Developing tools to evaluate genomic testing strategies at IPO Lisboa:

A multi-methodological approach

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Declaration

I declare that this document is an original work of my own authorship and that it fulfils all the requirements of the Code of Conduct and Good Practices of the Universidade de Lisboa.

Preface

The work presented in this thesis was performed at Centro de Estudos de Gestão do Instituto Superior Técnico, University of Lisbon (Lisbon, Portugal) and at Instituto Português de Oncologia de Lisboa Francisco Gentil, during the period March-October 2021. The thesis was supervised at Instituto Superior Técnico by Professor Mónica Duarte Correia de Oliveira and co-supervised by Doctor Carla Sofia Alves Pereira. This work was also developed within the scope of the MEDI-VALUE project (Developing HTA tools to consensualise MEDIcal devices' VALUE through multicriteria decision analysis; http://medivalue.tecnico.ulisboa.pt/; PTDC/EGE-OGE/29699/2017).

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Abstract

Precision medicine has long changed the paradigm of cancer treatment, a feat driven by the increasing number and quality of next generation sequencing (NGS) technologies available today. However, as new genomic tests are being introduced in the market, hospitals must decide which genomic testing strategy will better serve the care of their patients and the needs of the institution.

This thesis aims at developing methods to help the decision-makers of IPO Lisboa evaluate genomic testing strategies for patients diagnosed with acute myeloid leukemia (AML). For this purpose, a multi-methodology combining social and technical elements was design to approach this problem on three fronts: modelling clinical pathways (CP) of AML patients according to their risk stratification; modelling strategies value with the MACBETH technique, taking into consideration the views of several healthcare professionals; and estimating the direct costs of each strategy through Monte Carlo simulation modelling. The strategies value and costs were then combined into a strategy landscape graph, taking into consideration the impact of each strategy on the patients' CP.

The proposed multi-methodology, which can be adapted to other evaluation contexts, provided decision-makers with comprehensive and insightful information regarding the added value, the added cost, and the impact of each strategy. This study highlights the importance of involving different stakeholders in the decision-making process and shows the potential of multi-methodologies for the evaluation of health technologies in contexts of complex processes and uncertainty.

Keywords: Precision Medicine; Health Technology Assessment; Multi-methodology; Clinical Pathways; MACBETH; Monte Carlo Simulation.

Resumo

A medicina de precisão tem vindo a alterar o combate às doenças oncológicas, impulsionada pelo aumento do número e da qualidade das tecnologias de sequenciação de nova geração (SNG). Contudo, com a introdução de novos testes genómicos no mercado surge a necessidade de reavaliação por parte dos hospitais sobre que estratégia trará mais benefícios para os seus doentes e para a instituição.

Esta tese teve como objetivo desenvolver métodos para auxiliar os decisores do IPO Lisboa na avaliação de estratégias de teste genómico em doentes com leucemia mieloide aguda (LMA). Para tal, foi elaborada uma multi-metodologia com elementos sociais e técnicos que permitiu abordar este problema em três frontes: modelar os percursos clínicos (PC) dos doentes de acordo com a sua estratificação de risco; modelar o valor das estratégias usando a abordagem MACBETH e contemplando opiniões de diversos profissionais de saúde; e estimar os custos diretos de cada estratégia usando um modelo de Simulação de Monte Carlo. O valor e o custo das estratégias foram então conjugados num gráfico *strategy landscape*, considerando o impacto de cada estratégia nos PC dos doentes.

A multi-metodologia proposta, que poderá ser adaptada a outros contextos de avaliação, permitiu fornecer aos decisores informações relevantes relativas ao valor acrescentado, ao custo acrescentado e ao impacto de cada uma das estratégias. Este estudo demonstra a importância de envolver vários intervenientes no processo de tomada de decisão, e o potencial de aplicar multi-metodologias na avaliação de tecnologias da saúde, quando na presença de processos complexos e incerteza.

Palavras-chave: Medicina de Precisão; Avaliação de Tecnologias de Saúde; Multi-metodologia; Percursos Clínicos; MACBETH; Simulação de Monte Carlo.

Contents

List of Figures

List of Tables

Abbreviations

ACCE	Analytic validity, Clinical validity, Clinical utility and associated Ethical, legal and social implications
AI	Artificial Intelligence
AML	Acute Myeloid Leukemia
CDx	Companion Diagnostic
CP	Clinical Pathway
DM	Decision Maker
DNA	Deoxyribonucleic Acid
ELN	European LeukemiaNet
ELSI	Ethical, Legal and Social Implications
HTA	Health Technology Assessment
INFARMED	Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.
IPO Lisboa	Instituto Português de Oncologia de Lisboa Francisco Gentil
MACBETH	Measuring Attractiveness by a Categorical-Based Evaluation Technique
MCDA	Multicriteria Decision Analysis
MEDI-VALUE	Developing HTA tools to consensualise MEDIcal devices' VALUE through multicriteria decision analysis
MSI	Microsatellite Instability
NGS	Next Generation Sequencing
NSCLC	Non-Small Cell Lung Cancer
PCR	Polymerase Chain Reaction
RNA	Ribonucleic Acid
TANGO	Technology Assessment of Next Generation sequencing in personalised Oncology
TMB	Tumour Mutation Burden
UIPM	Unidade de Investigação em Patobiologia Molecular
WGS	Whole Genome Sequencing
WHO	World Health Organisation

1. Introduction

1.1. Motivation

Humankind is currently living in an era of constant technological innovation and scientifical breakthroughs. Some advancements are very evident in healthcare, where diseases that were once considered fatal are now fully treatable, and sometimes even curable [1]. One of the most impressive achievements in the field of health sciences in the last decades was the capacity to read and interpret people's genetic material, as it led to a more comprehensive understanding of many diseases and fuelled the development of new drugs and treatments [2].

Nowadays, following the steady decrease of the costs of genomic tests and the growing knowledge regarding genetic mutations and their implications in health, the traditional "one size fits all" approach is starting to be replaced by more personalised methods, chosen according to the patient's unique genetic and biochemical characteristics, behaviour, and environment, a practice referred to as precision medicine. Although there are some challenges related with this field, it certainly has the potential to change the practice of medicine in the upcoming years and benefit the wellbeing of many different people [3].

Nevertheless, delivering genomic-related care competes for funding with many other health care areas. Health systems must determine how to manage their scarce resources in the most efficient way possible, which can be assisted by health technology assessment (HTA), a systematic and transparent approach to evaluate the costs and benefits of health technologies, while incorporating scientific, social, economic and ethical considerations to better inform decision-making [4]. Since decisions regarding the adoption of new health technologies are usually done at a hospital level, hospital-based HTA emerges as a more context-specific and useful way of organizing HTA activity in hospitals [5]. This can be valuable to assist decision-makers, particularly in the evaluation of genomic technologies, considering the short- and long-term implications those can have both for the patients and the institution [6].

The Instituto Português de Oncologia de Lisboa Francisco Gentil E. P. E. (IPO Lisboa), a Portuguese reference centre in oncology located in Lisbon, treats tens of thousands of new cancer patients every year from all over the country, while also work as a research centre in the areas of basic, clinical and translational research for oncology diseases [7]. Being utterly focused on the patients' wellbeing and driven by values such as excellency and innovation, IPO Lisboa doctors and staff seek to provide the best available treatment to every patient, and the practice of precision medicine is deemed fundamental to achieve this goal.

However, the growing offer of different genomic tests creates the need to revaluate the currently applied strategies and compare them with the available alternatives in the market. In these circumstances, hospital-based HTA, supported by decision analysis methods, emerges as a valuable

process to assist in the decision-making process, especially considering the paucity of literature in the field of HTA of genomic biomarkers and the complexity of a hospital environment.

In conclusion, there is scope for developing decision analysis concepts and tools to inform the adoption of alternative genomic testing strategies in a hospital environment, so as to assist IPO professionals in decision-making.

1.2. Objectives and Thesis Outline

The goal of this thesis is to develop a multi-methodology to assist decision-makers (DM) of IPO Lisboa to assess the value and costs of adopting different next generation sequencing (NGS) tests for the care of acute myeloid leukemia (AML) patients.

The multi-methodology should: be informed both by state-of-the-art literature regarding genomic biomarkers and the economic evaluation of genomic biomarkers, and by the views of IPO Lisboa stakeholders; use sound methods; and be transparent and comprehensive, informing IPO Lisboa on the multiple benefits and costs associated with the pursuit of distinct genomic biomarkers strategies. So as to answer to these objectives and challenges, the proposed multi-methodology combines several methods in a novel way, contributing to hospital-based HTA and to genomic biomarkers' literature.

In order to provide a fluid and coherent read, further to this introduction this thesis is divided into six chapters. Chapter 2 provides information to contextualize this study, namely regarding AML and the use of precision medicine for cancer treatment. Chapter 3 a literature review, covering existing studies concerning the HTA of genomic biomarkers, the role of decision analysis in HTA and the importance of studying the patients' CP when facing a decision in the healthcare context. Chapter 4 describes the proposed multi-methodology, and results from implementing the methodology at IPO Lisboa are presented in Chapter 5. Finally, results are discussed in Chapter 6, and the last chapter summarizes the main conclusions of this study and presents some suggestions for future work.

2. Context

So as to frame the research developed along this thesis, this chapter presents some key concepts and relevant background information. Specifically, it presents the concept of health technology assessment and summarizes information on the use of biomarkers in clinical practice and the recent emergence of precision medicine, as well as provides insights regarding the diagnosis and treatment of AML and the role of IPO Lisboa in oncology care.

2.1. Health Technology Assessment (HTA)

According to the International Network of Agencies for Health Technology Assessment (INAHTA), HTA is "a multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle" [4]. There is, however, a great variety of health technologies or, more specifically, medical devices, which include instruments, *in vitro* diagnostics or even software used in the provision of healthcare [8]. Consequently, HTA methods can differ according to the taxonomy of the technology [8, 9], as well as the region and country where the evaluation takes place [10]. Nevertheless, comparative analyses are usually performed to evaluate alternative courses of action in terms of both their costs and consequences, the most common ones being cost benefit analysis (CBA), cost-effectiveness analysis (CEA) and cost-utility analysis (CUA) [11].

Even though HTA methods can vary a great deal according to the selected technology and the purpose of the assessment, these methods should be sound so as to accurately inform decision-making, and contributing to promote equitable, efficient, and high-quality health systems [12]. As shown in Figure 2.1, there is a multitude of dimensions that ought to be considered when assessing, or even comparing, different health technologies. Therefore, in recent years most governments and institutions have invested in developing tools and guidelines in an attempt to improve and standardize the practice of HTA, while trying to encompass all the relevant dimensions and perspectives which should be included for a comprehensive evaluation. A famous example is the HTA Core Model®, a framework developed by the European network for HTA (EUnetHTA), involving more than 70 institutions in 32 European countries, to assist in the methodological assessment and reporting of a health technology, in any phase of its life cycle [13]. By including a transversal set of dimensions, ranging from "description and technical characteristics of the device" to "ethical analysis" or even "patient and social aspects", this model is aimed at providing a systematic and transparent structure which can be adopted globally and in any context.

Regardless of how the assessment is executed, the HTA process is key to inform decision-making, that is, to help decision-makers deciding whether to implement a new health technology based on all the evidence collected beforehand and its subsequent appraisal. Thereby, decision-analysis methods play an important role in HTA, to guarantee an effective and well-informed judgment from all stakeholders involved [14]. A field that has shown a great potential in the field of HTA is multicriteria decision analysis (MCDA), due to its transparent format and understandable outputs, as well as the

ability to include multiple elements in the evaluation [15]. The role of decision analysis in HTA will be discussed ahead in further detail.

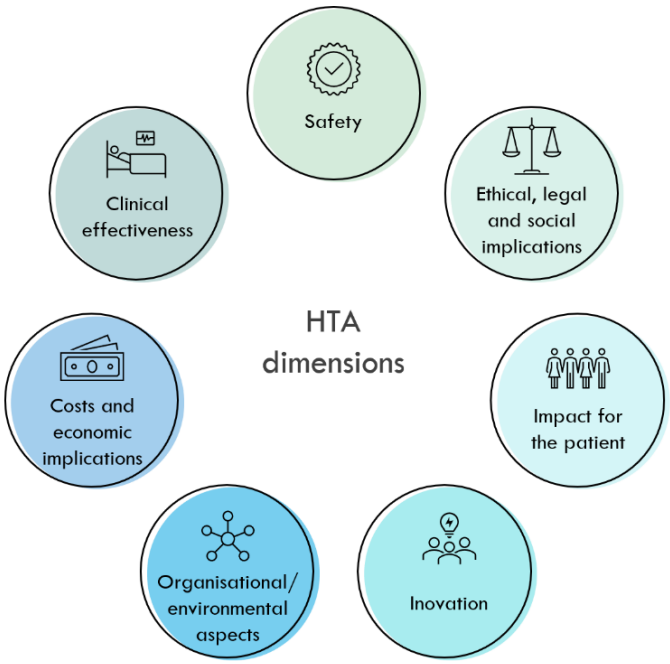


Figure 2.1. Examples of dimensions to consider when assessing a health technology. Adapted from [13] and [16].

Even though HTA is sometimes performed at a regional or even national level, there are many advantages to implementing HTA methods at the hospital level instead, as knowing the specific organizational context of the institution induces a more efficient use of the available resources [5]. Furthermore, hospital-based HTA creates an opportunity to develop customized methods and tools which will generate more accurate and useful recommendations directed to the particular needs of the healthcare organization, therefore creating additional value for the stakeholders involved. As a consequence, an increasing number of hospitals have been attempting to implement HTA activities at a local level, although usually based on existing methods and frameworks [17]. The present work is an example of applying decision analysis methods to evaluate strategies for the adoption of a health technology in the context of a specific hospital: IPO Lisboa.

2.2. Biomarkers as emerging health technologies

Humankind is currently living in an era of continuous scientific advancement, with new technologies constantly emerging in an attempt to satisfy the constant demand generated by population growth/aging, and concomitant needs and desires. Such trend can be observed in many businesses including in healthcare systems, where there is a constant search for novel medical devices able to unlock new insights regarding existing pathologies and inform clinical research. This includes *in vitro* medical devices such as biomarkers, which have many applications in the clinical practice and a great potential for the development of new diagnosis techniques and treatment approaches [8].

A biomarker is “a parameter that can objectively be measured and evaluated as an indicator of either normal or pathologic processes, or of a response to therapeutic intervention” [18]. With such a broad definition, the term “biomarker” encompasses a huge variety of molecules and alterations, such as enzymes, antibodies, nucleic acids, gene expression and metabolic signatures, among others [19]. Although the variation of a biomarker may not directly influence one’s sense of wellbeing, it carries important information regarding a patient’s medical condition, allowing for a more accurate diagnosis, as well as predicting the evolution of the disease and the effectiveness of a certain treatment [20]. Even though they are constantly used as the basis for important medical decisions, the paucity of consistent and standardized models of evaluation of biomarkers is still a matter of concern in the healthcare community [19].

Biomarkers, especially genomic biomarkers, are particularly relevant in oncology, leading to a better understanding, monitoring and treatment of cancer. Sawyers [21] describes three main types of cancer biomarkers, all relevant for studying the evolution of the disease and develop appropriate drugs: prognostic, predictive and pharmacodynamic biomarkers. While prognostic biomarkers allow us to predict the natural evolution of a cancer, including its possible recurrence, predictive biomarkers are used to access how the patient will react to a certain treatment. Finally, pharmacodynamic biomarkers indicate the effect a certain drug may have or is having in the tumour, helping to select the optimal dose in each situation. They are particularly relevant in the development of new anticancer drugs.

Since cancer cells result from mutations which lead to their erratic proliferation [22], genomic biomarkers, such as DNA mutations detected from a tumour biopsy or in circulating tumour DNA (ctDNA), are extremely relevant in oncology [19]. For example, determining the expression of oncogene HER2 in patients with breast cancer is essential to select an appropriate therapy, making it a genomic predictive biomarker [23]. Furthermore, certain types of germline mutations can lead to a greater cancer predisposition, and their study allows for a better prevention and early detection of tumours. For instance, inherited mutations in the tumour suppressor genes BRCA1 and BRCA2 have long been associated with a greater risk of developing breast and ovarian cancer [24].

As technology evolves, alongside our knowledge regarding oncological disorders, the use of biomarkers (in particular, genomic biomarkers) has gained an immense relevance for the practice of genomic and precision medicine in oncologic patients and can potentially change the way cancer is perceived and treated in the future.

2.3. Genomic and Precision Medicine

Genomic medicine is a field which has experienced an immense growth in recent years, especially following the completion of the Human Genome Project in 2003 [25]. The popularity of implementing this kind of personalised approach is easily justified, as considering the genetic information of each patient and treating them accordingly has allowed for major breakthroughs in medicine, namely in the areas of inherited diseases, reproductive health, and cancer [3]. Moreover, by contemplating not only one’s genetic blueprint but also other relevant factors (for instance, demographic

and socioeconomic factors, behavioural traits, or environmental and physiological characteristics), healthcare can be increasingly tailored toward specific patients or subgroups of patients, an approach referred to as precision medicine [26].

Nowadays, projects such as the European "1+ Million Genomes" Initiative, with the goal of having at least 1 million sequenced genomes available in the European Union by 2022 [27], continue to drive the research for better diagnostics and more targeted treatments. Furthermore, in the long run these approaches may help improve the accessibility and effectiveness of health systems worldwide. Therefore, considering the ongoing progresses and achievements in the field of precision medicine, it becomes important to analyse the challenges and pitfalls we will need to overcome in this area.

2.3.1. Main Challenges of Precision Medicine

Although precision medicine is undeniably important in the prevention, diagnosis and treatment of several medical conditions [28], the road for a systematic and consistent use of this approach in general clinical practice is not without obstacles. Being a relatively recent and complex field of studies, the use of genomic information to guide medical decisions poses many challenges to all relevant stakeholders. Such challenges, some of which are summarized in Figure 2.2, should not be overlooked if we want our society to fully benefit from such a promising technology.

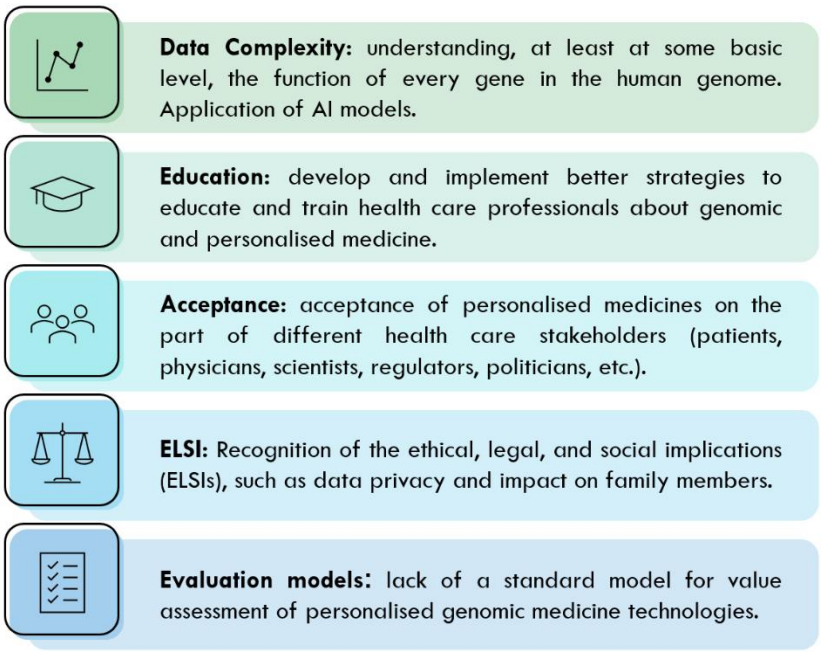


Figure 2.2. Examples of challenges in the areas of genomic and precision medicine.

The first and most common challenge associated with precision medicine results from the inherent complexity of the data obtained using genomic technology [29]. Every human being carries thousands of genes in his DNA, which we are now able to sequence, but whose functions are not always completely understood. Therefore, although mutations in specific genes or variations in the genetic

material have been indisputably associated with certain diseases, we are still far from being able to interpret all the relevant genetic data into clinically actionable knowledge [3]. Furthermore, the enormous amount of data contained in the human DNA poses another obstacle to the standard use of precision medicine, since medical professionals may not be able to correctly interpret and select all relevant results, due to lack of time and knowledge. However, artificial intelligence (AI) algorithms are emerging as a powerful solution for this problem, as they can help us overcome the challenges associated with big-data and transform it into clinically relevant knowledge [29].

In addition, the complexity of the human genome also generates a necessity to better educate and train healthcare professionals in the areas of genomic and precision medicine. Despite all the potential of these approaches, without the proper guidance and training it will be difficult to have them correctly and systematically implemented into clinical practice [30]. Therefore, the importance of developing and implementing strategies to educate and stimulate doctors in the proper use of genomic technologies should not be neglected, to ensure not only the correct interpretation of results but also the selection of adequate treatments, as well as creating a strong, valuable connection with the patient, necessary for a beneficial application of precision medicine.

On the other hand, no amount of training will be sufficient if there is no acceptance of precision medicine on the part of medical professionals and other healthcare stakeholders. Even though the benefits of genomic personalised healthcare have been demonstrated in various areas [3], not all relevant actors have embraced these promising methods. Some doctors are still sceptical about the lack of studies regarding clinical validity, clinical utility and cost-effectiveness of some personalised approaches, as proof that they indeed outperform traditional medicine strategies [30]. Such concerns are understandable, as it is difficult to properly evaluate some genetic tests, especially involving large gene panels or even whole genome sequencing (WGS), considering the complexity of the obtained data and the heterogeneity of diseases associated with the human genome [31]. Furthermore, acceptance on the part of the patient may also be difficult to obtain, due to numerous reasons. One of them is the fear of the knowledge a genetic test can bring to light, such as inherited disorders or the tendency for developing certain diseases, and the impact it can have on the patient and his family. Moreover, concerns regarding data privacy are also very common among patients, as most people wish for their medical status to remain confidential, as well as to avoid possible genetic discrimination [32]. In fact, these and other ethical, legal and social implications (ELSI), such as patient preferences and experiences, the effect on quality of life and fairness, should be carefully considered when resorting to genomic and personalised medicine [33].

Finally, one of the major obstacles to a larger dissemination of precision medicine is the lack of standardized methods and frameworks for the health technology assessment (HTA) of genomic technologies. A systematic review carried out by Hoxhaj *et al.* in 2020 [34] revealed not only the existence of a multitude of different frameworks used for the evaluation of genetic and/or genomic technologies, but also that, in practice, these frameworks end up not being applied in most reports from HTA agencies. Another review, written by Pitini and colleagues, adds that when evaluating genetic

testing “an economic dimension is always considered, but not in detail” and the “consideration of delivery models, organizational aspects, and consumer viewpoint is often lacking” [35].

As a consequence of the dearth of standardized value frameworks for genomic technologies, associated with the growing supply of such technologies, hospitals are faced with the difficult task of deciding whether the costs of implementing these new genomic tools are worth the benefit for their patients their institution.

2.3.2. Relevance of Precision Medicine in Oncology

In the past, cancer treatment was mostly guided by the original location of the tumour, an approach that sometimes led to no response or even adverse reactions from the patients being treated [36]. Although such outcomes were difficult to explain at the time, nowadays evidence shows that, despite similarities within a particular cancer type, every tumour is in fact unique, and has certain molecular variations which can be targeted to obtain better results. Hence the importance of precision medicine in oncology, which encouraged a global effort to identify relevant genomic biomarkers in order to achieve, for instance, better diagnostic accuracy, more accurate forecasts of a patients’ prognosis and to assist in the selection of suitable therapies [37].

Although most types of cancer already have multiple specific tests available for the detection of relevant biomarkers [38], multi-marker genomic tests have started to replace single biomarker tests whenever applicable, since they allow for a broader understanding of the tumour and alternative therapeutics [32]. This is possible mainly due to the dissemination of next generation sequencing (NGS), a technique which allows for massively parallel gene sequencing, and has become crucial in the application of genomic and precision medicine [3].

