalent in survival, quality of life, therapeutic effect, tolerability, safety, and compliance. In such a case the focus of the analysis shifts only to their treatment overall cost to choose the least costly as the preferable therapeutic option. It must be noted, however, that the equivalence of safety and efficacy is not very often in clinical practice, and in that sense, this approach is not so common in health economics literature.[27] It must be noted, however, that some cases were no substantial efficacy and safety differences among agents exist, and the decision makers have limited available resources for reimbursement, a CMA was considered the appropriate methodological approach to evaluate alternative therapies from an economic perspective.

16.4.2 COST-EFFECTIVENESS ANALYSIS

CEA is defined as an analytical technique intended for the systematic comparative evaluation of the overall cost and benefit generated by alternative therapeutic interventions for the management of a disease. This sort of analysis aims to determine whether a medical intervention for disease diagnosis, prevention, and/or treatment improves clinical outcomes enough to justify the additional costs compared with alternative approaches. At first, this method focuses on evaluating an intervention in physical units and also is interested in determining life expectancy (final outcome) and not the quality of life. In that sense, this very important method deals primarily with the patients' ultimate health outcomes instead of intermediate indicators. Such intermediate/clinical indicators are of interest only to the clinical scientist when making a diagnosis, proposing treatment, or deciding on future research but are not particularly useful in CEA except in the circumstances when an intermediate indicator is "translated" in life expectancy through a robust chain of evidence mainly via statistical modeling.

As an example, progression-free survival (PFS) in oncology has an important clinical interest because it defines the period, over which the patient is free from disease progression and could be used as a measure of effectiveness in an CEA, but it is not used indiscriminately in economic evaluation because in some type of cancers a different PFS is unable to demonstrate the physical equivalent of clinical observation, such as prolongation of life or improved life expectancy.[28–30]

In that sense, economic evaluation "ignores" a drug's mode of action, its route of administration, or its pharmacokinetic properties. Therefore provided a certain technology has been approved by the competent authorities for use in the general population, it is assessed by the single indicator that is of the most interest for insurance carriers and for individuals in charge of health-care budgets: patient survival. With this "flexible" (but objective) approach, it is possible to calculate the comparative cost and benefit generated by different health technologies targeting the same disease, as long as the outcomes are measured on the same scale (months or years of life), and the cost is presented in a common unit of measurement.

It should be noted that CEA is not a method to indicate which medical intervention or health-care technology reduces the cost, but rather it is used to inform which medical interventions and/or health-care technologies provide the greatest value for a given amount of health-care expenditure. Another feature of CEA is that it evaluates clinical events outcomes, such as cost per life-year gained, but does not allow for direct comparisons among technologies that are used in different therapeutic areas. For example, one cannot easily make a verdict in order to spend a certain amount of money to prevent a rare genetic disorder or a specific type of cancer within the cost-effectiveness context; for this, one should take into consideration other factors that will be discussed next.

When conducting a CEA, we face four different scenarios. Let us consider two different treatments, PGx (new/pharmacogenomic treatment) and S (standard treatment), each associated with a specific effectiveness (E) and cost (C) for the management of a disease. Comparative evaluation will give the following four possible scenarios (Fig. 16.1).

Scenario A: Innovative treatment has *greater* effectiveness but also *greater* total cost (upper right quadrant). This is the most common case. Usually, an increase in mean survival with the

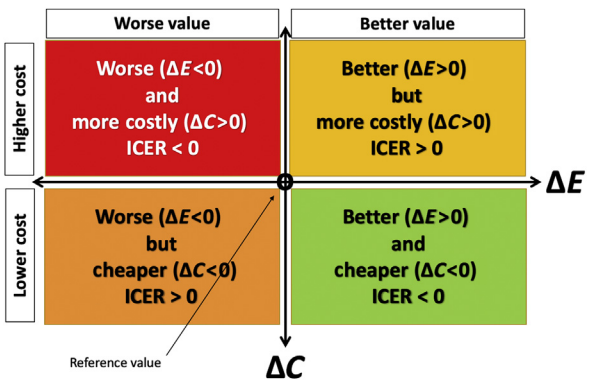

FIGURE 16.1

The cost-effectiveness plane.

innovative treatment and a corresponding increase in overall cost associated with its administration are observed. In recent years, new discoveries have been made continuously as new substances, new biological and gene therapies, new diagnostic methods, targeted treatments, or new procedures have been developed. Technology, in most cases, increases the cost of services because of the developing, purchasing, and operating expenses; the price of technology (which is a fraction of the overall cost of the intervention) tends to incorporate these costly processes. In such cases, there should be a criterion by which to assess whether the increased cost is justified by the additional effectiveness.

Scenario B: Innovative treatment has *greater* effectiveness but also *lesser* total cost (lower right quadrant). Here, the new treatment provides more effectiveness and is associated with lower cost than the standard treatment. This is not very often the case since health-care providers bear very high research and development costs that they wish to transfer to the end consumer or the public insurance funds while also making some profit because they are profit-seeking enterprises.

Scenario C: Innovative treatment has *lesser* effectiveness but also *greater* total cost (upper left quadrant). This unpromising scenario for the new technology includes increased cost but lower effectiveness from its use compared with the standard treatment. It is not very often the case in practice.

Scenario D: Innovative treatment has *lesser* effectiveness but also *lesser* total cost (lower left quadrant). Here, the difference in survival is for the standard treatment, even though the use of the new treatment is associated with resource savings. In scenario D (as in scenario A) the ultimate decision to adopt or reject the new technology will be based on weighing the savings (which is the desirable outcome) and the reduced effectiveness (which is a negative consequence) when comparing treatments. This scenario represents the generic health technologies.

Notably, CEA needs a quantitative criterion to judge when scenario A or D is the case to choose among health technologies. This is discussed in the following subsection.

16.4.3 COST-UTILITY ANALYSIS

CUA attempts to address the aforementioned CEA limitations by measuring outcomes through a metric called a quality-adjusted life-year (QALY)[31] that allows for comparisons across medical interventions and also taking into account the quality of life for a patient. Quality is often measured on a scale of 0, or of 100, where 0 represents the "worst possible" and 100 is the "highest or best possible" state of health. A QALY is a period of 1 year weighted by the quality of life that the patient is experiencing when suffering from a disease or when improving as a result of a treatment. For example, if a cancer patient is found to have 75% quality of life, then 1 year of life with this type of cancer is equivalent to 0.75 years of life with perfect health (0.75 QALYs). If the patient improves to 90% after treatment, then 1 year of life after treatment is equivalent to 0.9 years of life in perfect health, and the treatment benefit is 0.15 years of life. Various methodological tools are used to value a patient's health state and quality of life. Some of these are specialized for specific diseases, whereas others seek to evaluate a patient's general state of health. Some are based on simple indices, and others are more comprehensive but also more difficult to assess. The subjects in such studies are usually patients, but they may also be health professionals, such as nurses or physicians, or the general population. Examples of such efforts are the EuroQol EQ-5D and others.[32–34]

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, and many organizations such as the UK National Institute for Health and Care Excellence (NICE) encourage their use.[35]

As mentioned earlier in economic evaluation, there is a "gray zone" where the additional benefit is associated with higher cost, and the result will be uncertain until the expense considered acceptable for an additional year of life is fully quantified. The mathematical formula that quantifies the ratio of differences among alternative treatments is called incremental cost-effectiveness ratio (ICER) and is described as follows:

$$\text{ICER} = \frac{\Delta C}{\Delta E} \quad \text{or} \quad \text{ICER} = \frac{(C_{\text{IN}} - C_{\text{STD}})}{(E_{\text{IN}} - E_{\text{STD}})},$$