Nevertheless, there are still barriers which might prove a hindrance to the application of precision medicine in oncology. For instance, it is very difficult to identify relevant therapeutic targets among all known cancer genes [39]. Furthermore, most cancer genes are only rarely mutated in a certain tumour type, and numerous different combinations of mutations have been identified across thousands of patients [37]. Despite these obstacles, oncology continues to shift to more personalised methods, with very promising results.

2.4. Acute Myeloid Leukemia

Accounting for almost 10 million deaths in 2020 [40], cancer continues to be one of the leading causes of death worldwide, a number which is expected to continuously rise in the upcoming years, mostly due to demographic changes in our society [41]. Therefore, it is crucial to pursue improvements and innovation in the areas of cancer prevention, diagnosis, treatment, and palliative care.

Acute myeloid leukemia (AML) is a type of cancer caused by the infiltration of the bone marrow, blood, and eventually other tissues by abnormal myeloid cells [42]. While being considered an incurable

disease more than 50 years ago, its treatment has evolved since then, and it is possible for a patient to survive AML if given an adequate treatment [1]. According to the Portuguese National Cancer Registry (RON), in 2018 there were 389 new cases of myeloid leukemia in Portugal (including, but not restricted to, AML), most of them in men older than 60 years, and a total of 255 deaths related with this type of cancer [43]. The paucity of new cases in Portugal might therefore be an obstacle to the gathering of consistent and relevant knowledge pertaining to AML, emphasizing the importance of an international collaboration for better treating this disease.

2.4.1. Causes of AML

All cellular blood components are derived from haematopoietic stem cells through a process called haematopoiesis, which includes two main lineages: the lymphoid lineage and the myeloid lineage. In particular, the myeloid lineage of haematopoiesis comprises four other lineages, namely erythropoiesis, granulocytopoiesis, monocytopoiesis and thrombocytopoiesis [44]. AML is caused by the mutation and abnormal proliferation of cells from the myeloid lineage, resulting in the decrease of healthy blood cells [45]. Although AML can develop as a consequence of other blood disorders such as myelodysplastic syndromes, therefore being referred to as secondary AML, patients may also be diagnosed with primary AML. In any case, World Health Organization's (WHO) guidelines state that a marrow blast count of ≥20% is required for a diagnosis of AML, except in the presence of certain genetic abnormalities [46].

Risk factors for AML include previous blood disorders such as myeloproliferative or myelodysplastic syndromes, chemical or radiation exposure, demographics and genetic predisposition [37].

2.4.2. Diagnosis and Prognosis

Since the proliferation of abnormal stem cells in AML results in a decrease of healthy blood cells such as erythrocytes, leukocytes and platelets, early signs of AML include pale skin, tiredness, tendency to infections (due to weak immune system) and frequent bleeding. However, such symptoms might be vague and nonspecific, although they become more severe with the evolution of the disease, and are insufficient for a correct diagnosis of AML [45].

In reality, the initial diagnosis of AML is based upon four different techniques: cytomorphology, cytogenetics, molecular genetics, and immunophenotyping [46]. Usually, it starts with a complete blood count and a peripheral blood smear, which can reveal a high number of abnormal white cells or a low number of health erythrocytes and platelets. However, a bone marrow biopsy should be conducted to further confirm the diagnosis. According to WHO, a marrow or blood blast count of ≥20% is required for a patient to have AML, except when the following genetic translocations are present: t(15;17), t(8;21), inv(16), or t(16;16) [47]. Hence, requiring cytogenetic testing to identify these and other translocations or inversions. Additionally, fluorescence in situ hybridization (FISH) might be necessary to detect certain gene rearrangements. Furthermore, immunophenotyping, to identify specific cell-surface and

cytoplasmic markers, and molecular genetic testing, to screen for certain mutations, are other important techniques in the diagnosis and classification of AML [46]. In fact, there are different types of AML, which are listed in Table 2.1, as well as several subtypes.

Table 2.1. (2016) WHO classification of acute myeloid leukemia (AML) and related neoplasms [47].

Acute Myeloid Leukemia (AML) and Related Neoplasms
• AML with recurrent genetic abnormalities
• AML with myelodysplasia-related changes
• Therapy-related myeloid neoplasms
• AML, not otherwise specified (NOS)
• Myeloid sarcoma
• Myeloid proliferations related to Down syndrome

After diagnosis of AML, it is crucial to distinguish the patient's risk group, as it will impact the prognosis and the selection of an optimal treatment. According to the 2017 European LeukemiaNet (ELN) genetic risk stratification, AML patients can be classified into one of three risk groups (favourable-risk, intermediate-risk and adverse-risk) according to identified genetic abnormalities, as shown in Table 2.2 [46]. The majority of the gene alterations presented in the table can be identified during the previously mentioned diagnostic tests, namely via cytogenetic analysis. However, three of the genetic mutations independently associated with the adverse-risk group (RUNX1, ASXL1 and TP53) require a NGS test for proper identification. Being so, an NGS test is usually performed for patients in the favourable- and intermediate-risk group in order to refine their stratification and confirm their prognosis, as well as to identify further mutations that may provide clues regarding the best treatment that can be offered [48].

Table 2.2. 2017 ELN risk stratification by genetics. Adapted from [46].

Risk category	Genetic abnormality
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD or with FLT3-ITD^{low} = allelic ratio < 0.5
	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high} = allelic ratio > 0.5
	Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low} (without adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*
	Cytogenetic abnormalities not classified as favourable or adverse
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214*
	t(v;11q23.3); *KMT2A* rearranged
	t(9;22)(q34.1;q11.2); *BCR-ABL1*
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*
	25 or del(5q); 27; 217/abn(17p)
	Complex karyotype, monosomal karyotype
	Wild-type *NPM1* and *FLT3*-ITD^{high}
	Mutated *RUNX1*
	Mutated *ASXL1*
	Mutated *TP53*

Most patients are classified as intermediate-risk, the group with the most uncertain prognostic, as it encompasses all cytogenetic abnormalities which are not classified as favourable or adverse. Overall, favourable-risk patients are more likely to survive than intermediate- and adverse-risk patients [42], although it is challenging to predict a patients' prognosis as it depends on many different factors such as patient age, performance status, blood counts and genomic features, as well as the selected plan of care [46]. Therefore, the application of AI and machine learning methods is being studied in an effort to overcome this challenge and better predict the outcome of AML for a given patient [37, 49, 50].

2.4.3. Treatment

The most standardized treatment for AML is intensive chemotherapy, although not every patient is fit for this therapy due to its toxic effects and increased risk of infection. Therefore, medically unfit patients, for instance older patients with poor performance status and significant comorbidities, are usually offered alternative treatments such as low-intensity treatment, clinical trials with investigational drugs or simply best supportive care [46].

On the other hand, patients who are deemed fit undergo one cycle of induction chemotherapy, in an attempt to achieve complete remission without measurable residual disease [42], followed by postremission therapy. Studies indicate that approximately one quarter of younger adults and up to one third of older adults (60 years or above) achieve complete remission after undergoing intensive induction therapy, which typically consists of administering cytarabine for a period of seven days and anthracycline for three days (7+3 regimen) [46]. However, to ensure that no leukemia cells are left, patients usually proceed to receive postremission therapy. Being so, patients with a more favourable prognosis usually go through an additional three or four cycles of intensive chemotherapy, also referred to as consolidation or postremission chemotherapy. On the other hand, those with a higher risk of relapse are offered the option to receive a haematopoietic cell transplant in an attempt to improve the outcome of this disease, so long as they are deemed fit to undergo this therapy.

Throughout the whole treatment process, knowledge of the patient's genetic information can be a powerful tool, for example, as an indicator of which drugs the patient might be most responsive to, and in the identification of molecular targets that can be monitored for signs of relapse.

2.5. IPO Lisboa

The Instituto Português de Oncologia de Lisboa Francisco Gentil E.P.E. (IPO Lisboa) is a Portuguese reference centre in oncology care and research. Every year, more than fourteen thousand new patients are admitted at IPO Lisboa, of whom around sixty suffer from AML, a number which continues to rise due to the increased prevalence of cancer in our society [7]. The continuous search for excellency, innovation and improvement of this institution, alongside its patient-centred culture, make IPO Lisboa part of the best international reference centres. Therefore, IPO Lisboa is always looking for ways to improve care, and to select the best resources available to them.

However, the constant development of new genomic technologies drives IPO to revaluate the currently employed genomic testing strategies for various types of cancer, including AML, but the lack of standardised hospital-based HTA tools and methods might hinder this process. Thereby, the purpose of this thesis is to help IPO Lisboa at making informed decisions regarding the adoption of different genomic testing strategies for patients diagnosed with acute myeloid leukemia (AML). In order to understand how to better achieve the objectives of this work, a literature review was conducted focusing mainly on HTA of genomic technologies and existing tools to assist the decision-making process, which will be described in the following chapter.

3. Literature Review

In order to achieve the goal of this thesis, which is to develop an approach to evaluate genomic biomarkers adoption strategies at IPO Lisboa, a literature review was conducted to understand the state of the art regarding the evaluation of health technologies, particularly in genomic medicine, and decision analysis in the healthcare context. Therefore, a plan was devised to conduct a comprehensive review of all the aspects considered relevant to achieve the purpose of this work (Figure 3.1).

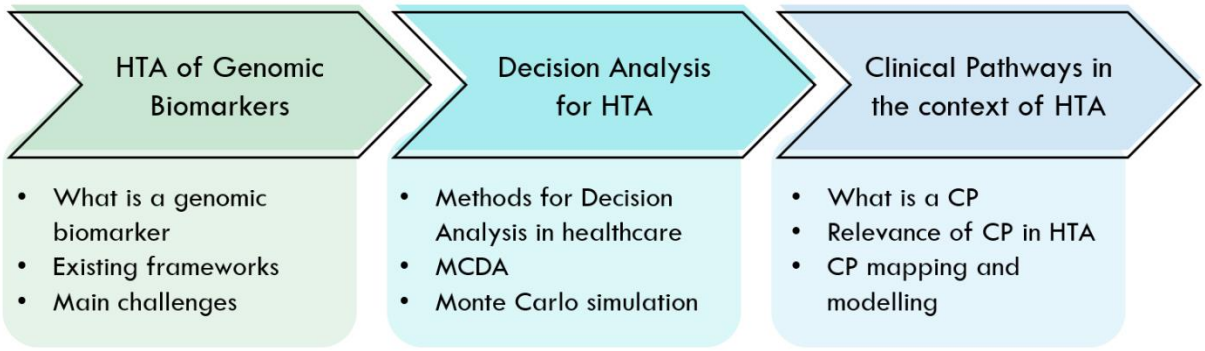


Figure 3.1. Main steps of the literature review.

Firstly, the current application of HTA in the evaluation of genomic biomarkers is presented. For this purpose, an extensive search of the literature was performed in multiple research databases, using keywords related with the subject. Secondly, the role of decision analysis in healthcare was studied, particularly in the HTA context. Special attention was given to the use of multicriteria decision models, due to their potential in comprehensively evaluating new health technologies. Lastly, some insights regarding clinical pathways and their relevance in the practice of medicine are presented, as they are useful to understand the impacts of adopting new health technologies.

Overall, this chapter aims at laying the foundations for creating well-informed and sound research, as well as to identify gaps in the literature for which this thesis can make a contribute.

3.1. HTA of Genomic Biomarkers

Nowadays, genetic testing plays an increasingly important role in medical practice, with ventures such as the Human Genome Project [25] and the European "1+ Million Genomes" Initiative [27] opening a path for a deeper understanding of the impact that an individual’s genetic material has on his health and on the development of certain diseases, as well as on his response to certain therapies. Even though genetics are just one of several factors which contribute to people's risk of developing most common diseases, the identification of relevant genomic biomarkers can potentially improve the screening, diagnosis, treatment, and monitoring of many patients with varied pathologies, in addition to the development of new drugs and a better understanding of the mechanisms of certain

diseases [19]. Hence the importance of thoroughly evaluating every emerging genomic technology, both in terms of the costs and the value it brings to the involved stakeholders.

According to the European Medicines Agency, a genomic biomarker is “a measurable DNA and/or RNA characteristic that is an indicator of normal biologic processes, pathogenic processes, and/or response to therapeutic or other interventions” [51]. Considering that tumour initiation and progressions is almost entirely driven by genetic events [52], genomic biomarkers are particularly relevant in the study and treatment of cancer, and international guidelines are constantly being updated in light of new evidence. For instance, the diagnostic of AML patients must include screening for certain genetic variations, such as mutations in NPM1, CEBPA, and RUNX1 genes, in order to classify the disease in terms of risk, and select an appropriate treatment [46]. In 2016, WHO published a revision to the classification of myeloid neoplasms and acute leukemia, which had been last updated only eight years before, where these and other indications were revised mainly due to the numerous advances in the genomic profiling of said pathologies, accomplished during that time period [47].

There are now multiple techniques that make it possible to characterize individual human cancers in unprecedented molecular detail [21], some of which are depicted in Figure 3.2. In terms of DNA sequencing, arguably the most known of these techniques, tests have evolved from single gene assessment to the use of multi-marker gene panels and, finally, to whole genome sequencing (WGS), which was possible due to the development of next generation sequencing (NGS) techniques [53]. Nevertheless, WGS is not yet frequently used in the clinical setting, as targeted gene panels provide faster results as well as a greater focus and depth in areas of interest, thereby generating more clinically relevant data. Furthermore, other factors such as technical efficiency and cost are also considered when choosing between these approaches [2].

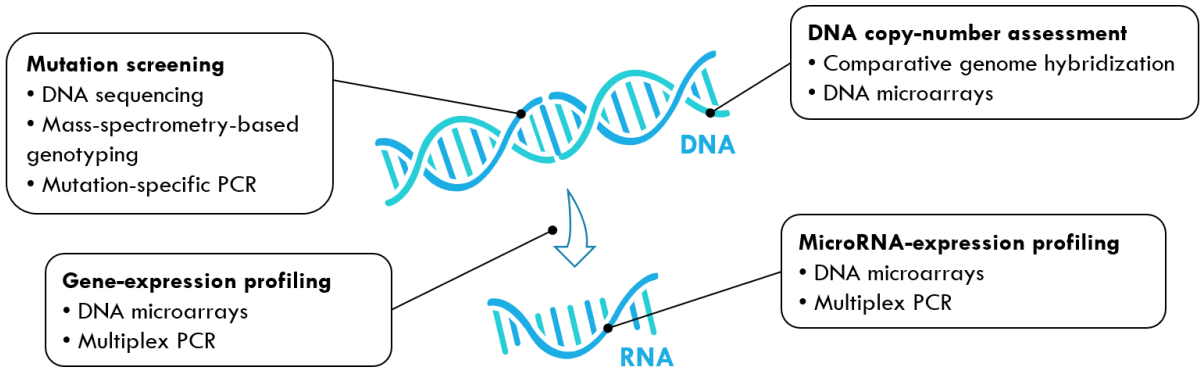


Figure 3.2. Examples of genomic technologies for tumour characterization. Adapted from [21].

In the past few years, the attractiveness of comprehensive genomic profiling assays has been on the rise, since multi-biomarkers genomic tests allow for a more thorough application of precision medicine, and the identification of potentially life-extending therapies as well as the patients that are most likely to benefit from them [32]. Even though there is still some lack of evidence regarding the relation between the use of larger gene panels and improved outcomes in patients with some types of

cancer [54], many researchers and physicians believe that looking into the human genome in a more comprehensive way, going as far as performing a WGS, proves to be one of the most robust strategies to reach a timely diagnosis for oncological and rare genomic diseases [31]. Furthermore, being able to consider both emerging and currently used biomarkers, such technologies allow for a better drug development and selection, as well as the stratification of patients for targeted and immune-based therapies [55, 56].

However, all the data collected through sequencing is only relevant if it is possible to correctly identify relevant biomarkers that will give information regarding the cancer and predict who will benefit from a particular targeted therapy [21]. In other words, it is crucial to coordinate basic, translational and clinical research as a means to provide oncology patients with the best care available. In addition, the constant surfacing of new and improved genomic technologies, which play such an important role in the lives of thousands of cancer patients worldwide, emphasizes the need to conduct a thorough and accurate evaluation in order to guarantee their quality and relevance in clinical practice [19].

Frameworks for HTA of Genomic Biomarkers

In a systematic review conducted in 2020, twenty-three articles were analysed to understand which frameworks are currently used for health technology assessment of “omics” technologies, as well as their actual adoption by HTA agencies [34]. Results demonstrated that, although being a very relevant field, studies regarding HTA of genomic biomarkers are still scarce, and there is an evident lack of a standardized evaluation framework for these technologies (Figure 3.3).

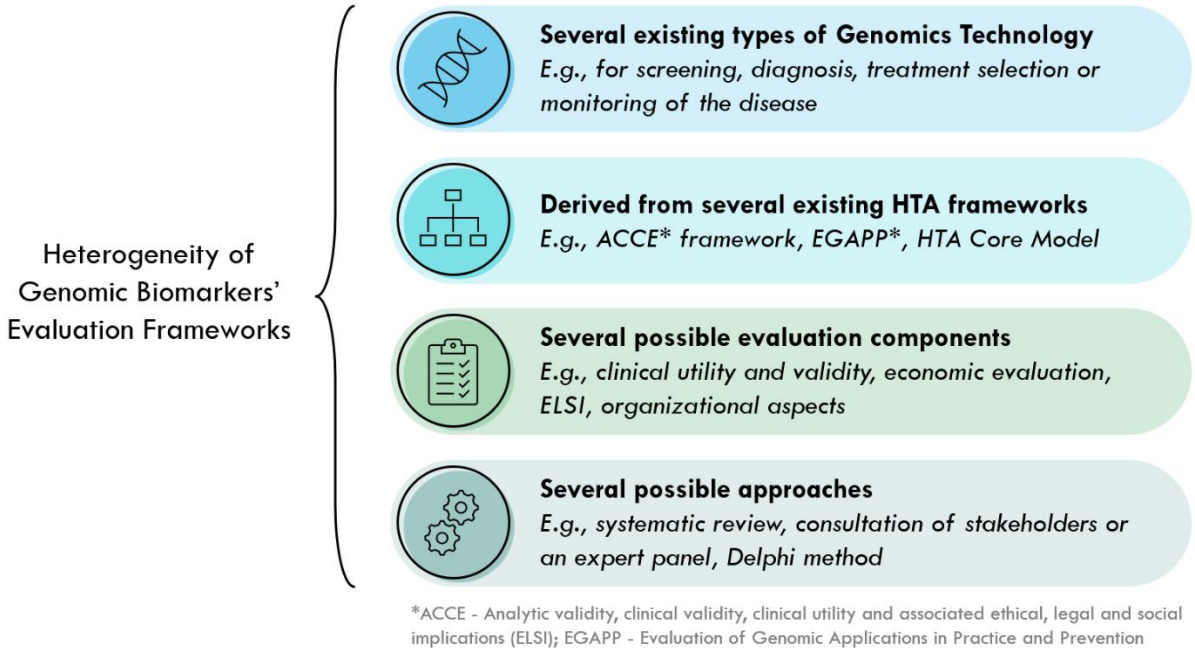


Figure 3.3. Examples of causes for the existing diversity of genomic technologies evaluation frameworks (synthesis using information from [34]).

First of all, twenty-two different evaluation frameworks were identified from the twenty-three articles which were included in the study, ten of which addressed genomics testing and genome-based applications, eight others addressed genetic testing, two addressed general precision medicine technology and one addressed new-born screening testing. Most of them were inspired in the ACCE framework (Analytic validity, Clinical validity, Clinical utility and associated Ethical, legal and social implications), which is claimed to include the four main criteria for evaluating a genetic test [57], and only four were presented as original frameworks. Besides the ACCE criteria, other commonly included evaluation aspects were the economic evaluation of the technology and related organizational aspects.

Furthermore, the authors of this review also identified multiple methodologies used to collect the information necessary for each assessment, such as conducting a literature review, consulting with an expert panel or even applying a Delphi method. Surprisingly, only one of the articles referred consulting stakeholders during the HTA process. Finally, to conclude the review the authors retrieved forty-five HTA reports from several HTA agencies to ascertain whether the previously identified frameworks were applied in real cases of genomic technologies' evaluation. The findings were not satisfactory, as less than ten reports were based on the frameworks described in the literature. Although these results do not mean that said reports were poorly conducted, they certainly reflect the lack of an accepted and standardized model for the assessment of genomic technologies, perhaps due to their great variety and the intrinsic uncertainty regarding benefits and possible long-term repercussions for the hospitals and the patients [53].

Another similar review, published in 2018, also emphasized the existence of multiple frameworks for the evaluation of genetic testing [35]. In this study, 29 frameworks were identified, most of which based in the ACCE framework, and it was observed that the context of the implementation and the patients' perspectives were frequently disregarded. To overcome the heterogeneity of the existing models, the authors suggest a broader HTA approach should be adopted by healthcare agencies, in order to "maximize population health benefits, facilitate decision-making and address the main challenges of the implementation of genetic tests" [35].

Stakeholders' Involvement and Sources of Information

An important aspect when conducting an evaluation of a health technology is selecting who will oversee the assessment and which stakeholders ought to be involved. According to Gagnon (2014), there are four main approaches to perform a hospital-based HTA, depending on the focus of action and the number of participants [58]. If the purpose of the evaluation is to support effective clinical practices, a potential approach is using the Ambassador Model, where a single clinician, selected at a national level, disseminates a series of recommendations to hospitals pertaining to HTA procedures. On the other hand, the hospital can also assemble an Internal Committee of multidisciplinary health-care professionals responsible for collecting evidence regarding new health technologies and communicate it to the hospital board, which is responsible for approving their implementation. In this case, multiple stakeholders should be engaged in the discussion, including managers, physicians, nurses, and administrative staff.

However, if the hospital intends to obtain evidence for managerial decision-making, suggested models are the mini-HTA, performed by a single health professional, and the HTA Unit Model, which requires full-time engagement from multiple people within the organization. The mini-HTA consists in a series of questions used to collect information pertaining to the health technology and its possible consequences, namely for the patients, the organization, and its financial state. Alternatively, the HTA Unit Model is a formal organizational structure which may comprise two entities: professional staff, who gather relevant scientific evidence, and a policy committee, which uses the collected information to produce pertinent recommendations [58].

In any case, hospitals should acknowledge the fact that the quality and pertinence of the collected evidence will be in part related to the number of stakeholders involved and their role in the institution, as well as the time invested in the evaluation. The participation of a multidisciplinary team, comprised by both healthcare professionals and administrative or management staff with different areas of expertise, opens a path for a richer and deeper assessment, where several perspectives are considered. Furthermore, considering the patient perspective may also contribute to a more contextualized and useful HTA report, as well as contribute to their knowledge and engagement in their own health care, although this hypothesis still needs further study [59].

Besides the selection of the evaluation team, the selected sources of information will also influence the quality of the assessment. In fact, multiple possible sources of data can be considered when performing a HTA of a certain genomic technology, ranging from systematic literature reviews to clinical studies or even the consultation of relevant stakeholders [34]. While conducting a systematic review of the literature results in a more objective and systematic appraisal, based on current scientific evidence, this approach is prone to neglect the specific context of the hospital and the necessities of the patients and the clinical staff. The same applies when consulting an expert panel which is not part of the organization. Contrarily, performing a HTA solely based on the opinions of stakeholders will end in a subjective assessment due to the lack of scientific evidence to support the obtained results. Therefore, both methodologies ought to be considered in order to obtain a contextualized and evidence-based HTA report, as long as all the information is collected in a systematic and transparent manner [13].

Personalised Frameworks

Even though a standard model would bring many advantages in the evaluation of genomic technologies, it is also true that each decision context is very specific, depending not only on the technology itself but also the hospital. Being so, it is important that each institution properly adapts every assessment to the hospital context and interact with the stakeholders to understand their needs and goals. An example of using a personalised approach to evaluate the impact of a genomic technology is the TANGO project (Technology Assessment of Next Generation sequencing in personalised Oncology), which aimed to assist the implementation of WGS, compared to the current diagnostics, for patients with advanced non-small cell lung cancer (NSCLC) in the Netherlands [6]. For this purpose, a plan was devised considering clinical, organizational, economical, ethical/legal and patient related issues, specific for patients with advanced NSCLC and melanoma in this country, using progression

free survival at six months, response rates, and toxicities as primary endpoints. It is expected that adopting this personalised approach will not only help achieve the goals of expanding molecular profiling of tumours and determine the cost-effectiveness and impact of WGS on several levels, but also inform and facilitate the responsible introduction of this promising sequencing technology.

In conclusion, genomic technologies are very promising tools for the practice of medicine which are powering the ongoing transition from traditional approaches to personalised health care, thus emphasizing the necessity of conducting an appropriate HTA prior to their adoption. Therefore, further research should be conducted to better define which aspects should be included in the analysis of these technologies, albeit leaving space for adaptation to the specific context of the analysis.

3.1.1. Challenges of HTA

Many obstacles are encountered while performing a HTA, particularly when considering a new genomic technology, some of which are worth emphasizing in this review. Firstly, as was previously mentioned there are a multitude of possible HTA frameworks described in the literature, leading to divergent methodologies and results, which also depend greatly on the context of the evaluation and the tools available [34]. Although this problem could be justified by the enormous variation of existing health technologies, even when restricting our focus to genomic technologies we find there is not a global standardized model which can be applied.

Secondly, another challenge when measuring the value of new technologies is the lack of relevant and precise data, which leads to uncertainty in the evaluation. Being so, expert opinion is usually considered to overcome this difficulty, which in turn might introduce bias and errors in the assessment [60]. Although there are a number of recent recommendations on how to better elicit expert judgements in HTA, common guidelines remain scarce [61].

Thirdly, if we consider the case of genomic technologies, which are frequently updated and improved due to the constant breakthroughs in the area of genetic knowledge, assessment frameworks should be continuously revised in order to keep up with such advancements [34]. Furthermore, both short-term and long-term impacts of genomic information should be included when evaluating this type of technologies, although some of these effects are very difficult to predict.

Finally, another issue worth mentioning is that the recent emergence of these technologies means there is still a great volatility in terms of costs and scientific evidence, with new studies released every day. For example, there are sometimes inconsistencies in the definition and measurement of clinical utility, as it varies according to the stakeholders perspective, clinical context and test purpose [31]. Furthermore, there are few studies reporting the consultation and involvement of stakeholders, namely the patients, in hospital-based HTA [59]. In conclusion, since HTA is an essential activity in the healthcare sector, more research should be conducted in order to tackle the previously mentioned obstacles and generate more valuable information that will eventually translate in the wellbeing of our society.

3.2. Decision Analysis for HTA

Ultimately, the goal of hospital-based HTA is to help deciding whether a certain health technology should be adopted by a healthcare organization, considering the available resources [58]. Therein lies the importance of developing and improving decision analysis techniques and tools within the healthcare context, as they enable a more comprehensive and transparent evaluation of health technologies.

Decision analysis role in healthcare is certainly not limited to HTA, as there are numerous situations within a hospital daily routine that require making choices, not only in the practice of medicine but in managerial settings as well. Nevertheless, the DM are usually healthcare professionals or hospital managers, and an impartial facilitator should be involved, whenever possible, to help the decision-making process.

3.2.1. Decision Analysis Methods in Healthcare

There are several factors that ought to be considered when making a decision regarding health technologies, which include a thorough description of the options, the selection of an appropriate comparator, the definition of a relevant time horizon and identifying possible sources of uncertainty [62]. Having this in mind, one can select the most suitable method from the extensive array of decision models available and described in the literature, according to the decision context.

Some examples of models which can be applied to the healthcare environment are decision trees, which are useful to visually and explicitly represent decisions [63]; Markov models, mostly used for predictive modelling and probabilistic forecasting [64]; Bayesian networks, particularly helpful for decisions involving uncertainty [65]; Monte Carlo simulation, useful to estimate the probability of different outcomes in the presence of random variables [66]; and MCDA, which allow to explicitly consider multiple criteria when choosing between several options [15].

The next sections will focus on two decision analysis methods which will be employed later in this study: MCDA and the Monte Carlo simulation.

3.2.2. Multicriteria Decision Analysis (MCDA)

In the last few years, MCDA has been gaining popularity in the field of HTA, as a result of its ability to encompass several criteria, and the transparency and informative nature of its outputs, which can be easily understood by all the stakeholders involved in the decision [15, 67]. Due to their versatility, MCDA models and tools can be applied in many contexts and produce valuable information for the DM, even though there are some concomitant limitations that should not be overlooked. Thereby, one should always follow the best practices available when using MCDA for HTA [68, 69]. Even though MCDA can be used in varied contexts, a socio-technical design should always be implemented from the beginning, defining the intended social and technical components of the analysis [70]. In other words, it is important

to define which stakeholders will participate and what will be their contribution to each step of the process, as well as the MCDA methods and software which will be employed. Furthermore, there are a series of steps which should be performed when conducting a MCDA, provided they are adapted to comply with the objectives and preferences of the stakeholders involved, particularly the DM. These include defining the decision problem, selecting and weighting the criteria, scoring the alternatives and calculating their aggregate scores [70].

Considering the increasing use of MCDA to assist decision-making in the health field, namely for the evaluation of health technologies, some reviews have already been published by several authors in an attempt to summarize the progresses made regarding the use of MCDA for HTA, along with the advantages and disadvantages associated with these methods [15, 60, 67].

In a review published in 2012, the authors claim there are three main categories of MCDA models: value measurement models, which are the most used for HTA as they allow to compare the options by assigning each of them an overall score; outranking models, where the alternatives are compared pairwise; and goal, aspiration, or reference-level models, involving selecting the alternative which better achieves the desirable levels for each criterion [67]. Furthermore, they state that MCDA value models are the most common type because are easy to understand and apply, well suited for visual presentation of the results, and able to incorporate uncertainty, all important qualities when applying them to healthcare decision-making.

In another review, written by Marsh *et al.* [60], forty studies describing examples of using MCDA in healthcare were retrieved, and a statistical and qualitative analysis were performed. More than half of the studies were published after 2011, proving the novelty of these approaches, although only one of them referred to the evaluation of genetic tests. Moreover, the number of criteria varied considerably according to the focus of the study, ranging from three to nineteen, and multiple information sources were considered, namely literature, expert opinion, and existing frameworks for the evaluation of health technologies. Overall, the authors state that the existing literature provides limited guidance because many distinct approaches are used, and the selected methods and results are seldom justified. Nonetheless, they acknowledge the potential of MCDA to improve decision making in healthcare and suggest investing more work in improving these methods.

Finally, a more recent study was published by Oliveira *et al.* [15] in 2019, describing a systematic review to assess the methodological quality of studies in which MCDA methods were applied for HTA. A total of one hundred and twenty-nine studies were included in this analysis, and a considerable number of them were found to present a poor compliance with good methodological practices. Even so, some of these studies discussed the relevance of using MCDA for HTA, namely its transparency and consistency, the capacity to account for the opinions of several stakeholders, and the potential to increase efficiency and objectivity in healthcare decision-making.

Even though there are many advantages of applying MDCA for HTA, all three articles mentioned above stated some challenges and disadvantages of this approach. First, the adoption of MDCA methods implies a significant amount of work and investment for the DM, even in the presence of a

facilitator, and it is essential to always perform an appropriate uncertainty analysis [67]. Besides that, existing gaps in the literature are often compensated using expert opinion, which may be less precise and therefore lead to higher uncertainty that must be quantified [60]. Furthermore, different weighting techniques may be selected according to the circumstances, and sometimes DM declare having some difficulties interpreting the results of the model [60]. Lastly, some studies report more practical problems such as difficulties in evidence and data synthesis, selection of the participants and modelling the criteria [15]. Considering that the previous examples do not encompass all the challenges of applying MCDA for decision analysis, it is clear that more work should be devoted to improving these methods and their application in the evaluation of health technologies.

MACBETH Approach

The first steps when employing a multicriteria analysis are defining the decision problem, which includes understanding the goals and motivations of the DM as well as characterizing the alternatives which will be compared, and choosing the criteria to be included in the analysis, guaranteeing that they satisfy the required properties: completeness, non-redundancy, non-overlap, and preference independence [70]. After that, to obtain the overall score of each alternative via an additive value model it is first necessary to score the alternatives in each criterion, as well as determine the criteria weights, processes for which there are a few numerical methods available. However, those can be difficult to apply when the stakeholders involved are not versed in the mathematical principles of MCDA [71].

Therefore, Bana et al. devised the MACBETH approach, short for Measuring Attractiveness by a Category-Based Evaluation Technique, which uses “only qualitative judgements to generate, by mathematical programming, value scores for options and weights for criteria” [72]. As a result, communication between the facilitator and the DM is more fluid, and the elicited judgements are more understandable, especially for those without a mathematical background. Moreover, users of the MACBETH technique, available through the software M-MACBETH [73], also enjoyed its visual display, consistency, and flexibility [72].

The MACBETH method has already been implemented in some studies involving MCDA in the context of healthcare [74-79], and its potential for assisting in HTA should be further explored, as the use of qualitative judgements may facilitate the interaction with healthcare professionals and therefore originate better decision models.

Uncertainty Analysis

Even though there are tools and techniques to diminish it, a certain degree of uncertainty will always be present when applying Decision Analysis methods [70]. In the case of MCDA, there are several possible sources of uncertainty, although they can be separated into two broad groups: uncertainty generated by the MCDA model itself and uncertainty derived from the data which were used in the model [80]. The first case refers to the impact that the selected weights, value functions or even the selected criteria have on the obtained results. In fact, the participation of several stakeholders with

divergent opinions, the complexity of the decision context and the presence of multiple conflicting objectives are all factors which may induce a higher degree of uncertainty in the attribution of value scores and when weighting the selected criteria [81]. On the other hand, the unavailability of sufficient and precise data can also lead to ambiguous performance measurement, even when relying on expert opinion to estimate the necessary information [70].

Despite the undisputable presence of uncertainty in MCDA analysis, research shows that a great number of studies applying MCDA in healthcare fail to acknowledge and analyse its presence and impact on the obtained results [60]. By performing a sensitivity analysis one can explore how changes in the weights of the criteria will impact the overall scores of the options, thereby testing the robustness of the model [70].

3.2.3. Monte Carlo Simulation

As previously mentioned, there are multiple sources of uncertainty when conducting a decision analysis, and it is imperative to acknowledge and incorporate them in the model through appropriate methods and techniques. One useful approach to incorporate data uncertainty, by predicting the probability of various outcomes in the presence of random variables, is the Monte Carlo simulation [80], whose basic principles are illustrated in Figure 3.4.

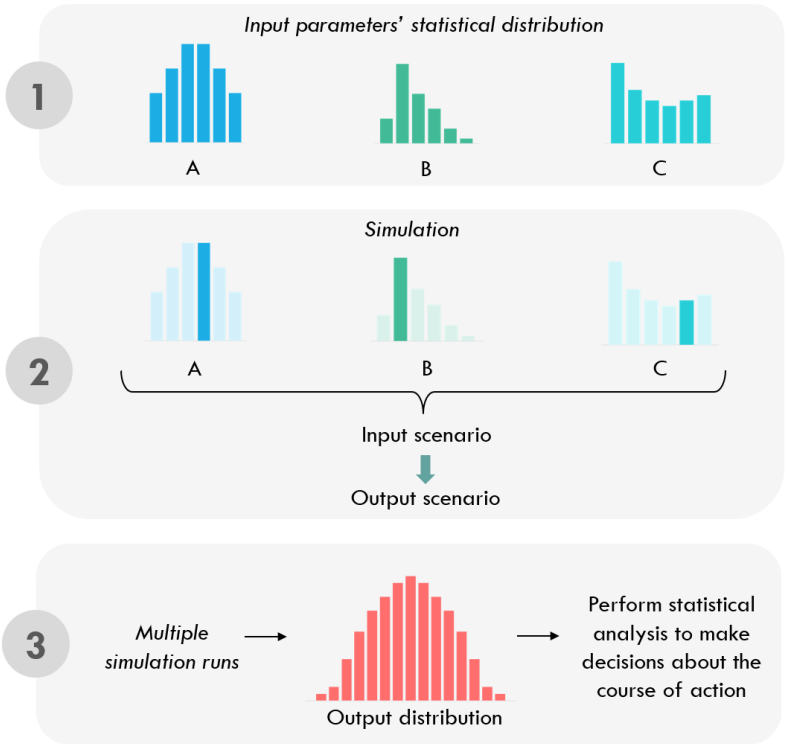


Figure 3.4. In Monte Carlo simulation, (1) first a statistical distribution is identified for each of the input parameters. (2) Then, in each simulation run, random samples are drawn from each distribution, from which an output is calculated. (3) After a number of simulation runs, a statistical analysis is performed on the values of the output parameters, and used to make decisions about the course of action (based on [82]).

Since this model is essentially used in cases where there is some degree of uncertainty surrounding the variables of interest, the first step is to determine the statistical distribution which best describes each of the input variables. Afterwards, one can simulate possible outputs by drawing random input samples from each distribution, and eventually, after performing enough simulation runs, a statistical distribution of the output values is attained. Therefore, one can perform a statistical analysis on the output distribution in order to better understand possible future scenarios and make more informed decisions [82].

Being so, Monte Carlo simulation is a simple but powerful tool to estimate potential scenarios in the presence of uncertainty, leading to more informed and pondered decisions [83]. Furthermore, it can be applied to several settings, including the analysis of clinical outcomes in a healthcare scenario by incorporating the variability from the clinical data [80], or even a more pragmatic evaluation of the costs involved in the implementation of new business strategies.

3.3. Clinical Pathways in the Context of HTA

The complexity inherent to healthcare settings, which involve a multitude of patients with various needs and a multitude of processes and resources, makes it important to establish rules and guidelines in order to standardize treatment in an effective and efficient way, as well as optimizing the quality and safety of all processes [84]. Therefore, the incorporation of clinical pathways in healthcare institutions is a natural and necessary consequence of such necessity.

However, there is still a lack of a global and consensual definition of what constitutes a clinical pathway, as well as multiple terms used to refer to it, such as ‘care pathway’, ‘critical pathway’, ‘care map’, among others [85]. According to Lawal et al. [84], who tried to overcome this disparity, for an intervention to be considered a clinical pathway it must include all the following criteria:

(1) The intervention is a structured multidisciplinary care plan;
(2) The intervention is used to channel the translation of guidelines or evidence into local structures;
(3) The intervention details the steps in a course of treatment or care in a plan, pathway, algorithm, guideline, protocol or other ‘inventory of actions’ (i.e. the intervention has time frames or criteria based progression);
(4) The intervention aims to standardize care for a specific clinical problem, procedure, or episode of care in a specific population.

Overall, the implementation of clinical pathways in hospitals and other healthcare institutions optimizes patient safety and reduces in-hospital complications and waiting times, while showing no negative impacts in terms of hospital costs and length of stay [86, 87]. Consequently, the number of publications related with clinical pathways and their application has been increasing in recent years, in an attempt to better understand the motivations, the process, and the consequences of establishing and studying such interventions.

Furthermore, the existence of structured and well-defined clinical pathways in a huge advantage (or even, some could argue, a necessity) when performing a complete and exhaustive HTA, particularly when targeting a medical device or a diagnostic test. Only by identifying and accurately mapping all relevant pathways can we assess the impact of a new health technology in terms of treatment, and the added value for all stakeholders, including the patient [88].

When assessing the value of implementing a new health technology in a hospital setting, it is important to predict how it might influence the current CP to allow for a better decision-making process. Thereby, mapping the existing CP or, in other words, describe them accurately and thoroughly, is an essential step when performing a HTA. Moreover, having a solid and accurate source of information regarding all the steps, ramifications and people who participate in the pathway is critical to ensure a proper evaluation.

In 2021, Aspland *et al.* [89] analysed 175 papers in a literature review that aimed to provide a general overview and classification of studies surrounding clinical pathways in healthcare. They stated that there are two main ways to obtain information related to a clinical pathway: either using existing data or by working with those we are involved in the pathway.

Evidently, deriving a pathway from existing data, such as electronic medical records or other hospital datasets, results in a more objective and factual description, as it is based on real occurrences. Therefore, whenever possible medical datasets are incorporated in the creation, mapping and modelling of clinical pathways, although they can have some limitations [90]. On the other hand, collaborating with experts, staff, patients and other relevant actors enables greater understanding of the reasons for structuring an intervention in a certain way, including the decisions and possible adjustments performed along the way. Hence, it is important to consider both data driven information and collected evidence from relevant stakeholders when deriving a clinical pathway [89], leading to a more comprehensive description and the inclusion of other relevant data besides clinical information, such as financial, demographic and even operational aspects [91].

On the other hand, sometimes mapping or representing the pathway is not sufficient to attain the desired objectives, thus being necessary to create an accurate model of the pathway. Many approaches can be selected for this purpose, simulation models being one of the most popular choices [89]. Finally, after modelling the pathway it is common to perform some type of scenario analysis and use it as a basis for recommendations for improvement. For example, Ajmi *et al.* [92] modelled the patient journey in a Pediatric Emergency Department in order to optimize them by identifying dysfunctions and propose and estimate prevention indicators of crowded situations.

Regardless of the purpose of the evaluation, defining the existing CP, sometimes solely by means of a graphical representation, is an important step when defining the context of a decision, and a valuable tool to access the impact of different strategies in the provision of health care.

4. Methodological Approach

The present chapter describes the approach developed to achieve the goal of this thesis, which is to provide means to compare different genomic testing strategies for AML patients at IPO Lisboa. Considering the complexity of this evaluation, which takes place in a healthcare setting and aims at capturing both the benefits and costs of the different alternatives for a multitude of stakeholders, it was decided that applying a multi-methodology instead of a single methodology would result in more complete and robust recommendations for the DM [93]. This included studying the AML patients' CP to understand how they might be affected by each strategy, building a multicriteria decision model to evaluate possible benefits and risks, and developing a Monte Carlo simulation model to estimate the costs of each alternative, due to the high level of uncertainty present. Even though this multi-methodology is focused on NGS tests for AML patients of IPO Lisboa, it can be adapted to other diseases and other contexts if necessary.

This chapter will present in detail the socio-technical approach design to implement the aforementioned multi-methodology, including the applied tools and the people involved in each step of the process.

4.1. Steps of the Multi-methodology

The multi-methodological approach followed during the development of this work can be divided in three steps, as shown in Figure 4.1.

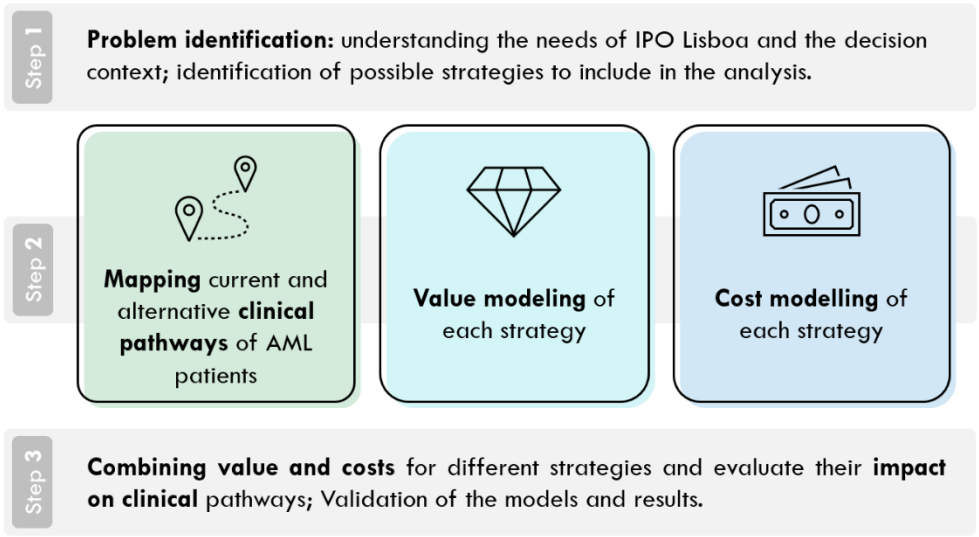


Figure 4.1. Overview of the methodological approach steps.

First, it was necessary to understand the decision context and define which genomic testing strategies should be included in the analysis. Secondly, time was invested in mapping the current and alternative CP of AML patients, as well as in building models to assess both the value and the cost of each selected strategy. Finally, the two models were combined, and the results were discussed keeping

in mind the possible short- and long-term impact of each strategy in the patients CP. Every model and every result obtained were validated by stakeholders involved in this study and subjected to a sensitivity analysis when deemed appropriate.

Each step was described beforehand, both in terms of the methods and techniques that would have to be applied (technical component) and the people to be involved, as well as the way they would participate (social component). In other words, a socio-technical approach was designed, to ensure the participation and involvement of all key-players in every step of the evaluation, as well as a correct implementation of the selected technical elements given the context of this study [94]. This socio-technical approach can be consulted in Figure 4.2.

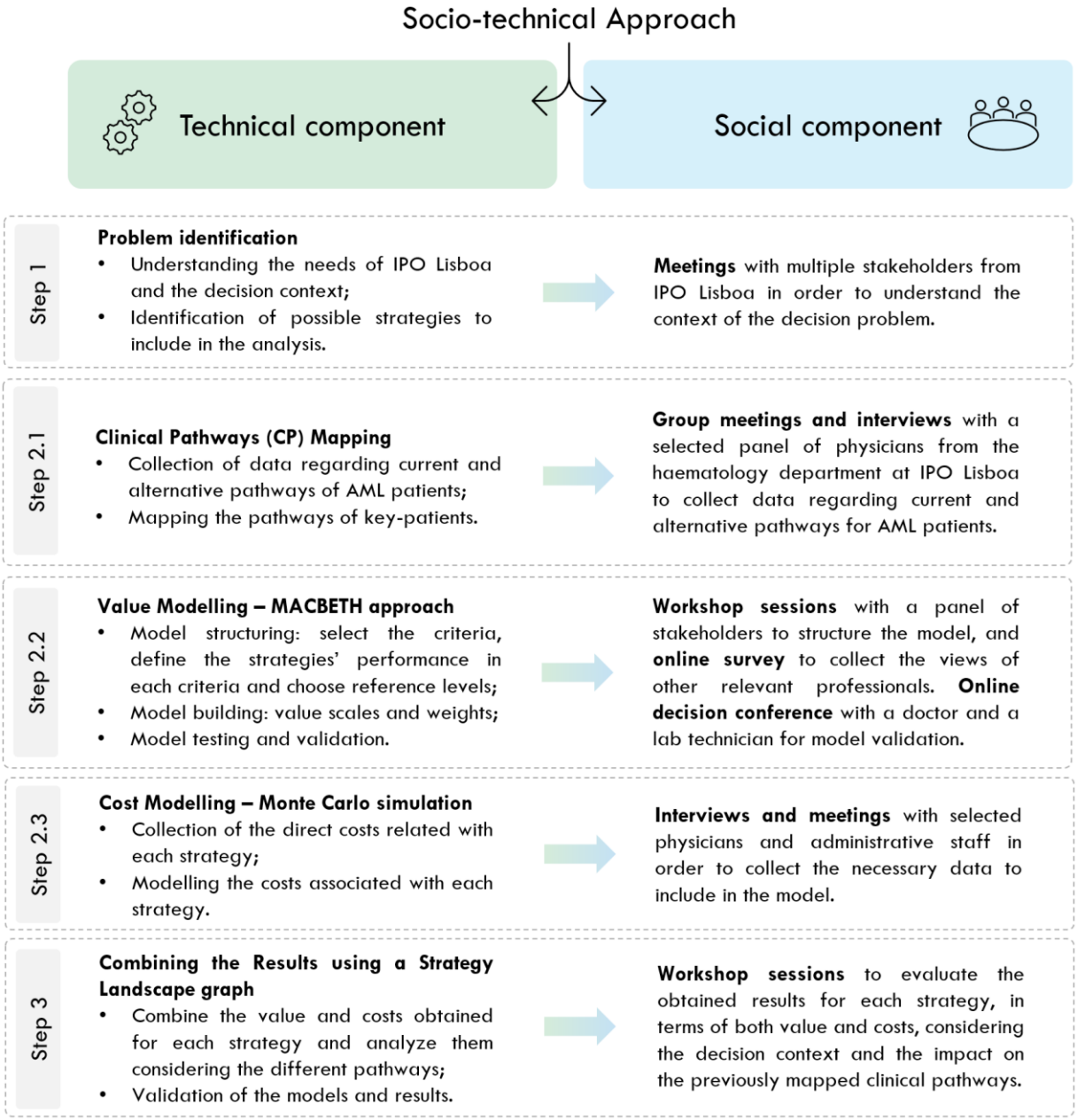


Figure 4.2. Detailed socio-technical approach.