where E_{IN}, E_{STD}, C_{IN}, and C_{STD} correspond to the mean effectiveness of the new (innovative) treatment, the mean effectiveness of the standard treatment, the mean cost of the new (innovative) treatment, and the mean cost of the standard treatment, whereas $\Delta E = E_{\text{IN}} - E_{\text{STD}}$ and $\Delta C = C_{\text{IN}} - C_{\text{STD}}$ are the definitions of the differences ("Δ," stands from Greek $\Delta\acute{\varepsilon}\lambda\tau\alpha$ which means "difference") in cost and effectiveness, respectively. ICER indicates the amount of money we have to spend in order to achieve one more unit of effectiveness. In this case, CUA indicates the amount we have to spend to achieve one more QALY. The amount a society is willing to pay to obtain 1 year of life is called willingness to pay (WTP) and is represented by the Greek letter lambda (λ). If λ is greater than ICER, then the new treatment is considered a cost-effective option. Let us consider the example next:

	Survival (year)	Quality of Life (%)	QALYs	Cost (€)
Genome-guided treatment	10	60	$10 \times 60\% = 6$	10,000
Standard treatment	8	50	$8 \times 50\% = 4$	6,000

ICER = (10,000 − 6000)/(6 − 4) = €2000 per QALY. If $\lambda = 5000$ per QALY, the genome-guided treatment might be considered a cost-effective option and must be reimbursed by the healthcare system. It must be noted that the determination of ICER is a technical manner, while the amount of λ represents a political decision. In many cases, such decisions regarding the distribution of resources for health care are contingent on each country's individual political and historical background and are not determined by economic models. The estimation of λ remains a subject of extensive debate,[36–44] and even large organizations, such as the UK NICE, have yet to announce a clear decision on its "correct" size. In various other countries, however, WTP values have been proposed for the "purchase" of 1 year of life to provide a transparent criterion for this difficult undertaking. According to the World Health Organization, the desired value for the indicator is approximately three times the average per capita income of the country, while for the United Kingdom, a value between £40,000 and £60,000 is the maximum accepted value in most cases. A value between $50,000 and $100,000 is considered cost-effective, a value less than $20,000 is considered particularly attractive, and values more than $100,000 are considered particularly costly and are rejected. It should be noted, however, that the determination of λ has direct effects on

health system budgets and therefore should not be done independently of each economy's available funds.

16.4.4 COST-BENEFIT ANALYSIS

This analysis gives a monetary value to every aspect of health care and medical intervention, which can be very challenging in health care because health-care providers are often very reluctant to place a monetary value on health; as such, this prominent approach is truly difficult to perform accurately.

16.4.5 COST-THRESHOLD ANALYSIS

This analysis operates in reverse in that the analyst defines a threshold of cost-effectiveness (usually derived from the calculated cost-effectiveness of a given intervention). Once this is defined, the analyst asks the question, what are the necessary performance characteristics of a given test or intervention such that the cost of the test/intervention meets or exceeds the threshold? This approach is being used more frequently by developers to understand whether their test or intervention is ready for clinical use or needs additional development. In genomics, this has been used to assess when a genomic risk panel or pharmacogenomics test would have sufficient discriminatory power to justify its use in clinical care. All these approaches consider the cost of the medical intervention itself together with the accompanying costs, but they differ in how they measure the outcome or utility of an intervention.

16.5 ECONOMIC EVALUATION IN GENOMIC AND PERSONALIZED MEDICINE

The recent evolution in the field of genomics has been remarkable. The first human genome was sequenced recently, costing between US$500 million and US$1 billion.[45] After 5 years of research, this cost fell considerably, making more realistic the incorporation of this novel discipline in the clinical setting. The biggest advances in genome sequencing have been increasing speed and accuracy, resulting in reduction in manpower and cost. The speed is thanks to parallel analysis and high-throughput technology (next-generation sequencing, NGS), which permits either whole-genome sequencing (WGS) or parts of it to be sequenced in hours, at great depth and increasing sensitivity.[46]

This information might be used to assist practitioners concerning the diagnosis, prognosis, and clinical management for a variety of disorders, particularly cancer and rare diseases.[45] Over the past decade, genomic sequencing research studies have increased in size, and the same will be the case in the future.