It is important to highlight the combination of techniques and social approaches – align with a single paradigm – that were combined to achieve the goal of this thesis, in an attempt to add diversity and robustness to the analysis by tackling the decision problem from many different angles. A more detailed description of each step of the socio-technical approach can be consulted in the following sections.

4.2. Step 1: Problem identification

With the purpose of better understanding the problem at hands and the needs of the institution, five virtual and physical meetings were held over the course of one month involving a total of six stakeholders from IPO Lisboa, including healthcare professionals, laboratory technicians and a board member. Besides that, these meetings were also essential in the selection of which genomic testing strategies should be compared in the course of this work, and whom to directly involve in each step of the evaluation.

4.2.1. Decision context

As explained previously, tumours are caused by genetic mutations in our cells, and in most cancers, as is the case of AML, knowing which genetic abnormalities are present is extremely important for selecting the best treatment and monitoring the disease [95]. Even though the most relevant mutations are almost immediately tested upon the arrival of the patient to the hospital, in some cases a NGS test is also requested a few days or weeks later to confirm the prognosis of the patient, adjust the therapy and identifying molecular targets which can be used to monitor the cancer from that point on.

Nowadays, the rapid evolution of genomic technologies together with the increasing knowledge of the human genome have propelled the development of an increasing number of NGS tests, including those targeting haematologic malignancies. As a result, IPO Lisboa decided to revaluate the current strategy applied for NGS testing of AML patients, considering other options available in the market.

4.2.2. Strategies to be compared

After identifying what motivated this decision analysis, it was necessary to select which genomic testing strategies should be included in the study. These strategies, which were chosen and refined by a member of the hospital Board of Administration, a doctor and two laboratory technicians, are summarized in Figure 4.3 and explained in more detail ahead.

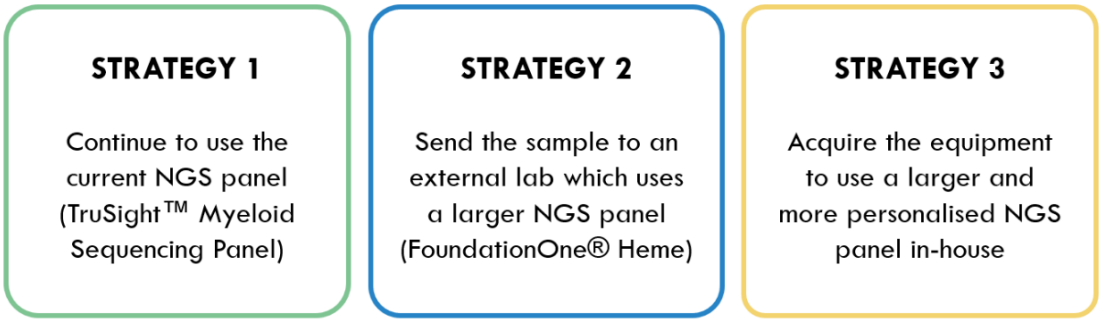


Figure 4.3. Genomic testing strategies selected for the decision analysis.

Strategy 1

The first strategy, which can be considered as the standard of care of this analysis, is maintaining the current NGS panel for patients with AML, which is the *TruSight™ Myeloid Sequencing Panel*, produced by Illumina Inc. [96]. This panel targets a full or partial exon region of 54 DNA genes frequently mutated in myeloid malignancies, including AML.

After purchasing the necessary material to perform this test from Illumina Inc. and other general laboratory suppliers, every step from collecting the sample to interpreting the results is done at IPO Lisboa by qualified professionals. Therefore, all the patient's genetic information is kept in the hospital's database and may be consulted at any time. Furthermore, the results and consequent actions can be discussed by a multidisciplinary team of healthcare professionals from IPO, including possible alterations to the patient's treatment or even enrolment in existent clinical trials.

On the other hand, considering the rapid pace at which new discoveries are made in the cancer and genetic field, one might consider disadvantageous restricting the test to only 54 genes, when there are other available options which encompass other genes, although with a less evident relation to AML.

Strategy 2

Instead of using the current NGS panel on AML patients, the institution is considering a new strategy, requiring the patient's blood and/or bone marrow samples to be sent to an outsourced company specialised in comprehensive genomic profiling. For this reason, the second strategy considered in this analysis is ordering the *FoundationOne Heme* test, provided by Roche Foundation Medicine, a company engaged on cancer genomic profiling [97]. Foundation Medicine mainly focuses on the development and commercialization of three genomic tests: *FoundationOne CDx*, *FoundationOne Liquid CDx* and *FoundationOne Heme*. Besides analysing multiple genes, all test results include microsatellite instability (MSI), which is the predisposition to mutation resulting from impaired DNA mismatch repair [98], and tumour mutational burden (TMB), or the number of mutations per coding area of a tumour genome [99].

FoundationOne Heme is a comprehensive genomic profiling assay for haematologic malignancies and sarcomas which uses NGS to identify the four main classes of genomic alterations:

base substitutions, insertions and deletions, copy number alterations, and rearrangements or fusions [97]. In total, it sequences DNA of the entire coding region of 406 genes, as well as selected introns of 31 genes involved in rearrangements. In addition, RNA of 265 genes is also sequenced to better identify known and novel gene fusions.

After reaching out to the company and agree on an appropriate budget, every time a NGS test is required the doctor simply sends the AML patient blood or marrow sample to the Foundation Medicine laboratories and waits approximately two weeks for the results. These results, given in the form of a report, include every biomarker and genomic finding, as well as suggested therapies and available clinical trials [97].

Even though an impressive number of genomic biomarkers are tested using this strategy, the fact that the patients' raw genetic data would no longer be available to the hospital is a major disadvantage to the institution, both in terms of research and sample/data privacy, and should therefore be carefully weighted in the decision. In addition, some of the alterations studied by the *FoundationOne Heme* test are always tested by IPO Lisboa on the first days after the patient's arrival, regardless of the possibility of doing a NGS test later, since they represent crucial information for a proper classification and early treatment of the disease. Thereby, even though the FoundationOne test studies considerably more genetic mutations than the current NGS test, it also provides some redundant information to the IPO clinicians.

Strategy 3

The last strategy to be included in this analysis is the acquisition of new equipment to study a larger and more personalised gene panel than the current one, given that the panel must encompass specific genes which are commonly mutated in AML, instead of a more generic panel directed to multiple myeloid pathologies, and evaluate other recently discovered mutations which have a potential interest for research and therapeutic purposes.

This comprises purchasing a more comprehensive test than the currently employed *TruSight™ Myeloid Sequencing Panel*, as well as the appropriate sequencing platforms and other equipment, if necessary. Although this strategy is considerably vague when compared to the previous two, the aforementioned stakeholders involved in their selection preferred not to further specify this option, in order to cover a wider range of alternatives.

4.2.3. Key Stakeholders

Whenever a healthcare institution is presented with a certain strategic decision, it is important to consider and balance the perspectives of different stakeholders, and to adapt them to the specific context of the institution [59]. Considering the case of selecting the best NGS test for AML patients, one should first understand the significance of these tests not only for the patient but also for the healthcare professionals and for the institution itself (Figure 4.4).

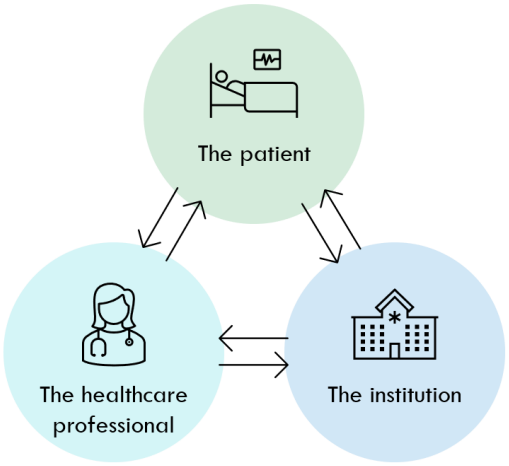


Figure 4.4. Different perspectives should be considered when making a strategic decision in a hospital context.

Although the patients' wellbeing will always be the primary focus of IPO Lisboa [7], a philosophy which is further supported by the implementation of a value-based healthcare delivery model [100], there are other relevant criteria which are taken into account when making a decision of this sorts, namely the cost and the ease of implementation of each strategy.

As was previously mentioned, the selection of the strategies to be compared in this study was carried out by a multidisciplinary group which included a hospital board member, a physician and two laboratory technicians, over the course of several asynchronous meetings. From that point on, most of the work, including structuring the value model and estimating the cost of each strategie, was made in collaboration with the medical doctor and the two laboratory technicians, as a smaller group focused on haematological pathologies was considered an advantage in terms of time management and the quality of the information. This group will be refered to as the "evaluators". Nevertheless, other proffessionals were also involved in the construction of the value model through an online survey, in an attempt to include a greater variety of opinions. In addition, the members of the IPO Lisboa Board of Admnistration, refered to as the "decision-makers" (DM), were also invited to validate the final results.

Due to privacy and logistical reasons, no meetings were held with AML patients during the course of this work. Consequently, clinicians were the main source of information regarding this subject.

4.3. Step 2.1: Clinical Pathway Mapping

After understanding the decision context and deciding which strategies should be included in the analysis, as well as the people who would make a better contribution in each step of the proposed methodology, the second part of the study consisted in developing personalised models to assist the DM. However, it was first necessary to map the clinical pathways of the AML patients at IPO Lisboa, a critical step due to several reasons. First, it allows to better understand the journey of a patient with this type of cancer, and the possible variations in terms of timings, treatment, and results. Second, we can estimate the timepoint when the NGS test is performed, and its implications in the whole CP. Finally, it

allows us to estimate potential changes the CP could undergo in case other NGS tests were implemented.

Therefore, a total of three meetings were held with the evaluators with the purpose of mapping the CP of IPO AML patients. Considering that AML can derive from several genomic mutations, there are different degrees of severity associated with this disease, resulting in distinct treatment approaches. For instance, although most patients undergo intensive chemotherapy, some can also receive a bone marrow transplant or even be referred to a promising clinical trial. Consequently, to map the CP the patients were divided into three groups according to their risk stratification, that is, whether they belong to the favourable-, intermediate- or adverse-risk group [46]. The process flowcharts representing the patients' CP, created using diagrams.net, a free online diagram software [101], will be presented in the next chapter.

After describing and mapping the CP of different key-patients, one can better understand the relevance of NGS tests in the whole process and the impact that each strategy might have in the treatment and monitoring of this disease. Thereby, the next sections will describe in detail the steps followed to ascertain the value and the costs of each strategy for different stakeholders involved in the process.

4.4. Step 2.2: Value Modelling

Within an HTA decision-making process, it is crucial not only to understand the relative value of each alternative course of action but also to consider the context wherein the decision is made, including the perspectives of a variety of stakeholders. In this context, MCDA emerges as a powerful tool, allowing to combine multiple criteria for the appraisal of several alternatives, without necessarily disregarding eventual sources of uncertainty [60]. Therefore, a multicriteria decision model was structured and built over the course of several months, following an approach which included both a social and a technical component. The social aspect of the model included holding several meetings with a selected group of stakeholders from IPO Lisboa to structure the model, an online survey to collect the opinions of other professionals used to build the model, and a final decision conference to validate the results. Regarding the technical component of the MCDA, the MACBETH method was applied since it only requires qualitative judgements to measure the attractiveness of the existing options [72]. This was done using the academic version of the user-friendly software M-MACBETH [73].

We hereby detail the process followed to construct a multicriteria model to evaluate different genomic testing strategies at IPO Lisboa for patients with AML, considering the opinions of several stakeholders.

4.4.1. MACBETH Approach

In order to assess the value of each strategy, the MACBETH (Measuring Attractiveness by a Category-Based Evaluation Technique) approach was applied, since it presents the advantage of only

requiring qualitative judgements to quantify the value of different options, an appealing characteristic when the people involved are not versed on the mathematical concepts governing MCDA [72]. Figure 4.5 shows the four main steps of the MACBETH decision-aiding process, which include understanding the decision context and planning the decision process, structuring the problem, building the model, and conducting a sensitivity and robustness analysis of the results to generate valuable recommendations for the DM.

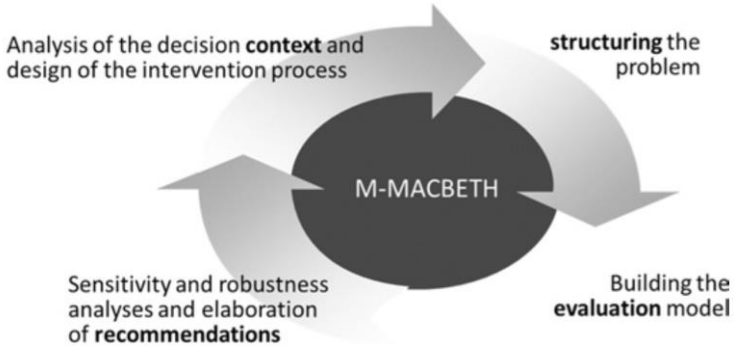


Figure 4.5. Phases of the MACBETH decision-aiding process [72].

As previously explained, a series of meetings were held in the beginning of this project to thoroughly describe the decision context and decide which strategies should be included in the analysis. Afterwards, it was necessary to structure the problem and the value model, and finally build the model and analyse the obtained results. To apply the MACBETH approach, the M-MACBETH software was used [73], as it was considered to be a useful tool since it is "simultaneously semantically meaningful, practically operational (user-friendly) and theoretically well founded" [72]. To generate a numerical score for each strategy, the M-MACTBETH software uses the following additive model:

$$V(s) = \sum_{j=1}^{n} k_j v_j(s), \quad (1)$$

where $V(s)$ represents the overall value of strategy s, $v_j(s)$ the partial value score of option s calculated using the value function constructed for criterion j, and $k_j > 0$ is the weighting coefficient of criterion j. In addition, the additive model should meet the following conditions: the sum of all the weighting coefficients must equal to one, and the partial value score of the lowest and highest reference level of each criterion must equal to 0 and 100, respectively [102].

1.1.1. Structuring the Value Model

After understanding the context of the strategic decision considered by IPO Lisboa, as well as defining the strategies to be compared, it was essential to define the criteria on which these strategies would be evaluated and characterize the performance of each strategy regarding each criterion. For this purpose, three workshops were held with the evaluators, during which the criteria were selected and refined until they met the necessary requirements: completeness, non-redundancy, non-overlap, and preference independence [70].

To initiate the discussion, a list of thirty-four potential evaluation aspects – relevant for the evaluation of *in vitro* medical devices – were presented to the evaluators in the first workshop, obtained from a Delphi survey previously created for the MEDI-VALUE project [103]. The group was then asked to classify each aspect as critical, fundamental, complementary, or irrelevant, considering their importance for the evaluation of genomic technologies. Afterwards, a debate was promoted for the participants to share their views and reach a compromise regarding which aspects should be included or not in the analysis. In the end, the evaluators agreed on six evaluation aspects deemed relevant for the study. During the second workshop, the six previously selected evaluation aspects were organised in two sets: the first set includes criteria directly relevant for the patient, and the second set comprises those which have a larger impact for the institution and its stakeholders. Furthermore, a detailed description of each aspect was formulated, and they were once more classified in terms of relevance. Finally, in the third workshop two of the evaluation aspects were merged to avoid redundancy, and the name of each aspect was refined in order to comply with the definition of an evaluation criterion. The final criteria are described in Table 4.1, along with their relevance to the provision of care to AML patients at IPO Lisboa.

Table 4.1. Criteria selected to evaluate different genomic testing strategies at IPO Lisboa, and their relevance for the provision of health care to AML patients.

	Criteria	Description	Relevance
Value of the genomic panel for the patient	**Clinical relevance of the genomic panel**	Number and relevance of the analyzed genomic variations for acute myeloid leukemia.	CRITICAL
	Time to access the results	Time between procedures and results (to what extent the results are available in a reasonable time period).	CRITICAL
Value of the genomic panel for IPO and its stakeholders	**Usability for the health professional**	Ease of use (to what extent the procedures for using the genomic technology are well defined and clear, and the final results are easy to understand and interpret) and need for training (need to provide the health professionals with some level of training to ensure they learn the specific knowledge necessary for using the technology).	COMPLEMENTARY
	Resource optimization	To what extent the institution has the capacity to adopt a certain strategy, in terms of available infrastructures and human resources.	COMPLEMENTARY
	Knowledge improvement	Access to the information (access to the sample and results, possibility of reanalysis and discussing the results with a multidisciplinary team).	FUNDAMENTAL

The first criterion to be considered is the “Clinical relevance of the genomic panel”, which will be evaluated in terms of the number of genomic variations analysed using a certain panel, alongside their relevance to myeloid pathologies, in particular to AML patients. This aspect was considered to be of critical relevance in this study since different genomic findings can lead to the adoption of new treatment strategies which will potentially impact the patient’s wellbeing and chances of survival. Therefore, a larger and more personalised gene panel might increase the chances of finding significant genomic variations, increasing the panel’s relevance to the DM.

The second criterion included in the value model is the “Time do access the results”, although it is important to emphasize that the time period for the result of any NGS test is usually longer than two weeks, due to operational and logistical reasons. For those cases in which the doctor decides to request an NGS test, minimizing the waiting time will increase the usefulness of the genomic findings in the patients’ care pathway. That is why this criterion was considered critical for the provision of health care to AML patients, and not because a delay would imply any immediate danger to the patient.

The third criterion to be included in the analysis is the “Usability for the health professional”, as it is important to maximize the ease of use and interpretation of the genomic device, and to consider the need to offer training to the health professionals involved in the process, both before and after implementing the new genomic test. Although this criterion can help ascertain the added value of a given alternative, it is not, by itself, fundamental to the evaluation of a specific strategy. Consequently, it was classified as complementary.

The fourth criterion that was selected was “Resource optimization”, since different strategies may imply different needs for human resources, infrastructures, and equipment. Once again, even though this criterion is significant to the institution, particularly in terms of the concomitant costs, it is not as significant as the first two criteria for health care provision to AML patients using genomic technologies and was thereby considered as complementary.

Finally, the fifth and last criterion considered in the value model was the “Knowledge improvement” that each strategy brings to the institution, due to the quantity and quality of accessible information. This includes the access to the original sample, as it allows to repeat the test at any point in time in order to confirm or compare results; the access to the raw genetic data of the patient, which consists of the results of the test before being processed and is critical to build genetic datasets that will be valuable for future research; and access to the final results, obtained by processing the raw data according to current medical and molecular biology knowledge, which can be discussed by a multidisciplinary team of professionals in order to decide the best plan of care for the patient. This criterion was considered fundamental for the analysis, as it is essential to estimate the added value of a certain strategy for the institution.

Following the choice of the criteria, a descriptor of performance must be associated with each one of them, consisting in a scale composed by several quantitative or qualitative levels, ordered by preference, which are used to describe the performance of a certain option on that criterion [72]. Establishing these descriptors of performance allows us to build value functions in which each level of the descriptor is assigned a numerical score.

In this case, a descriptor of performance composed of two or three performance levels was developed for each criterion, as displayed on Table 4.2. In the case of the criterion “Time to access the results”, a quantitative scale was used rather than a qualitative one. Furthermore, two reference levels were selected for each criterion, in this case the highest (superior) and lowest (inferior) performance level, which will be attributed a partial score of 100 and 0 in the model, respectively [72].

Lastly, to finish the structuring phase of the model each strategy was attributed a level of performance in each criterion, as depicted on Table 4.3. For this purpose, both literature review and expert consultation were considered.

Table 4.2. List of the evaluation criteria and respective descriptors of performance levels. For each descriptor, the superior reference level is identified as "(Sup.)" and the inferior reference level is identified as "(Inf.)"

	Criteria	Descriptor of performance
Value of the genomic panel for the patient 	Clinical relevance of the genomic panel	**Level 1:** The panel detects variations in the DNA of 406 genes and in the RNA of 265 genes, focusing on hematologic malignancies. ***(Sup.)*** **Level 2:** The panel detects variations in the DNA of a personalised number of genes, focusing on myeloid pathologies. **Level 3:** The panel detects variations in the DNA of 54 genes mutated frequently in myeloid malignancies. ***(Inf.)***
	Time to access the results	**Level 1:** The time interval between collecting the sample and obtaining the results is 2 weeks. ***(Sup.)*** **Level 2:** The time interval between collecting the sample and obtaining the results is 3 weeks. **Level 3:** The time interval between collecting the sample and obtaining the results is 4 weeks. ***(Inf.)***
Value of the genomic panel for IPO and its stakeholders 	Usability for the health professional	**Level 1:** The process is easy and simple to interpret. No training is needed. ***(Sup.)*** **Level 2:** The process is easy and simple to interpret. Some initial training is needed. **Level 3:** The process is easy, albeit sometimes difficult to interpret. Some occasional training is needed. ***(Inf.)***
	Resource optimization	**Level 1:** No infrastructures are needed. At least two people are involved in the process. ***(Sup.)*** **Level 2:** Requires using the currently available infrastructures. At least four people are involved in the process. **Level 3:** Requires using more infrastructures than the ones currently available. At least four people are involved in the process. ***(Inf.)***
	Knowledge improvement	**Level 1:** The institution has total access to the information (access to the sample, the raw data and the final results). ***(Sup.)*** **Level 2:** The institution cannot access all the information (only the final results). ***(Inf.)***

Table 4.3. Level of performance of each strategy in each criterion.

	Criteria	Strategy 1 Current panel (TruSight™)	Strategy 2 FoundationOne® Heme	Strategy 3 Larger panel than the current one
Value of the genomic panel for the patient	Clinical relevance of the genomic panel	L3	L1	L2
	Time to access the results	L3	L1	L2
Value of the genomic panel for IPO and its stakeholders	Usability for the health professional	L3	L1	L2
	Resource optimization	L2	L1	L3
	Knowledge improvement	L1	L2	L1

1.1.2. Building the Value Model

After carefully defining and structuring the decision problem, it was now possible to gather from the involved stakeholders the necessary qualitative judgements to build the model and obtain the score of each strategy. First, it was necessary to classify the differences in attractiveness between different levels of the descriptors of performance assigned to each criterion, using qualitative judgements. These judgements are inserted into a judgement matrix, which the M-MACTBETH software uses to generate a value function, attributing a score to each performance level. On the other hand, to assign a weight to each criterion, these must first be ordered by the difference of attractiveness between their reference levels. Afterwards, another judgement matrix is filled in order to generate the different weights.

As previously mentioned, contemplating the perspective and opinion of different stakeholders can result in a more comprehensive and reliable model, which in turn will be more relevant for the institution when facing an important strategic decision. Therefore, an online survey was prepared and sent to a diverse group of actors from IPO Lisboa, to collect their opinions regarding the different genomic testing strategies evaluated in the model. Later on, a decision conference was held to adjust and validate the prototype version of the model generated using the answers from the survey.

1.1.2.1. Online Survey

In order to consider the opinions of several stakeholders in the construction of the value model, an online survey was sent to a group of IPO professionals, which included two haematology doctors, one laboratory technician, one board member and a research manager (Figure 4.6). This survey, created using the web-based software Google Forms, allowed to collect their opinions pertaining to the different testing strategies evaluated in the model, which were considered to calculate the value functions and the weighting coefficients for each criterion.

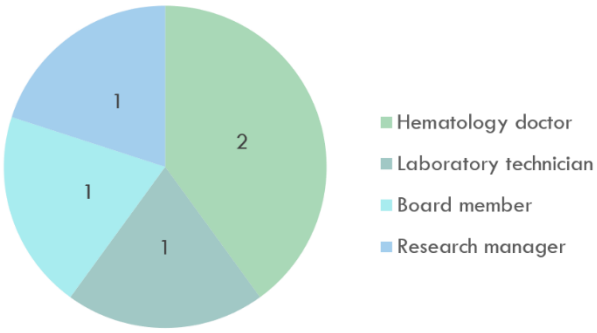


Figure 4.6. Number and profession of the stakeholders selected to participate in the online survey.