Large-scale sequencing projects such as the 100,000 Genome Project in the United Kingdom and the All of Us Program in the United States are collecting an unprecedented amount of genomic, clinical, and health-care resource use data on individuals with cancer or rare diseases, as well as healthy individuals, but the health economic evidence base for whole-exome sequencing (WES)

and WGS is very limited. A recent analysis identified just a few economic evaluations of either WGS or WES, but the majority of them do not fill the appropriate requirements for a full economic analysis.[47,48] This study has estimated the cost-effectiveness of generating information on incidental findings using NGS technologies but evaluated a population screening approach rather than estimating health outcomes for a particular disorder.[49] Methodological uncertainty among health economists may play its role for the lack of evidence on the health outcomes associated with genomic sequencing. Over the past decade, health economists have repeatedly questioned whether metrics such as the QALY, which focuses on clinical utility, can fully quantify the outcomes that are important to patients when they undergo genomic testing.[50–54]

Some applications of genomic sequencing generate information that may not improve quality of life or extend life expectancy, but this kind of applications may impact on patient wellbeing via nonclinical routes, generating "personal utility."

In evaluating the utility of human genome-wide assays the answer will differ depending on the interested parties. For the purposes of regulating medical tests a restrictive sense of clinical utility might be used, while for the purposes of using limited third party or public health resources, cost-effectiveness should be evaluated in a societal context. In taking account of personal utility, cost-effectiveness may be calculated on an individual and societal basis. Overall measures of utility may vary significantly between individuals depending on potential changes in lifestyle, health awareness and behaviors, family dynamics, and personal choice and interest as well as the psychological effects of disease risk perception.[51] For instance, this is the case for those suffering from rare diseases who often have lengthy diagnostic journeys but few treatment options. This could also be an issue if individuals without known health problems undergo genomic sequencing and find out that they have an elevated risk of a disease, but no preventive action can be taken to manage this risk.[45]

Conclusively, there is no consensus in the field on whether QALYs are sufficient to capture the clinical benefits of sequencing or on the best way to capture the nonclinical benefits of sequencing. In addition to that, health economists are also yet to agree on whether information on personal utility should feed into resource-allocation decisions at all in this context, given that the costs associated with genomic sequencing will be met by the health-care budget. In this light the majority of existing economic evaluations undertake via beyond "narrow" outcome measures such as diagnostic yield. Most existing studies evaluating the outcomes associated with WGS or WES are designed to inform "local" resource-allocation decisions (laboratories, individual hospitals, etc.), instead of contributing to within-country Health Technology Assessments.[55,56] In theory the large-scale sequencing projects can address all these issues involving experienced professionals and collecting a big amount of appropriate data in a structured manner, but this is not the case in practice, with the exception of the Cancer 2015 study in Australia which collected some EQ-5D data.[57]

Despite these challenges, evidence on the relative cost-effectiveness of WGS and WES will soon be required to inform the translation of these technologies into clinical practice and thus to be incorporated in daily routine aiming to improve population wellbeing. Among others, there are several steps that health economists can take to improve the evidence based on the clinical and nonclinical utilities of the available genome technologies such as WGS and WES that will underlie these implementation decisions.

Hence, it is crucial to generate the evidence on the clinical utility of genomic sequencing based on traditional methods used by the Health Technology Assessment Bodies around the world and in particular instruments such as EQ-5D questionnaires to generate utility weights that can be used to

calculate QALYs. Probably these instruments will not be enough sensitive to differentiate the quality of life before and after undergoing genomic sequencing, but this assumption should be tested in empirical studies[58] to ensure that any evolution in methods is evidence based.

Priority must be given to the fact that large-scale sequencing studies will incorporate preference-based HRQoL instruments to the participants. If this is not feasible since the data collection process is already underway, smaller studies that collect HRQoL data from smaller subgroups of patients could still provide useful information on the clinical utility of WGS and WES and then could to be extrapolated to related clinical populations.

The big challenge for a health economist will be to explore the use of alternative health-state valuation techniques to generate utility weights within the QALY framework. Studies that link this evidence to patients' survival and quality of life could inform decision-making regarding the translation of these technologies into clinical practice. There are some attempts in the related literature to allow analysts to combine information on both clinical and personal utilities within a single metric in order to perform a cost–benefit analysis.[59] In general, health economists will have a vital role to play in the translation of genomic sequencing into clinical practice and to ensure that appropriate and timely decisions will be made regarding the allocation of scarce health-care resources to genomic sequencing.

16.6 EXAMPLES OF ECONOMIC EVALUATION IN GENOMIC AND PERSONALIZED MEDICINE

As has been previously mentioned, the number of published studies is still relatively small[60] (Simeonidis et al., 2019). Nonetheless, the studies that have been published represent a diverse approach to the application of economic analysis to genomic medicine instances that emphasize examination of the critical aspects of the analysis that can impact its validity.

16.6.1 USING PHARMACOGENOMICS TO PREVENT ADVERSE DRUG REACTIONS

Adverse drug events (ADEs) are a major contributor to morbidity, mortality, and costs of care. One of the most well-known examples involves the drug abacavir. Abacavir is a synthetic carbocyclic nucleoside analog with inhibitory activity against human immunodeficiency virus (HIV-1). In combination with other antiretroviral agents, it is indicated for the treatment of HIV-1 infection. Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir. Studies of patients who experienced an abacavir-associated ADE identified an association between the ADE and a specific genetic variant in the HLA complex, HLA-B 57:01. Patients who carry the HLA-B 57:01 allele are at high risk for experiencing a hypersensitivity reaction to abacavir. Approximately 0.5% of patients who are HLA-B 57:01-negative will develop hypersensitivity, whereas more than 70% who are HLA-B 57:01 positive will develop hypersensitivity. This is a very straightforward case for the application of economic analysis. The first was performed in 2004.[61] The patient level data for abacavir ADE were obtained from a large HIV clinic, and the analysis included several types of cost (genetic cost, treatment of hypersensitivity, etc.) and the cost and selection of alternative antiretroviral regimens. The investigators concluded that based on

the choice of comparators, the testing strategy ranged from dominant (less expensive and more beneficial compared with no testing) to an ICER of €22,811. Several subsequent analyses have been performed, all of which have determined testing prior to the use of abacavir as being cost-effective and potentially cost saving under some assumptions. A study conducted in 2008[62] used a simulated model of HIV disease based on the prospective randomized evaluation of DNA screening in a clinical trial study. The study modeled three different approaches: (1) triple therapy including abacavir; (2) genetic testing prior to triple therapy with tenofovir substituted for abacavir for patients who carry the HLA-B 57:01 allele; and (3) triple therapy with tenofovir substituted for abacavir for all patients. Abacavir and tenofovir were assumed to have equal efficacy, and the cost of the tenofovir treatment was $4 more than the abacavir treatment. Outcomes were QALYs and lifetime medical costs. The authors concluded that the genetic testing strategy was preferred and resulted in a cost-effectiveness ratio of $36,700/QALY compared with no testing. The authors highlighted that the model was subjected to the assumption that abacavir and tenofovir had equivalent efficacy and abacavir therapy was less expensive. Hence, the results have to be considered strictly in this specific setting and on the basis of resources and drug prices. If any of the underlying parameters change, so may the results and the conclusions of this analysis. Thus periodically updated analysis is required in order to reexamine the results of the question at hand.

Another economic study[63] was conducted to compare a pharmacogenomics versus a nonpharmacogenomics-guided clopidogrel treatment for coronary artery syndrome patients undergoing percutaneous coronary intervention (PCI) in the Spanish health-care setting (549 participants). In this study, patients were classified into two groups: the Retrospective group was treated with clopidogrel based on the clinical routine practice and the Prospective group was initially genotyped for the presence of *CYP2C19* variant alleles before treatment with those carrying more than one *CYP2C19* variant alleles given prasugrel treatment. The analysis predicted a survival of 0.9446 QALYs in the pharmacogenomics arm and 0.9379 QALYs in the nonpharmacogenomics arm within a 1-year horizon. The cumulative costs per patient were €2971 and €3205 for the Prospective and Retrospective groups, respectively. Data analysis showed that pharmacogenomics-guided clopidogrel treatment strategy may represent a cost-effective choice compared with nonpharmacogenomics-guided strategy for patients undergoing PCI.