Calculating the Value Functions

To obtain the value function associated with each criterion, the participants were asked to classify the differences in attractiveness between the existent performance levels into one of the following categories: “null”, “very weak or weak”, “moderate”, “strong or very strong” and “extreme”. In addition, one could also avoid answering by selecting “I do not know / I do not want to answer”. Figure 4.7 shows an example taken from the online survey, regarding the collection of the necessary qualitative judgements to build a value function for one of the criteria. After obtaining the answers from the five participants, which will be presented in the next chapter, a simple majority system was applied to select the input for every entry of the M-MACBETH judgement matrix. In other words, for each pair of levels of performance, the category with the most votes was selected as the qualitative judgement to insert in the matrix. In the case of a draw between two adjacent categories, both were used as input in the matrix, as it is accepted by the software. On the other hand, in the case of a draw between non-adjacent categories, the matrix entry was defined as “positive”, which indicates one of the levels is more attractive than the other without specifying by how much.

After filling the judgement matrix with the results from the online survey, the software employed an algorithm to originate a value function, a process illustrated in Figure 4.8. However, in the decision conference held afterwards, some of the obtained scales were adjusted and validated according to the haematology doctor’s experience and expertise on the subject.

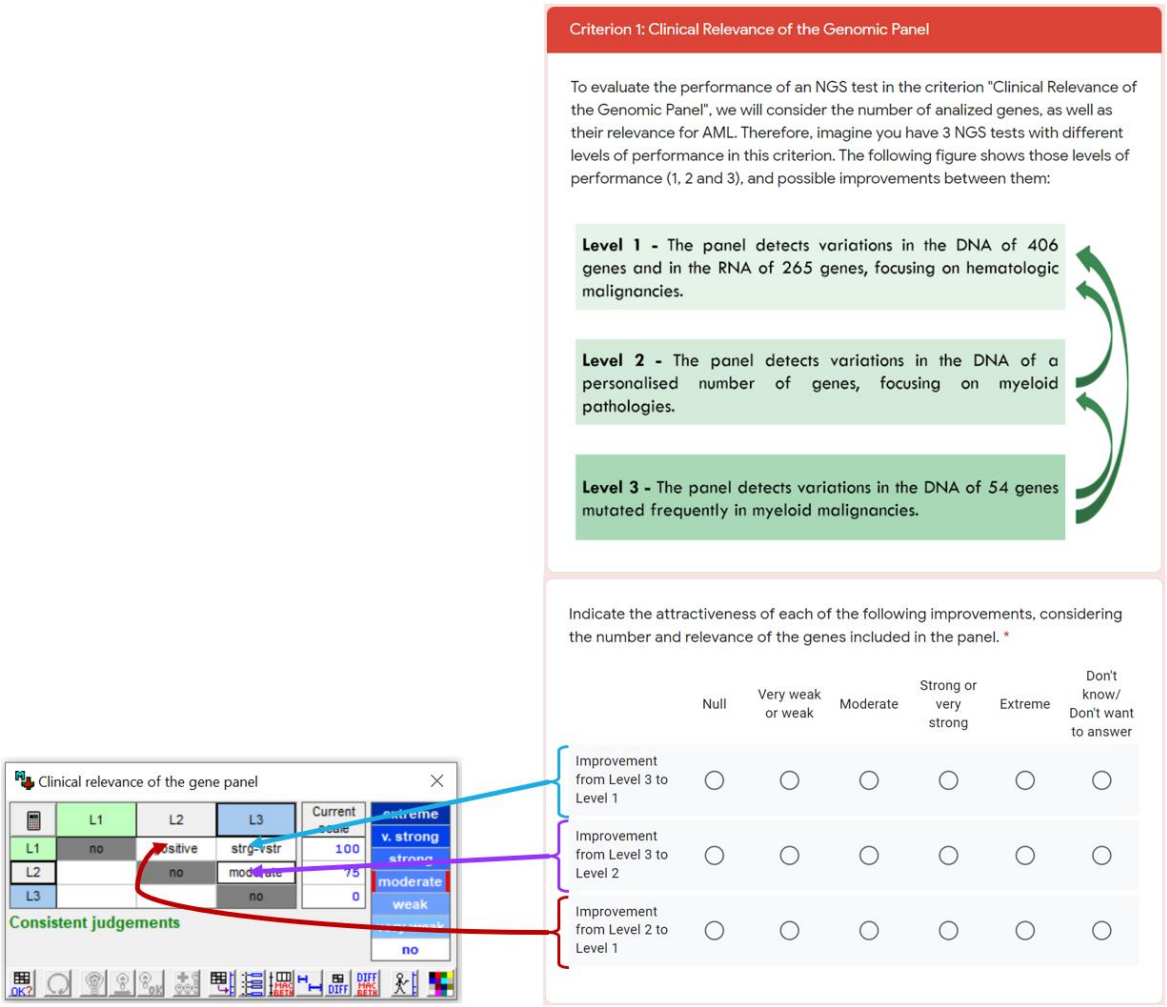


Figure 4.7. Question regarding the "Clinical Relevance of the Genomic Panel" criterion in the web-based platform to evaluate the difference of attractiveness between the three levels of performance (right), necessary to fill the M-MACBETH judgements matrix (left).

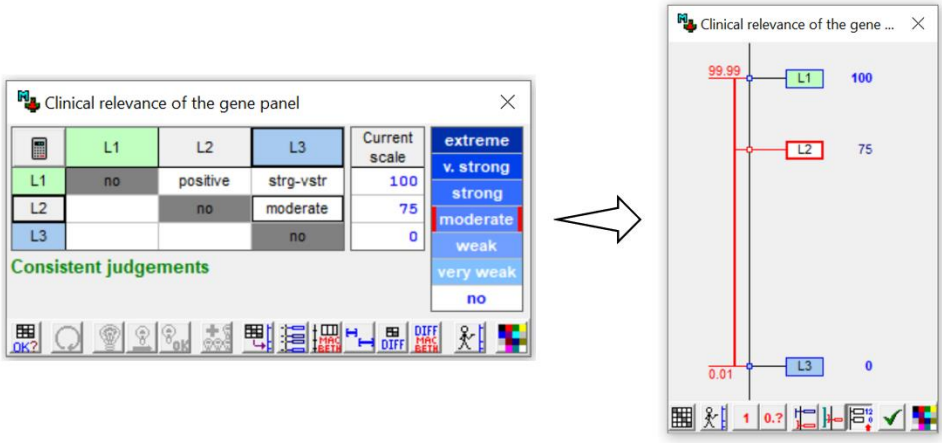


Figure 4.8. Resulting value judgements matrix (left) and respective value function (right) for the "Clinical Relevance of the Genomic Panel" criterion, obtained from the judgements collected with the online survey. The interval highlighted in red shows the range of possible values which Level 2 can be adjusted to.

Calculating the Weighting Coefficients

The second part of the online survey intended to collect information to estimate the weight coefficients of the five criteria included in the model. For this purpose, the participants were first asked to order the criteria, taking into the account the improvement from their lowest to their highest level for performance, as depicted in Figure 4.9. Next, the Borda voting system [104] was employed to select the most consensual order, since it allows to rank the criteria according to the given answers. Using this method, and considering we have a total of five criteria, for each given answer the first criterion to be selected was given 4 points, the second was given 3 points and so on until the last selected criterion received no points.

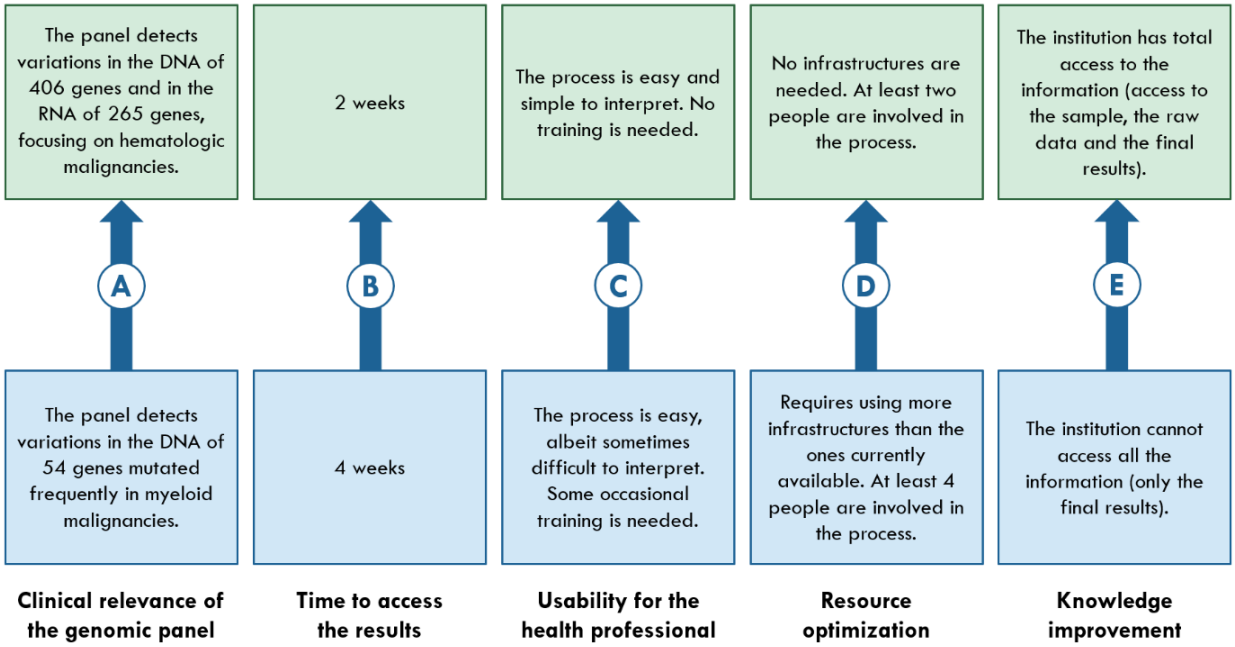


Figure 4.9. Improvements (named from A to E) from the "lowest" (blue) to the "highest" (green) level of performance of each criterion, which correspond to the previously selected reference levels.

Furthermore, the participants were also asked to describe each improvement as "null", "very weak or weak", "moderate", "strong or very strong" and "extreme", and this information was used to fill the judgement matrix which originated the criteria weight coefficients. Later on, both the order and the weights of the criteria were rectified in the decision conference, according to the stakeholder's expertise.

Thus, the overall value of each strategy was calculated first based solely on the answers collected in the online survey. However, a model should always be validated by the involved stakeholders, in order to generate appropriate recommendations for the DM [15]. Thereby, after inserting the data from the online survey into the M-MACBETH software, a decision conference was held with a haematology doctor and a laboratory technician, part of the group of evaluators, to discuss, adjust and validate the results.

1.1.2.2. Decision Conference

After using the answers obtained in the online survey to generate a prototype of the value model, a decision conference was held with the evaluators form the haematology department of IPO, with the purpose of adjusting the model and validating its results. Moreover, a sensitivity analysis was also performed, to assess if the overall scores of the strategies would be impacted by uncertainty in the weighting of the criteria.

First, it was necessary to validate the partial value scales obtained for each criterion. For this purpose, the judgment matrices were shown to the two participants, who were given the opportunity to alter any of the entries according to their expertise. Afterwards, the correspondent partial value scales were presented, and the participants were asked questions such as “Regarding criterion X, do you agree that an improvement from level 2 to level 1 is twice as attractive as an improvement from level 3 to level 2?”. The scales were then adjusted according to the given answers, within the interval allowed by the software.

Regarding the allocation of the weight coefficients, the participants of the decision conference started by confirming the ordering of the criteria by answering a series of questions starting with: "If it were possible to go from the worst to the best level in a single criterion, which one would you select for this change?”, followed by the same question while progressively excluding the criteria that were already selected. Subsequently, they were asked to adjust the histogram generated by the software from the qualitative judgements associated with each improvement, within the acceptable intervals.

To finish, the overall scores of each strategy were presented, and the two participants were given the opportunity to comment and ask questions regarding them. Furthermore, a sensitivity analysis was also performed to show the participants in which measure variations in the weighting coefficients of the criteria could possibly influence the obtained results. Lastly, some questions were posed in order to collect feedback pertaining to the overall process of structuring and building the MCDA model.

1.2. Step 2.3: Cost modelling

When facing a decision in the healthcare context, especially one related with the adoption of new genomic technologies which can directly impact the care of the patients, it is important to contemplate not only the benefits and risks, but also the costs of each alternative course of action [14]. By doing so, one can predict the economic impact that adopting a certain strategy will have for the institution, which in turn will influence the decision-making process [105].

Therefore, a cost analysis was performed to compare the three genomic testing strategies for AML patients, considering the direct costs related with each alternative. This was accomplished using a Monte Carlo simulation model, as it allows to incorporate inaccuracy and uncertainty associated with the available cost component’s data [82]. Monte Carlo modelling is specifically suitable when our output of interest is the result of summing uncertain input components, which is the case in cost analysis.

Prior to building the simulation model, it was necessary to identify the relevant groups of costs to be considered. Furthermore, for each group of costs a minimum, maximum and expected value were defined, in order to construct the necessary probability distributions for the Monte Carlo simulation model. Each of these steps will be explained in further detail in the following sections.

1.2.1. Identification and Collection of Costs

Within Monte Carlo simulation modeling, it was first necessary to identify and collect the relevant costs to consider in this analysis.

To simplify the process, indirect costs were not considered, due to the added complexity they would introduce in the model, and only costs which would differentiate among the strategies were included, as suggested in the literature [14, 105]. For example, all costs related with sample collection were not considered as they are transversal to all strategies. This approach was discussed with the group of evaluators and with one of the DM, which agreed to only consider direct and differentiating costs, starting from the point after the patient's sample had already been collected. The main groups of costs to be included are represented in Figure 4.10, and explained in more detail below.

Afterwards, the monetary value of each group of costs was estimated using data and information provided by accounting records, laboratory technicians and administrative staff. Expert opinion was collected to fill any existing gaps whenever necessary [106] and registered as a possible source of uncertainty to be later assessed by means of an appropriate sensitivity analysis.

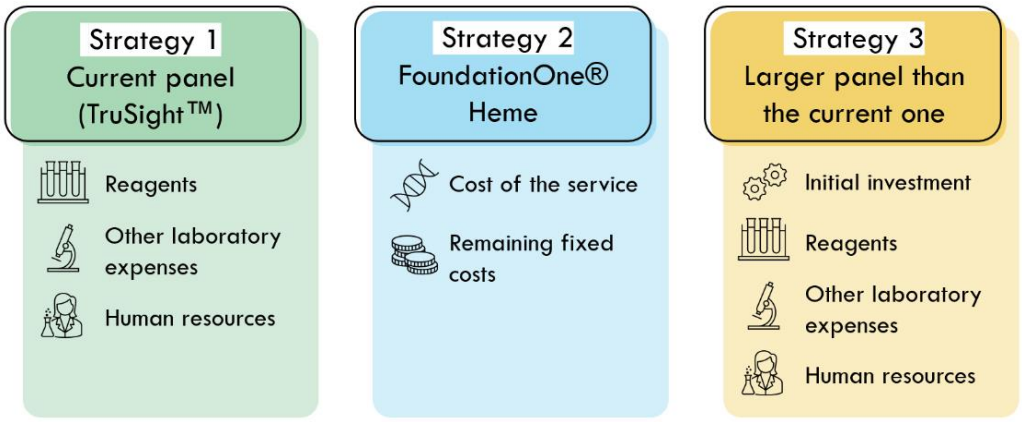


Figure 4.10. Main costs identified for each of the genomic testing strategies considered in the analysis.

Reagents and Other laboratory expenses

One of the greatest expenses of any diagnostic laboratory comes from consumables, particularly from purchasing great quantities of reagents and kits which are essential for daily work of the diagnostic and research teams [107]. In addition, a lot of material is used when performing an NGS test, from pipets to DNA sequencers, which require constant maintenance and lead to considerable annual expenses for the laboratory. Therefore, both groups of costs were included in the analysis of strategies 1 and 3.

To estimate these costs, data was collected from the accounting reports of UIPM (Unidade de Investigação em Patobiologia Molecular [108]), ranging from 2018 to 2020 (Appendix A). Since UIPM comprises not only the haematology laboratory but also other pathology units from IPO, the proportion of annual AML genetic reports compared with the total number of UIPM reports was calculated and used to estimate the costs directly associated with AML NGS tests.

Human Resources

Regarding the genomic testing performed in-house, a significant number of laboratory professionals are involved in the process of preparing, analysing and interpreting the genetic material of the patients. In fact, the greatest spending of most hospitals is done on salaries and benefits, a tendency which can be extended to their diagnostic and research laboratories [107]. Thereby, the costs associated with the salaries of the haematology laboratory team, which are mostly employed as Superior Technicians, were considered for strategies 1 and 3.

For this purpose, the recently updated salary table issued by the Portuguese government in 2021 [109] plus legal benefits (social security, meal, vacation and Christmas subsidies) were considered. In addition, the team leader of the haematology laboratory was consulted regarding the current number of Superior Technicians stationed there. Salary costs related with sending the sample to Foundation Medicine were considered as negligible and were therefore not considered in the cost estimation of strategy 2.

Cost of the Service and Remaining fixed costs

In the case of strategy 2, which corresponds to acquiring an external service from Roche Foundation Medicine, no costs will be directly incurred from equipment use, reagents or personnel. However, since IPO intends to preserve all equipment and human resources regardless of the chosen strategy, one must continue to include a certain percentage of the present fixed costs in the analysis of strategy 2. This includes every group of costs considered in strategy 1 except for the reagents, as they are specific for the currently used genomic panel. Thereby, after consulting with the DM, it was decided that 70% of the fixed costs of strategy 1 would be included in strategy 2. Furthermore, the cost of purchasing the genomic testing service, *FoundationOne Heme*, was estimated using the budget presented by Roche to IPO for a similar genomic test, along with the listed prices the company made available to their patients [110].

Initial Investment

Finally, the initial investment of strategy 3, which consists in purchasing the equipment necessary to employ a larger and more personalised NGS panel at IPO, was estimated using data regarding all the genetic related equipment acquired by IPO in recent years. It is important to mention

that, regardless of the adoption of any of the considered strategies, none of the equipment currently owned by IPO would be sold.

1.2.2. Monte Carlo Simulation Model

The complexity of assessing genomic technologies, along with the scarcity of exact data and consequent extrapolations, introduce a lot of uncertainty in the cost evaluation of each strategy. In this context, the Monte Carlo simulation arises as a simple and useful solution as it allows to incorporate uncertainty surrounding the variables of interest, namely by describing each input as a statistical distribution [82].

The first step to build a Monte Carlo simulation model is to determine the statistical distribution which best describes each of the input variables. Next, an output function must be defined, which relates the input variables with the desired results. Finally, one can simulate possible outputs by drawing random input samples from each distribution and applying the output function [82]. After enough iterations, a statistical distribution of the output values is attained, which can be submitted to a statistical analysis to better understand possible scenarios and make more informed decisions. Furthermore, a sensitivity analysis will help us understand the impact each variable has on the final results.

1.2.2.1. Statistical Distributions

Considering the nature of the available data, every input of the simulation was assigned a triangular distribution, as they provide a good description of a population when there is limited information regarding it [111]. Therefore, the expected value of each variable was calculated, along with a minimum and a maximum value.

Regarding the time frame, a period of five years was considered in the cost analysis. On the one hand, many authors suggest the time horizon should be longer in order to capture the major health and economic effects of a genomic technology for the patient and the institution [14]. In this case, however, since only direct costs were evaluated and there was access to limited data, a shorter time period was used, although long enough to properly encompass the major expenses for the institution. A discount rate of 4% was applied when calculating the present value of each group of costs, as suggested by the Portuguese National Authority of Medicines and Health Products (INFARMED) [106].

The following table shows the values used to build the triangular functions for each group of costs, which were later used as inputs in the Monte Carlo simulation model.

Table 4.4. Expected, minimum and maximum present value of each group of costs over the next 5 years, used to build the triangular functions for the Monte Carlo simulation.

Group of Costs	Expected Value	Minimum Value	Maximum Value
Total cost of reagents at UIPM	2 621 147,16 €	2 509 984,89 €	2 732 309,42 €
Total of other lab expenses at UIPM	89 727,44 €	73 385,30 €	106 069,59 €
Salary/Superior Technician	172 612,84 €	77 012,13 €	260 247,01 €
Cost of *FoundationOne Heme**	5 526,40 €	4 451,82 €	27 642,61 €
Initial Investment	200 000,00 €	160 000,00 €	240 000,00 €

* *Per patient, considering the purchase of one test every year.*

As mentioned previously, a time horizon of five years was considered, and all costs were adjusted to the present value. The mean cost of reagents and the mean cost of other laboratory expenses from years 2018 to 2020 were used as the expected value of subsequent years, and the corresponding standard deviations were added and subtracted to the mean cost to obtain the maximum and the minimum values, respectively. Regarding the cost of human resources, the most recent salary table was consulted in order to obtain the minimum, expected and maximum annual salary of a Superior Technician [109].

In order to obtain the expected cost of purchasing the services of Foundation Medicine over the next five years, the budget presented to IPO had to be adjusted, since it referred to the *FoundationOne CDx* test. Being so, using the listed prices of *FoundationOne CDx* and *FoundationOne Heme* available in the USA [110], the cost increment from one test to another was calculated and used to estimate the cost of purchasing one *FoundationOne Heme* test, as shown on Table 4.5. For the minimum and maximum values, the lowest (1 000,00 €) and highest (6 209,28 €) costs were used, respectively.

Table 4.5. Listed prices and budget for the FoundationOne CDx *and the* FoundationOne Heme *tests.*

Prices	*FoundationOne CDx*	*FoundationOne Heme*	Increment
Listed prices in the USA (in €)	5 001,92 €	6 209,28 €	124,138%
Budget presented to IPO	1 000,00 €	-	-
Expected budget	-	1 241,38 €	-

Furthermore, data regarding all the equipment purchases made by IPO were consulted to predict the cost of acquiring new equipment, necessary to implement strategy 3. Such purchases might include DNA sequencing machines, bioanalyzer systems and thermal cyclers, and were estimated to a total cost of 200 thousand euros. For the minimum and maximum values, a 20% deviation was applied to the expected value, which is the approximate variation between different equipment.

Lastly, it was necessary to estimate the number of human resources involved in the genomic testing process, as well as the annual number of NGS reports (Table 4.6). The current number of laboratory technicians from the haematology laboratory working at UIPM (7 Superior Technicians) is expected to remain constant during the upcoming years, with the possibility of increasing or decreasing this number by one element, for instance due to maternity leaves. Furthermore, it was estimated that

haematology technicians at IPO invest approximately 15% of their time in tasks related with NGS tests for AML patients. Regarding the number of AML reports, the current annual number of NGS reports (50 reports) was selected as the expected value for the next five years, and a variation of 20% was applied to obtain the minimum and maximum values for this input. Finally, since limited data was available regarding the total number of NGS reports at UIPM, the number of patients from 2020 was used as the expected value for the upcoming years, and a variation of 500 reports was considered to calculate the minimum and maximum values associate with this variable.

Table 4.6. Expected, minimum and maximum value for the number of HR from the haematology laboratory working at UIPM, the annual number of reports related with AML NGS tests and the total annual number of UIPM reports.