In a very recent economic study that was conducted by our group to estimate the effectiveness of *DPYD* genotyping based on the cost of toxicity management and the clinical benefit per genotype group [noncarriers (Group A) vs carriers (Group B)], in a large group of patients, treated with a fluoropyrimidines (FL)-based chemotherapy, who suffered from various types of cancer within the Italian health-care setting.[64] The mean QALYs was 4.18 [95% Confidence Interval (CI): 3.16−5.55] in Group A, while it was 3.03 (95% CI: 1.94−4.25) in Group B, indicating a difference at −1.15 (95% CI: −2.90 to 0.46). The most frequent adverse reactions occurred in Group A was Grade IV Neutropenia at 5.71% (95% CI: 3.78%−7.81%), followed by febrile neutropenia at 0.94% (95% CI: 0.19%−1.89%). For Group B the percentage of those experiencing a Grade IV neutropenia was estimated at 7.35% (95% CI: 4.14%−17.07%) a difference of 1.63% (95% CI: 4.26%−10.85%) compared to the corresponding percentage of Group A. febrile neutropenia was 4.92% (95% CI: 3.37%−12.20%) in Group B, a difference of 3.97% (95% CI: 3.40%−11.44%) compared to Group A. Analysis showed that there was evidence for survival and cost difference

between DPYD variants noncarriers and carriers in favor of the first group taking also into consideration the quality of life of patients.

16.6.2 BETWEEN ADVERSE DRUG REACTIONS AND EFFICACY

Thiopurine medications [including 6-mercaptopurine (6-MP), 6-thioguanine, and azathioprine] interfere with purine metabolism and are used for a variety of indications, including acute lymphoblastic leukemia (ALL) and inflammatory and autoimmune diseases, and as immunosuppressants in organ transplant recipients. Myelosuppression is generally considered an adverse event; however, in the case of ALL, it is the goal of the treatment, in so far as myelotoxicity is needed, to eliminate the malignant lymphoblasts and induce remission. The end point of the induction therapy in ALL is elimination of at least 99.9% of blasts from the blood and peripheral bone marrow, which necessitates a significant degree of generalized myelosuppression. In this context, myelosuppression can be looked at as both a beneficial and potentially harmful outcome. A previous study[65] examined an important outcome of ALL therapy, minimal residual disease (MRD) in a population of pediatric patients treated with standard therapies that included 6-MP who had undergone thiopurine methyltransferase (*TPMT*) genotyping. MRD is the strongest predictor of relapse of ALL, so it is a very important intermediate outcome of treatment. The genotype information collected was not used to adjust the dose of 6-MP. Analysis of the study data showed that patients with a genotype that predicted reduced TPMT activity had an MRD rate of 9.1% compared with 22.8% in the group predicted to have normal TPMT activity. This study emphasized the importance of considering outcomes that reflect both efficacy and harm.

In one of the earliest published CEA performed by the Institute for Prospective Technological Studies,[65] the cost-effectiveness of TMPT genotyping prior to thiopurine treatment in children with ALL was examined. Information for the cost-effectiveness model parameters was collected from literature surveys and interviews with experts from four European countries. The model indicated that *TPMT* gene testing in ALL patients has a favorable cost-effectiveness ratio. This conclusion was based on parameters collected for *TPMT* genotyping costs, estimates for frequency of TMPT deficiency, rates of thiopurine-mediated myelosuppression in TPMT-deficient individuals, and myelosuppression-related hospitalization costs in each of the four countries studied. The mean calculated cost per life-year gained by *TPMT* genotyping in ALL patients in the four study countries was €2100 (or €4800 after 3% discount) based on genotyping costs of €150 per patient. Based on their work, the most severe adverse event was myelosuppression. The estimates of the frequency were derived primarily from adult studies in which 6-MP was used for inflammatory bowel disease or other inflammatory conditions. A challenging parameter to determine is how many of the adverse events can be attributed to the presence of a *TPMT* gene variant. Although the presence of decreased TPMT activity is associated with increased risk of myelosuppression, the nature of the treatment means that even those with normal activity are at risk for a severe adverse event. In discussing the results the authors note that *TPMT* genotyping can reduce health-care costs through the avoidance of myelosuppression episodes compared with no genotyping. However, a different clinical approach could have an impact in efficacy was not taken into consideration. The authors assumed that the alterations in management would reduce ADEs with no impact on the treatment response for the primary disease; ALL but this assumption may not be the case for these patients.[66]

16.7 COST-EFFECTIVENESS ANALYSIS IN GENOMIC MEDICINE AND THE DEVELOPING WORLD

In an economic evaluation study involving elderly atrial fibrillation patients using warfarin treatment, it was shown that 97% of elderly Croatian patients with atrial fibrillation belonging to the pharmacogenomics-guided group did not have any major complications, compared with 89% in the control group, and, most importantly, the ICER of the pharmacogenomics-guided versus the control groups was calculated to be just €31,225/QALY.[67] These data suggest that pharmacogenomics-guided warfarin treatment may represent a cost-effective therapy option for the management of elderly patients with atrial fibrillation in Croatia, which may be the case for the same and other anticoagulation treatment modalities in neighboring countries.

In another study conducted in Serbia[68] the aim was to be assessed whether genotyping for the *CYP2C19**2 allele was cost-effective for myocardial infarction patients receiving clopidogrel treatment in the Serbian population compared with the nongenotype-guided treatment. Results shown that 59% of the *CYP2C19**1/*1 patients had a minor or major bleeding event versus 42.9% of the *CYP2C19**1/*2 and *CYP2C19**2/*2, while a reinfarction event occurred only in 2.3% of the *CYP2C19**1/*1 patients, compared with 11.2% of the *CYP2C19**1/*2 and *CYP2C19**2/*2 patients. Under the study's assumptions the analysis indicated that performing the genetic test prior to drug prescription represents a cost-saving option.

Apart from the differences in current drug prices and resource utilization in different countries, another important parameter to determine the cost-effectiveness of a certain medical intervention in different health-care systems is the variable frequencies of the pharmacogenomic biomarkers. As such, one should bear in mind that a pharmacogenomics-guided medical intervention that is not cost-effective in a certain country may be cost-effective in another country, even if no significant cost differences exist between these two countries because of the higher frequency of a pharmacogenomic biomarker in the general population. This suggests that economic evaluation studies in pharmacogenomics must be replicated in every country to inform policymakers prior to the implementation of a pharmacogenomic-guided medical intervention to evaluate its cost-effectiveness based on characteristics specific to each country.

16.8 MODELS FOR ECONOMIC EVALUATION IN GENOMIC MEDICINE

The primary question that health economics attempts to answer is how to distribute the available funds to the various public and private health-care providers in order to cover the existing needs in an economically viable way. In practice, when evaluating an innovative (genomic) treatment in comparison to an existing treatment, we determine the ICER.[69] This ratio is the difference between the overall costs of the two health technologies divided by the difference in benefit. The ICER indicates the additional amount of resources that must be expended in order to provide 1 additional year of life to society. In order to reach a final decision as to which of the two health technologies should be adopted by a country's health-care system, we should have a rule to determine whether the ICER is attractive or not. Thus we need to compare the amount of money needed in order to achieve higher effectiveness (the ICER) with the amount of money that the responsible agencies

(budget holders) are willing to invest to obtain it. The latter amount is called "willingness to pay" and is denoted by "WTP" or by the Greek letter λ. λ represents the state's institutional representatives' willingness to invest additional resources in order to obtain more QALYs. When the ICER is lower than the λ, then a new health technology is considered to be advantageous for the society and is adopted by the system.