Human Resources (HR) and NGS Reports	Expected Value	Minimum Value	Maximum Value
Haematology HR at UIPM	7	6	8
Annual AML reports	50	40	60
Annual UIPM reports	2300	1800	2800

1.2.2.2. Output functions

After defining the statistical distributions for every variable, an output function was devised for each strategy, to combine all the existing inputs into the result of the simulation. The output function for strategy 1 is

$$Cost_1 = \frac{AML\ reports}{UIPM\ reports} \times (reagents + other\ expenses) + salary \times HR \times 0{,}15, \quad (2)$$

where $Cost_1$ is the present cost of strategy 1 considering a time horizon of five years, $AML\ reports$ is the annual number of NGS reports for AML patients, $UIPM\ reports$ corresponds to the annual number of NGS reports at UIPM, $reagents$ refers to the cost of reagents at UIPM, $other\ expenses$ is the cost of other laboratory expenses at UIPM, $salary$ refers to the salary of a Superior Technician and HR is the number of human resources from the haematology laboratory working at UIPM. A factor of 0,15 was applied considering that only approximately 15% of an haematology technician's time is spent with AML NGS related tasks. For strategy 2, the output function applied was

$$Cost_2 = FoundationOne \times AML\ reports + Remaining\ FC, \quad (3)$$

where $Cost_2$ is the present cost of strategy 2 considering a time horizon of five years, $FoundationOne$ refers to the cost of purchasing the *FoundationOne Heme* test, $AML\ reports$ is the annual number of NGS reports for AML patients and $Remaining\ FC$ corresponds to 70% of the current fixed costs. Lastly, the output function for strategy 3 is

$$Cost_3 = Inv.capital + \frac{AML\ reports}{UIPM\ reports} \times (reagents + other\ expenses) + salary \times HR \times 0{,}15, \quad (4)$$

where $Cost_3$ represents the present cost of strategy 3 considering a time horizon of five years, $Inv.\ capital$ includes the initial costs of purchasing new equipment, $AML\ reports$ refers to the annual number of NGS reports for AML patients, $UIPM\ reports$ is the annual number NGS reports at UIPM, $reagents$ corresponds

to the cost of reagents at UIPM, *other expenses* refers the cost of other laboratory expenses at UIPM, *salary* is the salary of a Superior Technician and *HR* is the number of human resources from the haematology laboratory working at UIPM. For the same reason as in strategy 1, a factor of 0,15 was applied.

1.2.2.3. Simulation results and sensitivity analysis

Following the choice of the statistical distributions and the definition of the output functions, the software @RISK, from Palisade [112], was used to perform a Monte Carlo simulation for the three genomic testing strategies. The number of iterations was set to 'Automatic', meaning that @RISK performed iterations until all distributions had achieved convergence. After that, the results of the simulation would become available in the form of graphs and tables with the corresponding statistics report. This allows to have a more visual and general sense of the possible output scenarios and, at the same time, perform a deeper statistical analysis of the results if necessary.

In addition, a variety of tornado graphs can be consulted to understand the effect of each input distribution in an output, which is vital considering the uncertainty surrounding most of the data. This form of sensitivity analysis presents a chart with multiple horizontal bars, each corresponding to an input variable. The variables which have the largest impact on the output distribution correspond to the longest and topmost bars in the graph [113]. Consequently, one can easily identify the most critical inputs and concentrate on them when deciding between alternative plans of action.

In Chapter 5, the results obtained for each strategy using the Monte Carlo simulation model will be presented, along with the corresponding sensitivity analysis. Both were validated with the DM, represented by one of the IPO Lisboa board members.

1.3. Step 3: Combining the Results

At this point, the most relevant aspects of AML patients' clinical pathways had been mapped, and all three strategies had been compared using two types of models, a value model and a cost model. Consequently, there was a need to combine those scattered results in a clear way which would provide the DM with useful and valuable information for the decision-making process.

First, the mean value of each strategy's cost distribution was inserted into the M-MACBETH software, to originate a simple XY plot. Then, the output distributions obtained with the Monte Carlo simulation model were combined with the overall scores of the strategies from the MACBETH model and represented in a three-dimensional graph ("strategy landscape" graph) for better visualization.

Finally, a brief description of the expected impact the adoption of each alternative strategy would have on the current CP was presented, in order to further understand the implications of the decision in the care of the patients.

2. Results

The described multi-methodology was applied to help evaluate the three considered genomic testing strategies for patients with AML at IPO Lisboa, based upon a socio-technical approach. In this chapter, the results of implementing the developed multi-methodology will be presented, and their combination is shown to provide valuable information to assist the DM at IPO Lisboa in the discussion and comparison of each of the genomic testing strategies considered in the analysis, in light of the decision context and of their goals.

2.1. Clinical Pathway Mapping

After understanding the decision context and selecting the genomic testing strategies to consider in the evaluation, the CP of AML key-patients were described, in order to have a better understanding of their journey and the potential impact of performing a genomic test.

Approximately sixty patients are diagnosed with AML at IPO Lisboa every year, coming mostly from the centre and the south regions of Portugal, and the characteristics of the disease can vary a lot from person to person. As was explained in the Chapter 2, AML can be caused by a number of genetic mutations which prevent our blood cells from proper maturation and proliferation, originating a great spectrum of cases. Nevertheless, a risk stratification based on cytogenetic studies and mutation status was internationally devised and adopted [46], which was also considered when mapping the CP of the patients for this study. According to this stratification, AML patients are divided into three risk groups: favourable, intermediate and adverse.

Figure 2.1 shows a process flowchart representing the beginning of the CP of any AML patient up to the point when the risk stratification is performed. The depicted steps take a minimum of twenty-four hours and a maximum of one week to perform. After being referred to IPO with suspects of AML diagnosis, the patient is called for a first consultation with a haematology doctor, and several laboratory tests are carried out to confirm the diagnosis and understand which is the patient's risk group. These tests include searching for mutations in a small number of specific genes related with myeloid pathologies. However, this is different from the NGS test that might be performed later, as it only involves a small rapidly analysed number of genes, decisive for an accurate risk assessment.

Figure 2.2 and Figure 2.3 represent the remainder of the CP for patients belonging to the favourable-risk group, and to the intermediate- or adverse-risk groups, respectively (the CP of the intermediate- and adverse-risk groups were represented in the same flowchart because of their similarities).

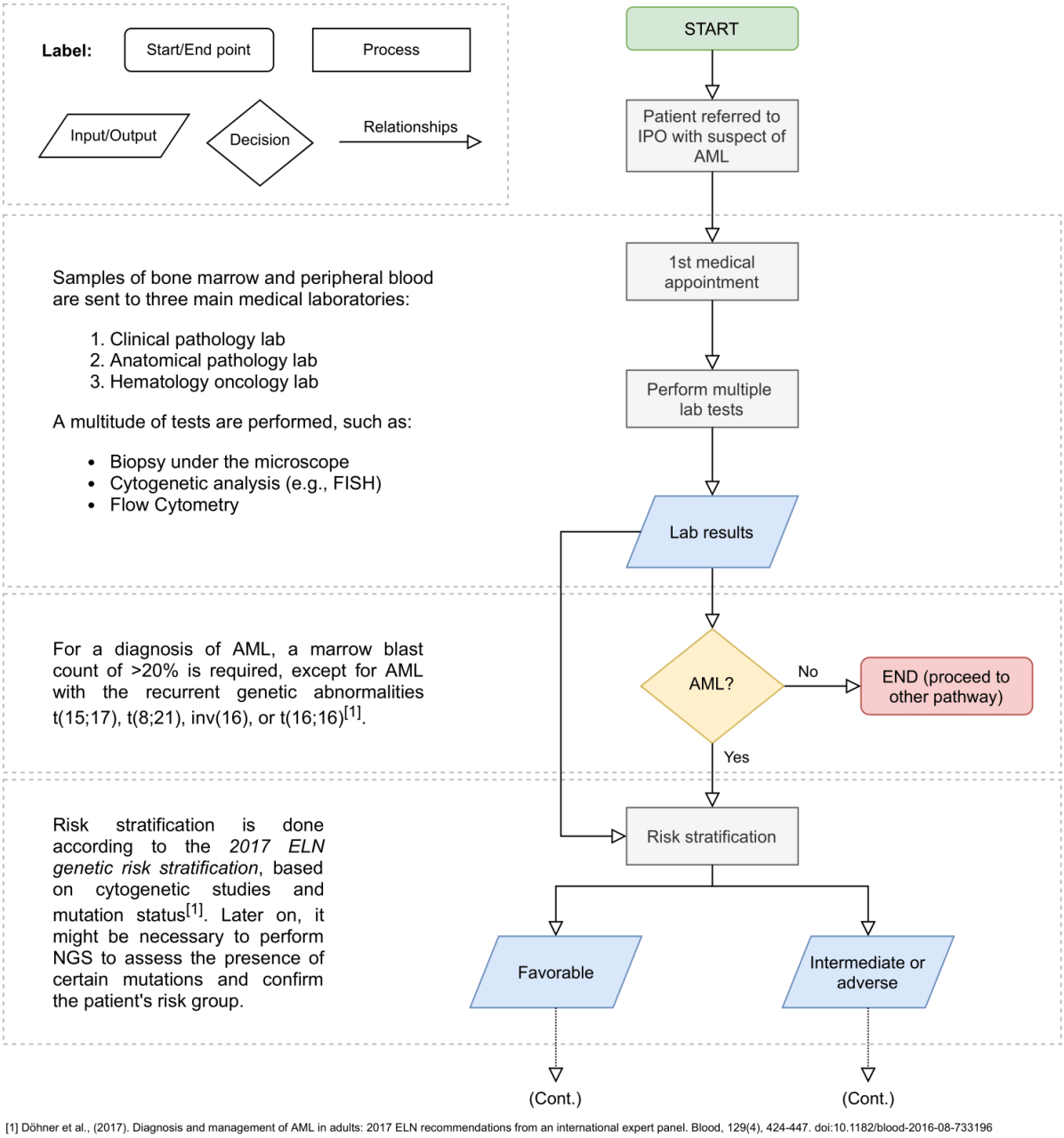
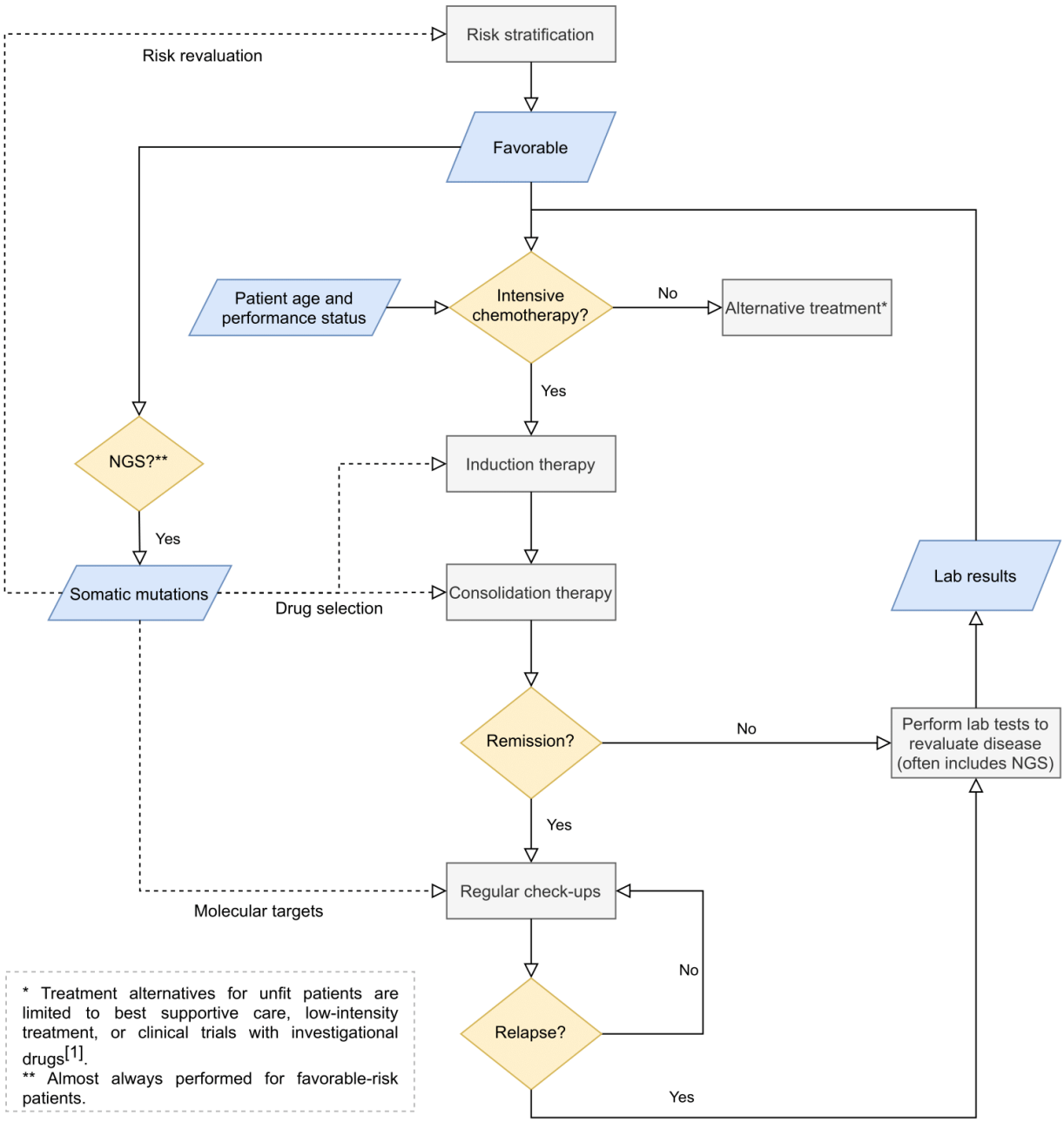


Figure 2.1. Flowchart of the simplified clinical pathway of Acute Myeloid Leukemia (AML) patients at IPO Lisboa, up until risk stratification. The depicted steps are carried out in less than one week.

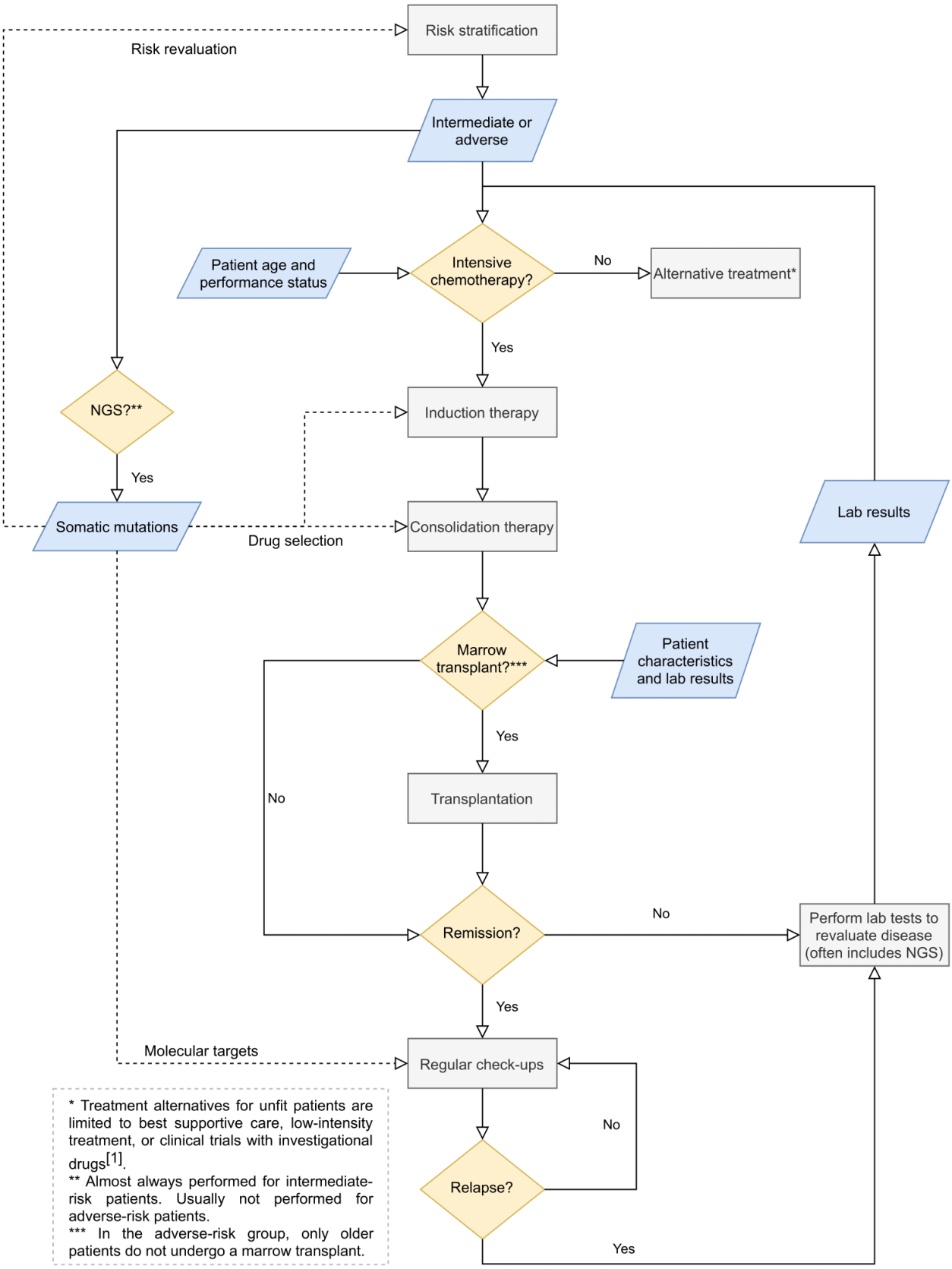
Due to the urgency of this disease, patients start their treatment as soon as possible, usually less than a week after their first consultation. If the patient has a good performance status and is thereby deemed to be fit for intensive chemotherapy, they will undergo one cycle of induction chemotherapy followed by three or four cycles of postremission therapy to guarantee that a state of complete remission is achieved [46]. The daily administration of the drugs is carried out daily for a period of ten days (7+3 regimen), and the patient will normally remain in the hospital for the remainder of the month to recover from the side effects of such an aggressive treatment. Therefore, it can take up to five months for a patient to finish all the induction and postremission cycles. In addition, patients belonging to the

intermediate- or adverse-risk groups (Figure 2.3) might be offered the option to receive a haematopoietic cell transplant, as long as they are deemed fit to undergo this therapy [46]. This is more common for patients belonging to the adverse-risk group for whom, most of the times, a transplant might be their only hope of surviving. On the other hand, if the patient is not deemed fit to go through intensive chemotherapy nor a transplant, alternative treatments are presented such as low-intensity treatment or simply best supportive care. In any case, even if complete remission is achieved, the patient will be carefully monitored for the rest of their life to check for any signs of relapse, in which case a new treatment would be necessary.



[1] Döhner et al., (2017). Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood, 129(4), 424-447. doi:10.1182/blood-2016-08-733196

Figure 2.2. Flowchart of the simplified clinical pathway of Acute Myeloid Leukemia (AML) favourable-risk patients at IPO Lisboa.



[1] Döhner et al., (2017). Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood, 129(4), 424-447. doi:10.1182/blood-2016-08-733196

Figure 2.3. Flowchart of the simplified clinical pathway of Acute Myeloid Leukemia (AML) intermediate- and adverse-risk patients at IPO Lisboa.

At some point during this process, the doctor might consider requesting a NGS test for the patient. Since the results can take from two to four weeks to be delivered, these findings are not used in the initial diagnosis and choice of treatment. Nevertheless, they can be relevant to adjust the patient therapy, to identify relevant molecular targets to monitor throughout the disease or even to find existing clinical trials for which the patient is eligible. Therefore, the results of an NGS test can potentially alter the individual CP of an AML patient, although the benefits of applying a larger gene panel need further assessment.

2.2. Value Modelling

As previously described, a MCDA model was also developed to assess the value of each genomic testing strategy considering a certain number of criteria. After selecting the criteria to include in the model, an online survey was performed to collect the opinions of five IPO professionals regarding the performance levels and the weight of each criterion. These judgements were then used to build a prototype of the value model, using the software M-MACBETH, and were later adjusted and validated by the evaluators during a decision conference, originating the final model.

Being so, this section will start by presenting the answers obtained through the online survey and the prototype model built using those judgements. Afterwards, the adjustments proposed during the decision conference will be described, and the final value model will be presented. Lastly, a sensitivity analysis was performed in order to assess the potential impact of changing the criteria weights on the final results.

2.2.1. Results from the Online Survey

After choosing and describing a set of five relevant criteria with the help of a selected panel of stakeholders from the haematology department of IPO (Figure 2.4), an online survey was sent to several professionals of the institution to collect their opinions on the subject before constructing the value model. The responding participants included two haematology doctors, one laboratory technician, one board member and a research manager.

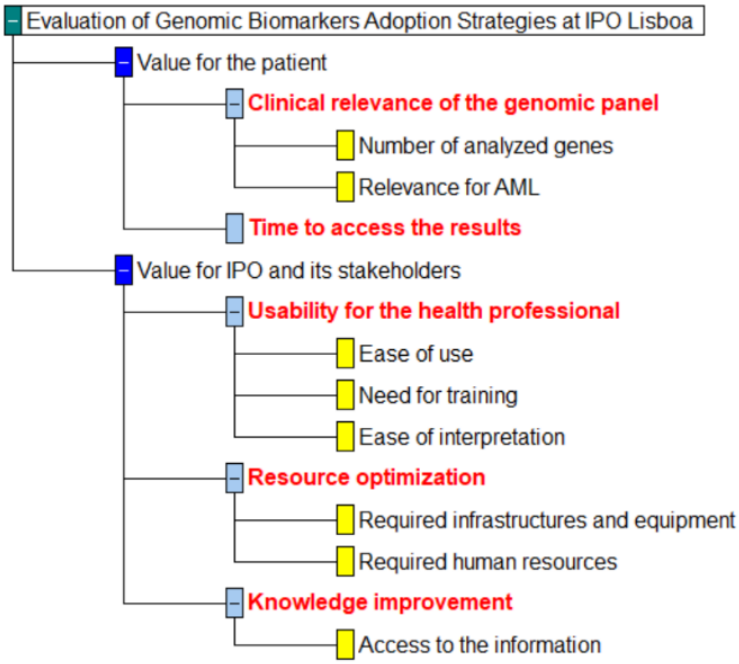


Figure 2.4. Value tree with the selected criteria to evaluate different genomic testing strategies for AML patients in IPO Lisboa, built using the software M-MACBETH.

During the first part of the survey, participants were asked to classify the improvements between different performance levels of the criteria as "null", "very weak or weak", "moderate", "strong or very strong" or "extreme", following the MACBETH approach [72]. Table 2.1 summarizes the collected judgements, highlighting in green the category (or categories, in case of a draw) with the most votes for each question, which was used as input in the judgement matrix. In the case of a draw between non-adjacent categories, the matrix entry was simply defined as "positive".

Table 2.1. Summary of the results of the first part of the online survey, used to build a value scale for each criterion. For each pair of levels of performance, the category/categories with the most votes is/are highlighted in green and were selected as the qualitative judgement to insert in the judgement matrix.

Criteria	Improvements	Judgements					Total of answers
		Null	Very weak or weak	Moderate	Strong or very strong	Extreme	
Clinical relevance of the genomic panel	L3 to L1	0	0	1	3	1	5
	L3 to L2	0	2	3	0	0	5
	L2 to L1	0	2	0	2	1	5
Time to access the results	L3 to L1	0	0	3	1	1	5
	L3 to L2	0	3	1	1	0	5
	L2 to L1	0	1	2	2	0	5
Usability for the health professional	L3 to L1	1	0	0	3	1	5
	L3 to L2	1	0	3	1	0	5
	L2 to L1	1	0	2	2	0	5
Resource optimization	L3 to L1	0	0	2	2	1	5
	L3 to L2	0	1	1	3	0	5
	L2 to L1	0	0	2	3	0	5
Knowledge improvement	L2 to L1	0	0	0	1	4	5

After inputting the obtained data into the judgement matrix of each criterion, the software M-MACBETH generated the corresponding value scale. Figure 2.5 shows the value scales generated by the program, before being adjusted and validated in the decision conference held afterwards.

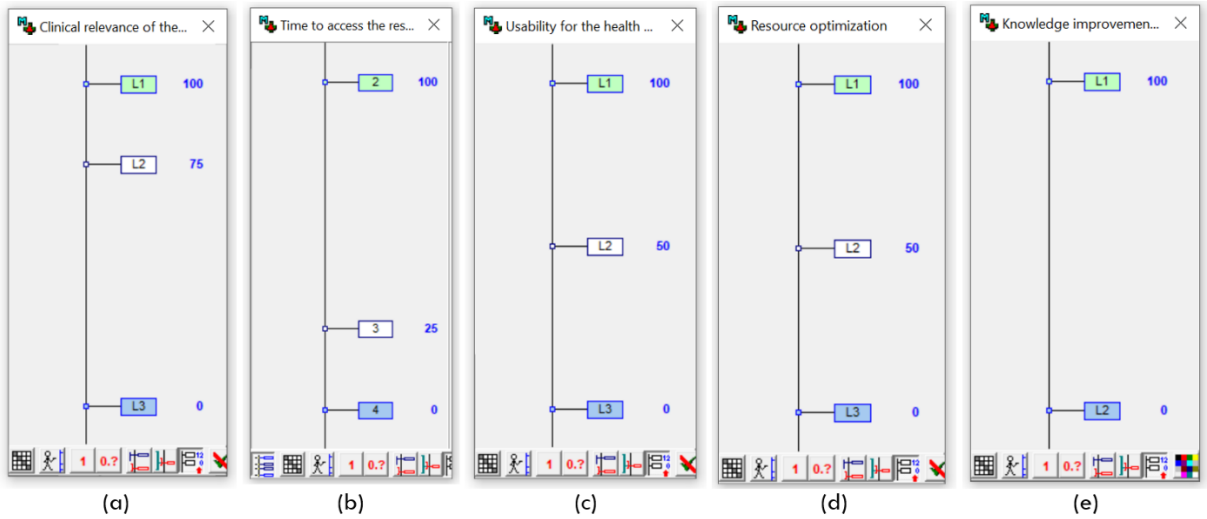


Figure 2.5. Partial value scales for the criteria (a) "Clinical Relevance of the Genomic Panel", (b) "Time to Access the Results" (quantitative scale), (c) "Usability for the Health Professional", (d) "Resource Optimization" and (e) "Knowledge Improvement".

The second part of the survey was aimed at collecting the necessary information to help generate the weight coefficients of each criterion. Thereby, participants were first asked to order the criteria according to the attractiveness of improving a strategy from the lowest to the highest performance level. Afterwards, the Borda voting system [104] was applied to obtain a score for each criterion and assess the most consensual order for the criteria, as shown on Table 2.2.

Table 2.2. Answers to the online survey regarding the ordering of the criteria, and the scoring obtained using the Borda voting system.

	Clinical relevance of the genomic panel	Time to access the results	Usability for the health professional	Resource optimization	Knowledge improvement
Most attractive improvement	2	0	1	0	3
2nd most attractive improvement	0	3	0	1	2
3rd most attractive improvement	2	1	0	2	0
4th most attractive improvement	0	0	3	1	0
5th most attractive improvement	1	1	1	1	0
Borda voting system	12	11	7	8	18
Ordered criteria	2nd	3rd	5th	4th	1st

Finally, participants had to classify this improvement between the reference levels, that is, between the lowest and the highest performance level, as "null", "very weak or weak", "moderate",

"strong or very strong" or "extreme", and their answers were summarized in Table 2.3. By inserting the data in the judgement matrix, the corresponding weights were calculated, as depicted in Figure 2.6.

Table 2.3. Summary of the results of the second part of the online survey, used to obtain the weight coefficient of each criterion. For each criterion, the most voted categories are highlighted in green and were selected as the qualitative judgement to insert into the judgement matrix.

Criteria	Judgements					Total of answers
	Null	Very weak or weak	Moderate	Strong or very strong	Extreme	
Clinical Relevance of the Genomic Panel	0	1	2	2	0	5
Time to Access the Results	0	1	2	1	1	5
Usability for the health professional	0	0	4	1	0	5
Resource optimization	0	2	2	1	0	5
Knowledge Improvement	0	0	0	2	3	5

Figure 2.6. Histogram depicting the weights of the criteria, obtained using the data from the online survey.

In the end, by considering the weight and the partial value scales of every criterion, as well as the performance of each strategy on each criterion, the overall score of each genomic testing strategy was calculated. As is shown in Figure 2.7, strategy 2, which consists in requesting the *FoundationOne Heme* test, has the highest overall score (70,00), while strategy 1, which is the one being currently employed, obtained the lowest score (37,50). However, no conclusions should be drawn before holding a decision conference, in order to execute any necessary adjustments to the model and validate the results, as will be explained in the next section.

Table of scores

Options	Overall	Relevance	Time	Usability	Resources	Knowledge
[all higher]	100.00	100.00	100.00	100.00	100.00	100.00
Strategy 2	70.00	100.00	100.00	100.00	100.00	0.00
Strategy 3	59.00	75.00	25.00	50.00	0.00	100.00
Strategy 1	37.50	0.00	0.00	0.00	50.00	100.00
[all lower]	0.00	0.00	0.00	0.00	0.00	0.00
Weights :		0.2500	0.1900	0.1100	0.1500	0.3000

Figure 2.7. Table of scores of the three genomic testing strategies, obtained with the M-MACBETH software, considering the qualitative judgements collected in the online survey.

2.2.2. Results from the Decision Conference

After building a prototype of the value model considering the opinions of the surveyed IPO professionals, a decision conference was held to adjust the model and validate the results. In this conference participated one medical doctor and a laboratory technician, both from the haematology department of IPO.

Regarding the judgement matrices and the partial value scales of the five criteria, the two participants chose to make only one adjustment, on the partial scale of the criteria “Clinical Relevance of the Genomic Panel”. This consisted in altering the partial score of the second level of performance of that criterion from 75 to 40. Considering the weighting coefficients, the participants preserved the ordering of the criteria derived from the online survey, although they made some adjustments to the weights generated by the software. Both modifications are depicted in Figure 2.8.

Figure 2.8. Adjustments made to the value model during the decision conference: (a) modification of the partial value scale of the criterion “Clinical Relevance of the Genomic Panel” and (b) changes to the criteria weights.

Following these adjustments, new scores were calculated for the three strategies according to the additive model, which are represented in Figure 2.9. On the one hand, the score of strategy 2 increased from 70,00 to 72,00. On the other hand, the scores of strategies 3 and 1 decreased from 59,00 to 49,80 and from 37,50 to 35,00, respectively.

Table of scores

Options	Overall	Relevance	Time	Usability	Resources	Knowledge
[all higher]	100.00	100.00	100.00	100.00	100.00	100.00
Strategy 2	72.00	100.00	100.00	100.00	100.00	0.00
Strategy 3	49.80	40.00	25.00	50.00	0.00	100.00
Strategy 1	35.00	0.00	0.00	0.00	50.00	100.00
[all lower]	0.00	0.00	0.00	0.00	0.00	0.00
Weights :		0.2700	0.1800	0.1300	0.1400	0.2800

Figure 2.9. Table of scores of the three genomic testing strategies, obtained in the M-MACBETH software, after the adjustments made during the decision conference.

In addition, a sensitivity analysis was performed on the weights of the criteria, in order to assess whether changes in them would significantly affect the overall score of each strategy. As can be seen in Figure 2.10, one would need to increase the weight of the “Resource Optimization” criterion by 19,6 percentual points for strategy 1 to surpass strategy 3. However, in the case of the “Knowledge Improvement” criterion, an increase in weight by 13,1 percentual points would be sufficient for strategy 3 to surpass strategy 2 as the criterion with the highest overall score.

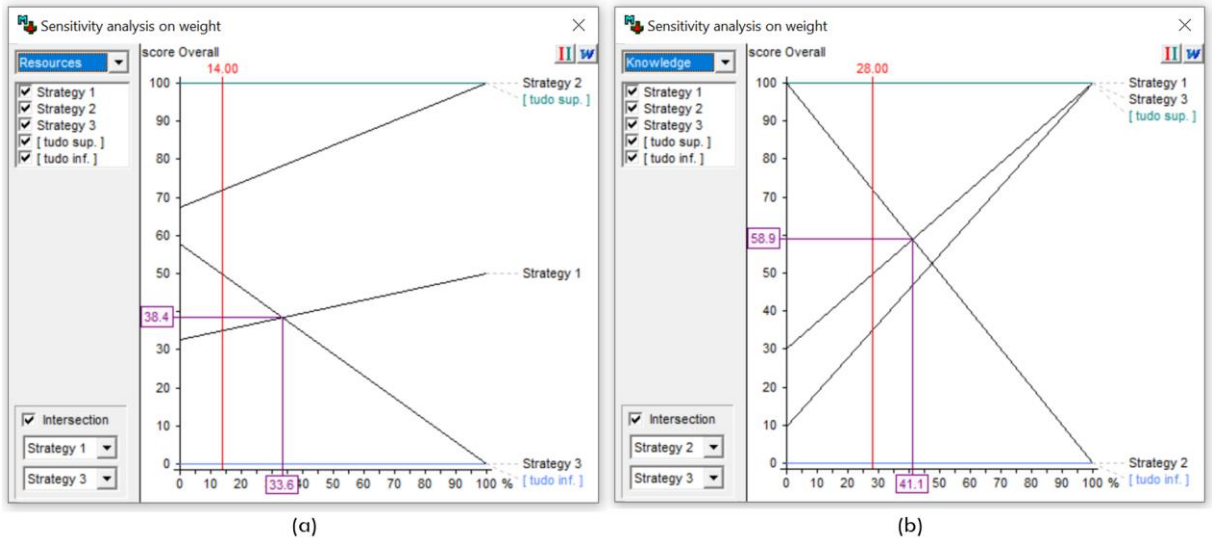


Figure 2.10. Sensitivity analysis on the weight of the criteria (a) "Resource Optimization" and (b) "Knowledge Improvement".

2.3. Cost Modelling

As described in the previous chapter, a Monte Carlo simulation model was built to estimate the potential economic impact of implementing each of the genomic testing strategies, using available data regarding the direct costs deemed relevant for the analysis, and considering the opinion of experts whenever necessary. After performing the simulation, an output distribution was obtained for every strategy, representing different cost scenarios and the probability associated with each of them. These results can be consulted in Figure 2.11, Figure 2.12 and Figure 2.13.

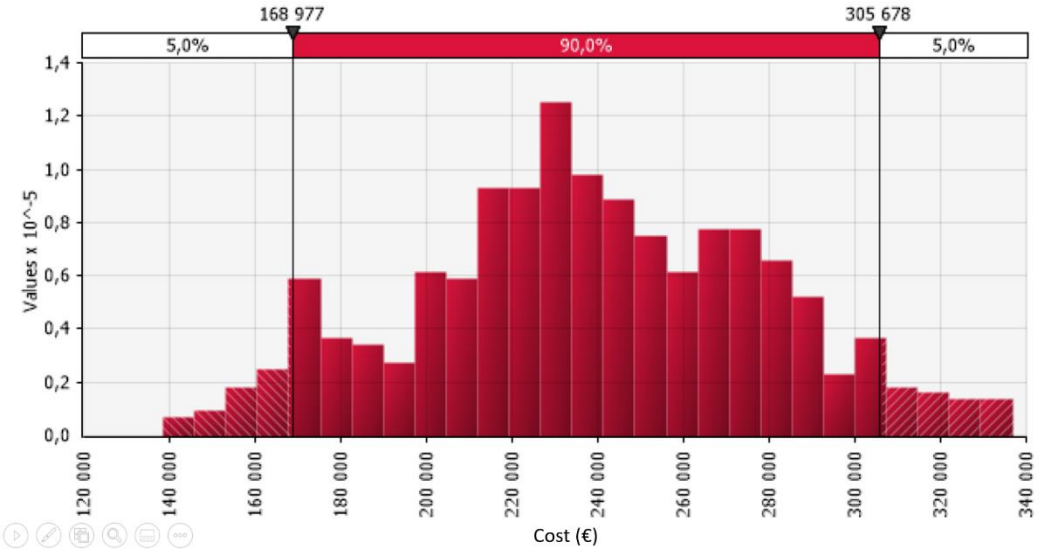


Figure 2.11. Output distribution obtained for the present value of the costs of strategy 1 for the next 5 years, using a Monte Carlo simulation model. The horizontal axis shows the cost, in euros, and the vertical axis shows the probability associated with each possible outcome.

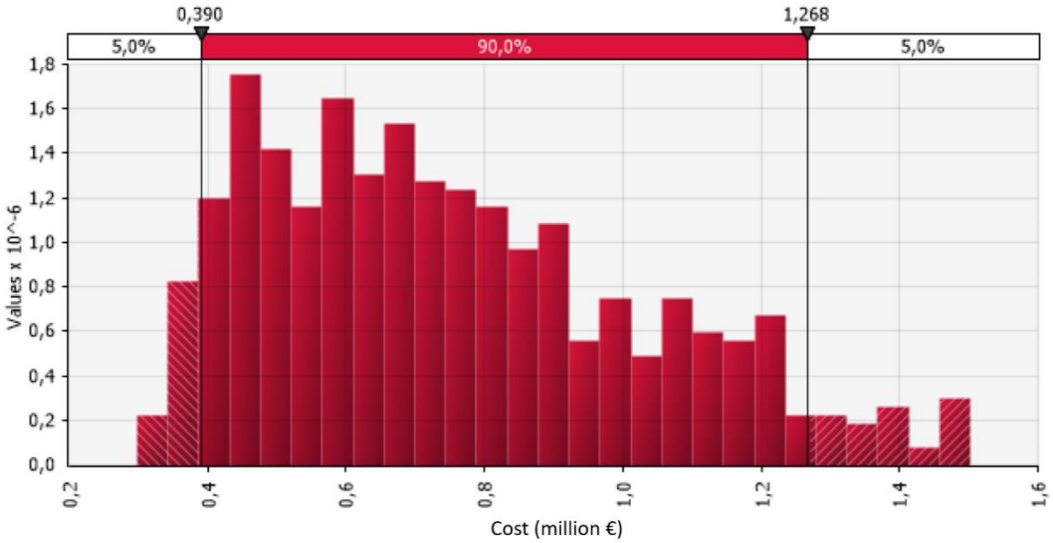


Figure 2.12. Output distribution obtained for the present value of the costs of strategy 2 for the next 5 years, using a Monte Carlo simulation model. The horizontal axis shows the cost, in million euros, and the vertical axis shows the probability associated with each possible outcome.

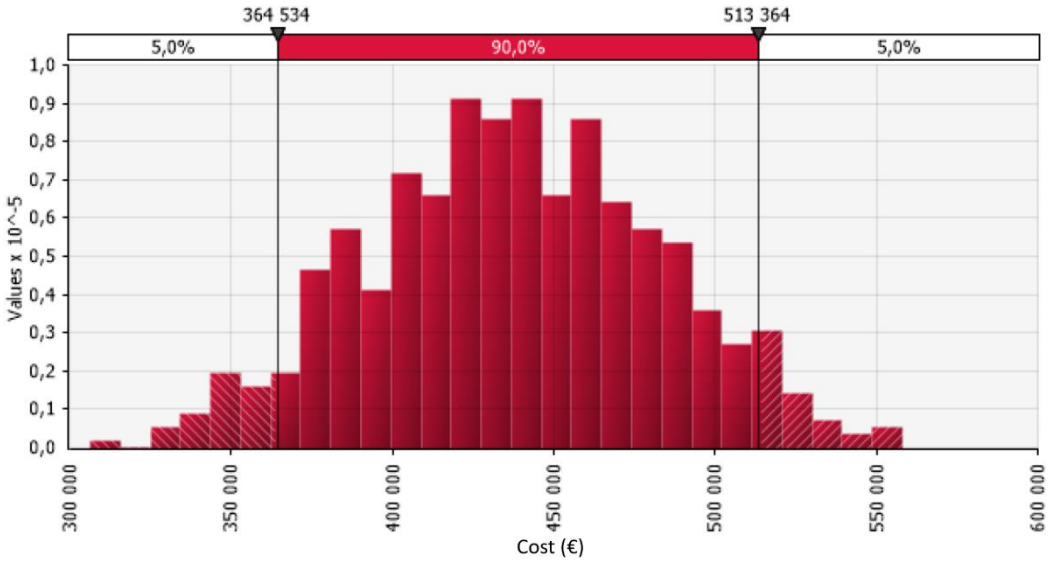


Figure 2.13. Output distribution obtained for the present value of the costs of strategy 3 for the next 5 years, using a Monte Carlo simulation model. The horizontal axis shows the cost, in euros, and the vertical axis shows the probability associated with each possible outcome.

Table 2.4 shows a summary of the most relevant statistics obtained for each strategy. As one can see, strategy 1 has the lowest predicted costs, with a mean value of 237 632,03 €, followed by strategy 3 with a mean of 437 921,60 €. Strategy 2 has the highest mean cost, 754 313,30 €, but also the highest standard deviation, reflecting the uncertainty surrounding the prices of the *FoundationOne Heme* test. Figure 2.14 conjugates the three results in one picture, providing a more visual comparison of these results.

Table 2.4. Mean value, minimum value, maximum value and standard deviation obtained for each genomic testing strategy using a Monte Carlo simulation model.

Output statistics	**Strategy 1** Current panel (TruSight™)	**Strategy 2** FoundationOne® Heme	**Strategy 3** Larger panel than the current one
Mean (€)	237 632,03	754 313,30	437 921,60
Minimum (€)	131 854,40	312 645,07	319 950,80
Maximum (€)	349 527,26	1 709 731,81	557 807,95
Standard Deviation (€)	42 118,52	278 292,80	44 140,32

Finally, a sensitivity analysis was performed to understand the impact of each input variable in the results of the cost model. As shown in Figure 2.15, for strategy 1 the salary of the haematology Superior Technicians is the variable with the highest impact in the output cost distribution, followed by the number of human resources. In the case of strategy 2, however, the variable with the strongest effect on the output mean is the price of each *FoundationOne Heme* test, followed by the expected

number on annual AML reports (Figure 2.16). Lastly, for strategy 3 the salary is once again the variable with the highest potential impact, followed by the estimated invested capital (Figure 2.17). The results of the cost model were validated by a board member of IPO, who also provided some feedback regarding this study, which will be presented in the last section of this chapter.

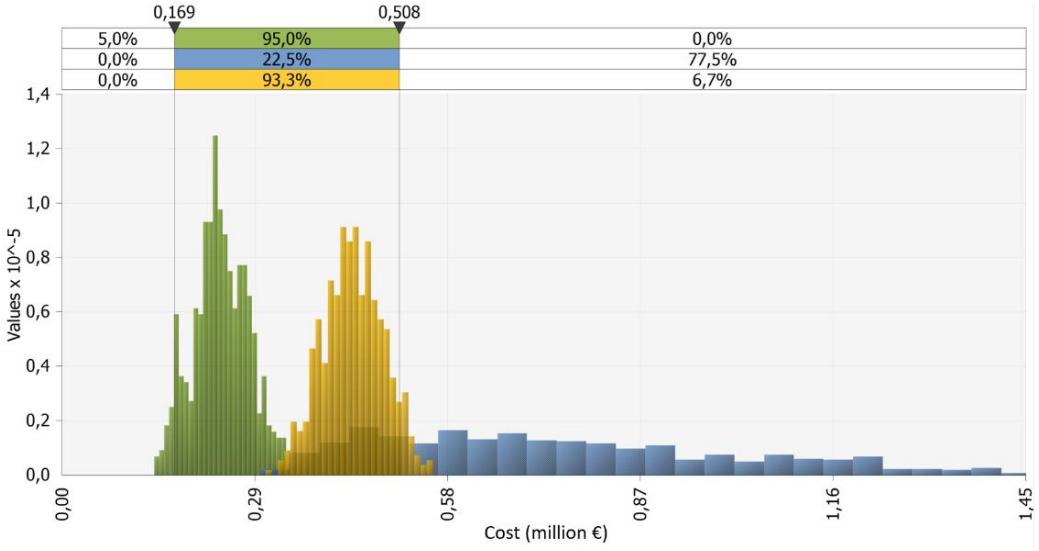


Figure 2.14. Combined output distributions obtained for the costs of the three genomic testing strategies using a Monte Carlo simulation model (strategy 1 in green, strategy 2 in blue and strategy 3 in yellow).

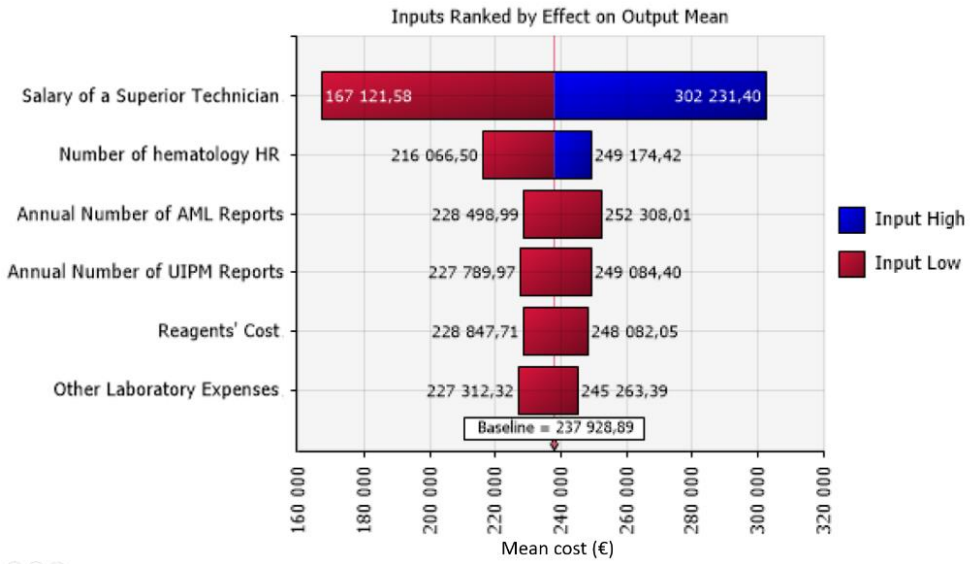


Figure 2.15. Tornado chart showing the findings of the sensitivity analysis performed on the results obtained for strategy 1, using a Monte Carlo simulation model.

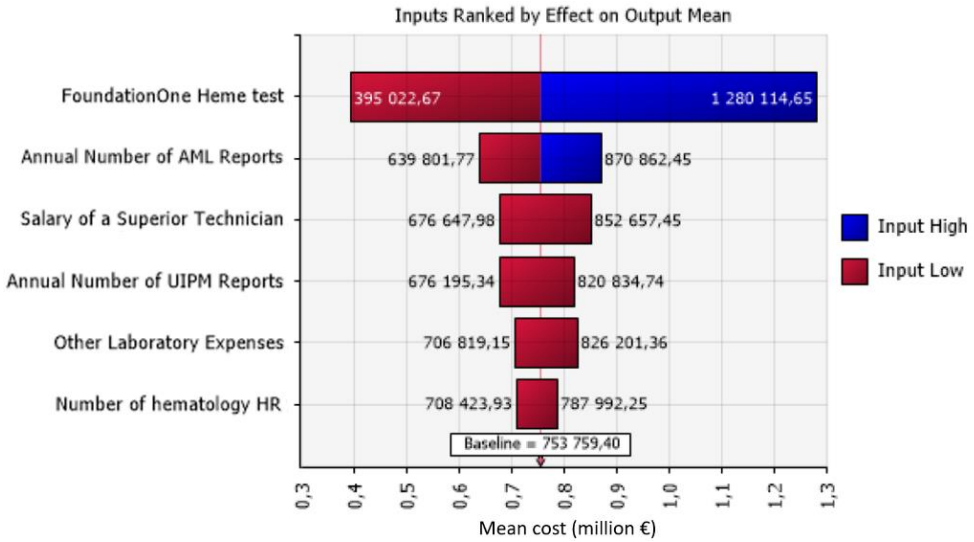


Figure 2.16. Tornado chart showing the findings of the sensitivity analysis performed on the results obtained for strategy 2, using a Monte Carlo simulation model.