Even though this rule appears to be methodologically attractive, it has several issues that need to be addressed.[70–73] Among others, the major weaknesses of the analysis are that (1) it assumes that the available funds are limitless and can be directly adjusted to the cost of new technologies; (2) λ is determined arbitrarily; (3) the budget analysis does not depend on λ, something that is not true for any health-care system; (4) innovation—as defined by the difference in effectiveness between health technologies (difference in QALYs)—is not included in any way in the model but is assumed to be socially irrelevant; and (5) issues of ethical patient management can be examined using purely economic criteria.

For genomic medicine the development of a new a model is important because the newer personalized medicine treatments appear to be more advantageous compared to older standard treatments. In order to overcome the simplistic aforementioned assumptions, a new genome economic model (GEM) was developed.[26] The GEM model proposes that at least two limits should be applied in relation to the λ. One of these limits is defined by the budget and determines which options are cost-effective as well as cost-affordable, meaning that they can be adopted by the health-care system based on the available funds. The GEM model also addresses the issue as to whether there is also a lower limit for health technologies which can save resources. In other words, once a society has achieved a certain level of health through technology, it is reluctant to sacrifice that effectiveness based solely on economic criteria, an assumption that has been ignored by the classical analysis. Another special feature of this model is that it also handles the concept of innovation. In order to also incorporate this concept in the GEM model, the λ was modified (not fixed as in classical model) to correlate with the magnitude of the difference between the standard treatment and the new treatment.

If, for example, a new technology is marginally better than the standard treatment in terms of effectiveness (and also similar in terms of manufacture, active ingredient, etc.), we would expect to see a very small λ because the budget holders would consider the two technologies almost identical based on evidence from the final outcomes. If the new technology had a small difference in effectiveness, the λ would be lower than the one proposed by the classic model, with a tendency to increase, and if the new technology had a significant difference to the standard treatment then the λ would be greater than the one proposed by the classic model. As we approach the income restriction, of course, the additional amount of money that society is willing to invest in order to obtain a little more effectiveness would tend to become zero, since the value of money at that point would be more important. The highest effectiveness that the society is determined to incrementally reimburse should be specified in advance in this model.

Although the GEM addresses certain simplifying abovementioned assumptions, in the form previously presented, it cannot solve the problem of distribution of a given budget to different health technologies that treat different conditions, so as to achieve maximal societal utility. The generalization of the GEM model resolves the problem of distribution of a given budget to different health technologies that treat different conditions, so as to achieve maximal societal utility. This represents

an important issue, and thus the presentation of this model is out of scope of the chapter and can be found by the interested reader elsewhere.[74]

16.9 CONCLUSIONS AND FUTURE CHALLENGES

Genomic CEA has the potential to inform assessments about the value of current and emerging technologies and prioritize value-based decisions about adoption and investment. Efforts to close evidence gaps can strategically target areas of greatest need and potential health and cost impacts. Economic evaluations from the perspective of the relevant stakeholder can provide information and guidance for decision-making and policy-making.

Results from these evaluations can include estimated rages and threshold levels for key outcome variables to achieve desirable real-world results. Most importantly, economic models must be developed for genomic medicine that is flexible and adaptable.[75] Ultimately, high-quality and robust models have to be developed that can be utilized by experienced stakeholders without high-level training in economics to encourage routine use of these models to assist in decision-making.

Lastly, it must be stressed that the ICER calculation by itself does not allow conclusions to be drawn about the cost-effectiveness of the various intervention options. Such conclusions require a quantitative criterion, below which an option is considered effective and above which the option is rejected. The estimation of this indicator remains a subject of extensive political debate rather than scientific analysis, and even large organizations such as the UK NICE have yet to announce a clear decision on its "correct" size. In other words the actual subject of financial resource management is in practice, fundamentally a political problem and, unfortunately, quantitative methods used by health economists represent a tool and not an integrated procedure, while also the translation of "economic knowledge" into "political decision" involves other factors that are mostly outside the scope of the academic/research community.

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