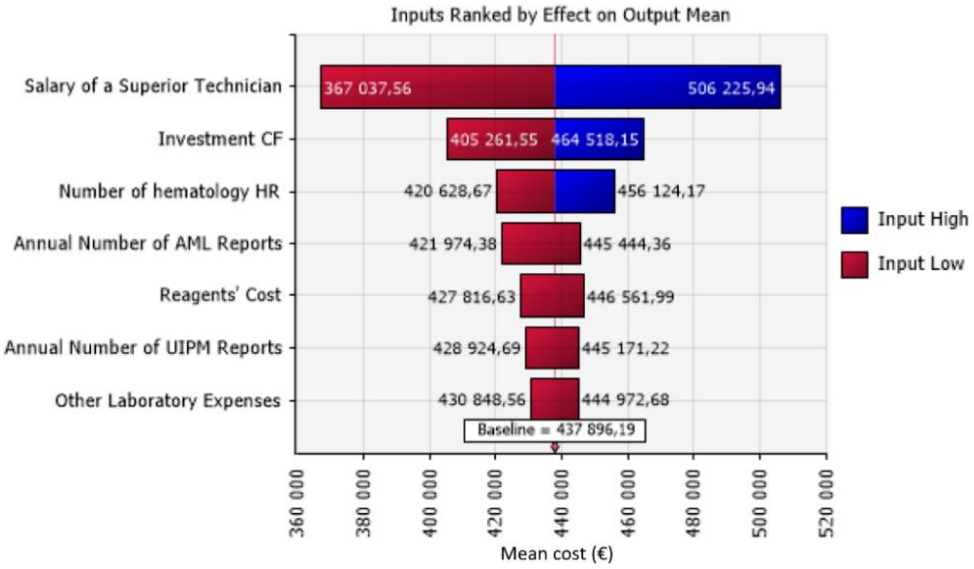


Figure 2.17. Tornado chart showing the findings of the sensitivity analysis performed on the results obtained for strategy 3, using a Monte Carlo simulation model.

2.4. Combination of the Results

Although the separate results of the various steps of the multi-methodology already provide useful information for the DM regarding the genomic testing strategies considered, further and more relevant conclusions may be drawn from their combination. Therefore, results were aggregated in different ways to generate visual and simple representations of the most significant information for the decision-making process.

First, the M-MACBETH software was used to create the XY plot represented in Figure 2.18, which combines the overall score of each strategy, obtained with the MACBETH model, with the mean

cost obtained from the Monte Carlo simulation model. Interestingly, results seem to show a linear distribution, with higher global score (in this case, strategy 2) corresponding to a higher mean cost. Consequently, all strategies are in the efficient frontier, represented in red. Such findings highlight the importance of contemplating both the costs and the benefits of all the alternatives considered in a decision, as including solely one of these dimensions may not provide sufficient information for an accurate judgement.

Afterwards, a strategy landscape graph was generated with similar information to the previous one, adding only the complete output distribution function of the cost model (Figure 2.19). This allows a better visualization of the aforementioned results. Once again, one can see that although strategy 2 was given the highest score in the value model, its cost output function shows a greater standard deviation when compared to the other strategies, caused by the higher level of uncertainty associated with its input variables.

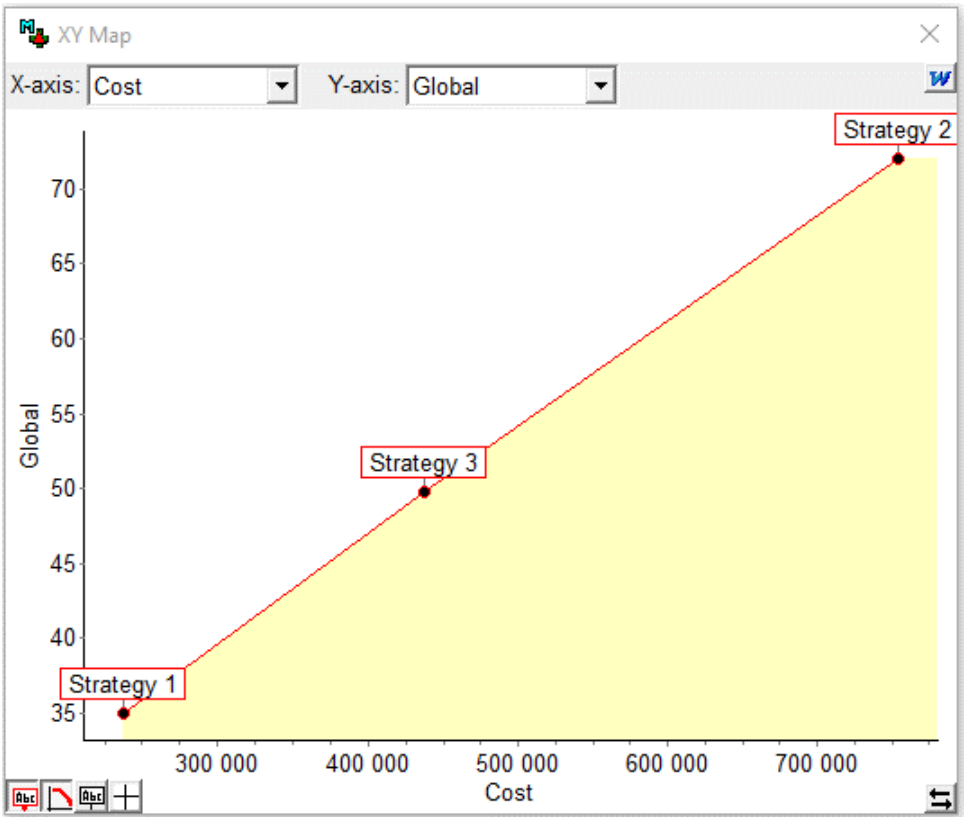


Figure 2.18. XY plot representing the mean cost and the global score of each genomic testing strategy. The red line shows the efficient frontier, and the inefficient area is highlighted in yellow.

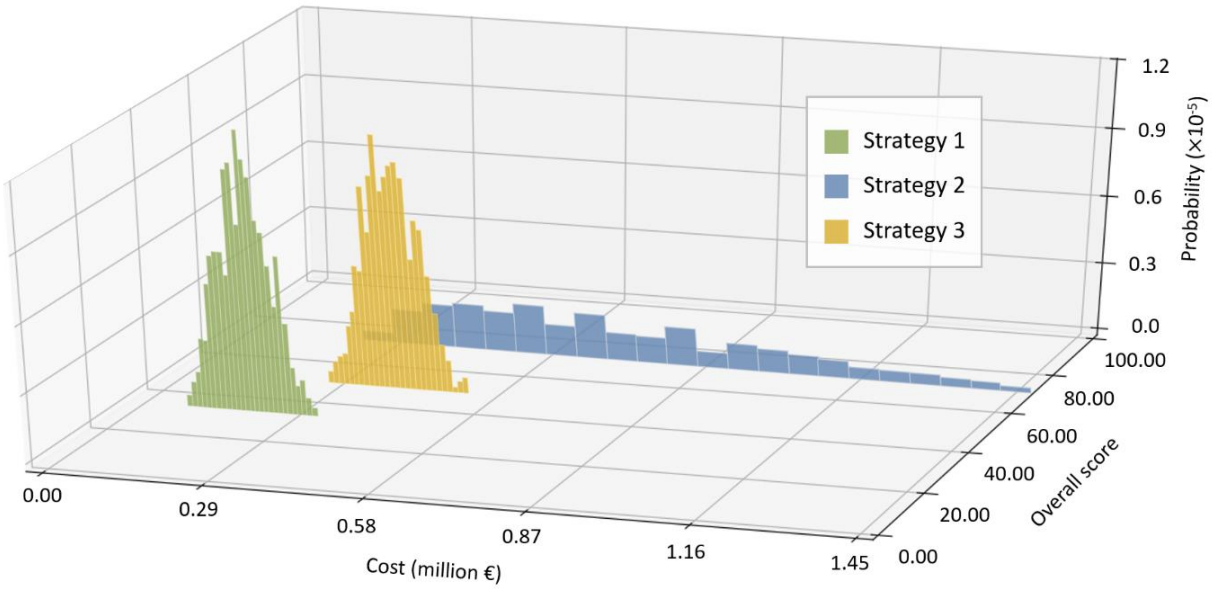


Figure 2.19. Strategy landscape graph depicting the cost distribution of each strategy and the corresponding score in the value model.

Finally, Table 2.5 describes the expected impact in the AML patients' current CP given the implementation of each strategy, according to the interviews with the evaluators. As was explained previously, the implementation of a larger gene panel (strategies 2 and 3) could potentially lead to additional genetic findings and result in an even more personalised treatment and monitorization of a specific patient. However, this would not reflect in any major changes in the general pathways which were mapped for the three different groups of patients.

Table 2.5. Summary of the value score and mean cost of each strategy, and the expected impact its implementation would have on the current CP of AML patients at IPO Lisboa.

Results	**Strategy 1** Current panel (TruSight™)	**Strategy 2** FoundationOne® Heme	**Strategy 3** Larger panel than the current one
Value Model (overall score)	35.00	72.00	49.80
Cost Model (mean cost in €)	237 632,03	754 313,30	437 921,60
Clinical Pathways (predicted impact)	Performing a NGS test allows to: • Confirm the patient's risk group; • Adjust therapy; • Identify molecular targets; • Assess eligibility for clinical trials.	No direct impact on the mapped CP. On a patient level, it is possible it will provide access to a wider range of clinical trials.	No direct impact on the mapped CP. By sequencing new genes, IPO will have more complete databases which can be beneficial in the future.

2.5. Feedback from Participants

In order to better understand the impact and usefulness of this study for the people involved, two feedback sessions were organized with the participants. One of these meetings was held with the group of evaluators, which consisted of a haematology doctor and two laboratory technicians, and the other one with an IPO board member, on behalf of the DM. The posed questions and a summary of the given answers are presented in Table 2.6. Overall, participants claimed the study to be very positive, although they mentioned some points of improvement and suggestions for future work.

Table 2.6. Feedback collected from the group of evaluators and one of the DM, regarding the study conducted to assist IPO in the assessment of different genomic testing strategies.

Question	Topics taken from the answers of the participants
Was this **study relevant** for IPO?	• Yes, the study was relevant, especially considering the everchanging landscape of genetic diseases and constant turnover of genomic technologies.
Was the **objective clear** from the beginning?	• Some aspects of the study were not entirely clear from the beginning, mostly due to some unfamiliar concepts and tools which were used, and the different points of view from which the analysis could be conducted; • The role of the facilitator was crucial in the whole process, working as a bridge between the clinical and the technical fields, and reaching out to different stakeholders.
Was the applied **multi-methodology adequate** for this study?	• Yes, mostly because it was carefully personalised according to the needs of the institution; • Regarding the value model, the online survey was considered to be a very useful and simple method to collect the opinions of several stakeholders. However, more people should have been involved in order to avoid bias and obtain more consensual results; • Regarding the cost model, the Monte Carlo simulation was a valuable tool for encompassing the uncertainty of all variables; • Lastly, it would have been important to hold an initial meeting with all the stakeholders involved in the project, which was not possible due to logistical constraints.
Were the **results relevant** for IPO?	• Yes, the obtained results provide a good foundation for IPO to better assess and discuss different genomic testing strategies available in the market.
What could be done as **future work**?	• Involving more stakeholders in the study will better reflect the different perspectives which can be considered in the decision-making process; • Finally, it would also be interesting to apply a similar method for other pathologies within IPO.

3. Discussion

Precision medicine is becoming an indispensable approach for the prevention and treatment of many diseases including cancer, as it brings significant survival benefits for the patients and thrives efficiency in healthcare institutions worldwide [2, 30]. This transition to more personalised methods was only possible due to numerous developments in the field of genomic technologies, which were fuelled by ventures such as the Human Genome Project [25]. However, the increase in the number and quality of these genomic technologies is accompanied by many challenges. From the complex process of interpreting genomic data according to the latest scientific findings, to all the ethical, legal and social implications which surface from unravelling one's genetic code, precision medicine will eventually affect all healthcare stakeholders in many different ways, both at an individual and a community level [32]. Thereby, it is essential to develop harmonised methods and tools to assess the impact and value of these technologies for the hospitals and the patients.

Although a standardised solution has not yet been achieved, mostly due to the heterogeneity related with this field, many authors have already embraced this challenge by attempting to understand common practises within published genomic HTA reports or even suggesting guidelines to help improve the evaluation process [33-35, 88]. On the other hand, considering the intricacy of the genomic testing field, and the different contexts and perspectives encountered when deciding between different genomic technologies, conducting a personalised HTA at the hospital level can result in more accurate and relevant recommendations for the DM, and be more beneficial for all the involved stakeholders [5].

With that in mind, it was agreed the best approach to help IPO Lisboa assess different genomic testing strategies would be by employing a multi-methodology which would encompass not only the categorization of the alternatives in terms of value and cost, but also the potential impact they could have on the AML patients' clinical pathways. As an institution which primarily focuses on the patients' wellbeing, IPO Lisboa has always aimed to be in the forefront of cancer treatment by adopting the best practices and techniques available [7]. Being so, the results obtained from this study offer a good foundation for the assessment and eventual decision between different genomic testing strategies for patients diagnosed with AML, a pathology which requires a fast and accurate response from the healthcare providers.

Overall, all stakeholders involved in the study provided positive feedback regarding the employed methodology and the subsequent results, but there are also a number of limitations that should be acknowledged. Therefore, this chapter will start by discussing the results obtained throughout the various steps of this work, followed by the advantages of the chosen multi-methodology. Finally, some limitations of the study are presented, along with a few suggestions for future work.

3.1. Discussion of the Results

The proposed multi-methodology had three main points of focus: mapping the clinical pathways of AML patients, building a value model using the MACBETH approach to evaluate each genomic testing strategy according to several criteria, and estimating the cost of each strategy with a Monte Carlo simulation model. Nevertheless, one should not overlook the very first step of the employed multi-

methodology, which sets the bases on which the remaining work was built: the problem identification. Spanned across several meetings, this process comprised the discussion and selection of the alternatives which would be included in the study, and the selection of a group of stakeholders to accompany the numerous steps of the work. By aligning the expectations of the DM with the ideas and availability of other relevant participants, a fitting socio-technical approach was developed to better conduct the intended multi-methodology.

Regarding the choice of the genomic testing alternatives to include in the study, it is important to highlight how various strategic viewpoints were incorporated even though only three strategies were selected. First of all, strategies 1 and 3 refer to in-house procedures, in which IPO Lisboa is completely responsible for collecting, processing, analysing and interpreting each patient's genomic data. Although this consumes more resources and time, the process can be carefully monitored, and all data can be stored and further used for research purposes. On the other hand, strategy 2 consists in purchasing an external service, which can deliver the intended results while consuming less resources and without compromising the quality of the analysis. However, only the final results of the test would be available to IPO, hindering any further analysis (either confirmatory or investigational) from their part. Another topic which was discussed when selecting the alternatives was the number of genes tested in each strategy, due to the progressive spread of NGS techniques and concomitant drop in prices [3]. While the currently employed genomic strategy tests a panel of 54 DNA genes, both strategies 2 and 3 consider a larger number of genomic biomarkers. Even though the currently tested genes already comprise the most common mutations in the AML pathology, studying a larger number of genes might not only benefit future research at IPO Lisboa (in the specific case of strategy 3), but also potentially help finding better treatment alternatives, as long as new studies and clinical trials continue to be developed in this area. This is particularly relevant for AML, a cancer type for which guidelines have recently been updated in light of such new discoveries [47]. Additionally, one must consider how each of the selected strategies might economically impact the institution, as none of them can succeed without a proper investment from IPO Lisboa.

Finally, one must acknowledge how the uncertainty surrounding the definition of strategy 3 might have affected the results. Although every strategy and every step of the methodology has a certain level of uncertainty associated with it (caused, for instance, by subjectivity or imprecise data), the vague definition of strategy 3 gives rise to potentially different results depending on how one interprets it in each step of the valuation. For example, since the number of genes evaluated with this genomic testing strategy was not specified, when filling the judgement matrix on M-MACBETH different stakeholders might position this strategy in many different ways when comparing it with the other two. Nevertheless, and as stated in the methodology chapter (Chapter 4), this concern was properly discussed with the evaluators, who decided it was best to keep the broad definition of strategy 3 as it allows for a larger range of options to be encompassed in the analysis, as long as they correspond to a larger and more personalised gene panel than the currently employed.

Before discussing the results from the core steps of the methodology, some attention should be given to the stakeholders which were involved from the beginning to the end of the study. There are two

main groups of people which were engaged throughout the whole process: the DM and the evaluators. The DM are the members of IPO Lisboa Board of Administration, who are ultimately responsible for making any strategic decision which impacts the future of the hospital and its patients. However, in order to collect relevant knowledge to perform an adequate HTA, one should always consult with those which are more closely related with the problem at hands. Thereby, three members of the haematology department, denominated as “evaluators”, agreed to help on this study, especially in the construction of the value model, which led to an overall more agile and accurate process. Even though the DM were not directly involved in all steps of the study, one of the board members helped more closely in the construction of the Monte Carlo simulation model, and promptly validated the results upon the completion of the study.

After defining the strategies that most interested the DM and describing them with the help of the evaluators, it was important to better understand the clinical pathways of AML patients and how NGS tests impact their care. As stated in the literature, CP are structured multidisciplinary plans of care which help hospitals reduce variation in the treatment of their patients, while improving the quality of care and maximizing the outcomes for specific groups of patients [84]. Therefore, it is important to assess how changes in the techniques or tools employed may affect the hospital’s current CP. For this purpose, patients were divided into three groups according to their risk stratification [42] and a flowchart was created for each group, representing the series of steps that occur from the moment they are referenced to IPO Lisboa. First of all, from the results one can understand the intricacy of the whole process, and urgency and speed needed in many of the steps, which would be expected considering the nature of the disease. Some critical points should be highlighted due to their importance and impact on the remaining pathway, such as cancer diagnosis, the risk stratification, the choice between undergoing chemotherapy or an alternative treatment, and deciding if receiving a bone marrow transplant is the better plan for the patient. Regarding the diagnosis of AML, this should be done in the days upon the arrival of the patient and may include undergoing some important genomic tests, which should not be mistaken with the later performed NGS test.

NGS tests are usually performed at a later stage of the process, after the patient has already initiated the treatment, and results can take up to four weeks. As depicted in all flowcharts, these genomic tests might provide important insight to confirm the patients risk group, revaluate the selected treatment, identify molecular targets to monitor the disease or even assess the patient’s eligibility to existing clinical trials. Thereby, NGS tests are usually performed for all patients belonging to the favourable- and intermediate-risk groups. However, regardless of the impact a NGS test can have on the patient care, changing between different testing strategies would not directly impact the mapped clinical pathways, as the results would be used for the same purpose. Hence the conclusion that the implementation of strategies 2 or 3 would not result in any visible change in the current CP. Strategy 3 could, in any case, benefit the research conducted at IPO Lisboa since it allows to study a larger number of genomic biomarkers, which might be relevant for the future of the institution and ultimately translate into treatment of the patients. To summarise, mapping the CP of AML patients in the beginning of this study was a crucial step to better understand the context of the disease and the role of NGS in the care

process, and should be seen as an important tool in any healthcare decision-making process, as stated in the literature [89].

Afterwards, the elected strategies were compared by means of a multicriteria value model, built with the MACBETH approach, and a cost model, constructed using a Monte Carlo simulation. The value model was a live example of the advantages of using MCDA, referred in the literature review (Chapter 3), namely for allowing to assess several alternatives against multiple criteria, and to model subjective views from different stakeholders [114]. Although MCDA has been increasingly used in the healthcare context [74-79], there is no standardised choice of criteria or alternatives to be included in a model, as these depend on the specific context of the decision. In this case, five criteria where carefully chosen and refined by the group of evaluators involved in the study, which had a deep knowledge regarding the intricacies of the disease, the complexities surrounding the related NGS tests and the functioning and priorities of the institution. Nevertheless, some difficulties were met when structuring the model, namely avoiding redundancies or bias associated with the chosen criteria and the accompanying descriptors of performance.

Furthermore, using an online survey to collect the views of other stakeholders was a very positive aspect of the process, as it gave the evaluators some opinions to rely on when building the model in the later decision conference. However, the fact that only a small group of people answered the survey is a limitation since their answers might not accurately reflect the relative importance of each aspect for the institution. For instance, a physician might emphasize the number of genes evaluated with a certain NGS panel, while a laboratory technician could prioritize knowledge improvement or the ease of using the test.

Looking at the results, it is clear that strategy 2 obtained the highest score, mostly because it performed well in almost every criterion, as depicted on Table 4.3. With a somewhat more modest score, strategy 3 also stands out not only for its clinical relevance but also for increasing knowledge retention at the institution. Lastly, although strategy 1 shares some of the advantages of the other two strategies, it became last in the scoreboard. This outcome echoes the recent tendency in the healthcare community of investing in larger gene panels, parallel to the increased knowledge regarding human genetics, with some going as far as studying the possibility of implementing WGS as the standard diagnostic test in oncology [6, 53]. If we were to focus merely on the results from the value model, one might recommend IPO Lisboa to drop their current genomic testing strategy and instead purchase the services of Foundation Medicine. However, another important evaluation should be conducted to better understand the implications of every alternative course of action: the study of the economic impact caused by each strategy, using cost estimation techniques [14].

Although there are some published studies in the field of cost estimation of sequencing tests [105, 115], the difficulty of assessing the long term impact of genomic findings is a recurrently referred challenge. In this case, only the short-term direct costs of each strategy were considered, and a sensitivity analysis was conducted to address possible sources of uncertainty related with the collected data. The results from the Monte Carlo simulation model reveal the opposite trend of the value model, with strategy 1 being the less costly for IPO Lisboa, and strategy 2 the costliest in terms of mean value.

However, the high level of uncertainty surrounding the price of the *FoundationOne Heme* test, reflected in the corresponding triangular input function, causes strategy 2 to be the one with the higher standard deviation, as can be seen on the output graph represented in Figure 2.14. This means the price of this test will greatly influence the mean cost this strategy has for the institution, as further evidenced by the sensitivity analysis, which shows the decrease in the price of *FoundationOne Heme* could lower the mean cost of strategy 2 up to 395 023 €, lower than strategy 3 current mean cost. On the other hand, the sensitivity analysis performed on strategies 1 and 3 show the variable with the highest impact in the output is the salary of the laboratory technicians who perform the NGS tests. Considering that these values will most likely remain constant in the following years, one could claim the estimated costs of these strategies to be fairly solid. Nevertheless, the mean cost of strategy 3 will also vary according to the capital needed to invest in the purchase of new material, which was broadly estimated due to the higher level of uncertainty surrounding this strategy, as previously stated.

Combined, the results of the two models reveal a linear trend between the overall value of a strategy and its mean cost. Such outcome reinforces the need for carefully assessing the costs and the benefits of every course of action when making an important strategic decision, framed by the specific context of the institution and those who have a role to play in it. Furthermore, one should also consider the direct and indirect impact each choice can have on the patients' CP. In this case, no major changes would be triggered in the CP mapped for each risk group, but we also found that applying a different strategy might potentially impact the outcome of a patient at an individual level. Therefore, all findings must be wisely measured and critically reviewed by the DM, to avoid being blindly used in the decision-making process [14].

3.2. Advantages of the Multi-methodology

Every step of the implemented multi-methodology, thoroughly described in Chapter 4, was carefully designed and planned to contribute to the goal of this thesis in a fluid and logical manner. By deciding to tackle the decision problem from three different angles, incorporating a cost model with a value model and the mapping of the AML patients' CP, one could better identify the strengths and the limitations of each of the strategies considered. Not surprisingly, this also added an additional layer of complexity to the analysis, but such obstacle is preferred to a lack of depth which would derive from using a simpler unidimensional methodology. Furthermore, the employed socio-technical approach, in which every phase of the work had an assigned technical component and some form of social interaction with the people involved, brought richness and solidity to the analysis.

In terms of the multicriteria value model, the use of the MACBETH approach had the advantage of requiring only qualitative judgements on the part of the stakeholders in order to build the model, which is easier and more intuitive. On the other hand, using a Monte Carlo simulation to estimate the costs of the different strategies also brought many benefits, mostly because it helped incorporate uncertainty derived from the existing and non-existing data. Finally, evaluating these results taking into account the

current AML CP allowed a broader view of the implications each decision can have in the care of the patients.

In sum, considering the complexity and increasing importance of precision medicine and concomitant technologies in the care of cancer patients, the employed multi-methodology and the obtained results show it is possible to develop a personalised evaluation method for the implementation of different genomic technologies without neglecting the specific needs and views of the institution. In addition, the applied approach can be considered a contribution to the literature as, to the author's knowledge, this is the first time CP mapping, a MCDA model, and a Monte Carlo simulation model where combined to assess the value of different genomic testing techniques for a healthcare institution, especially considering the current lack of standardised frameworks to evaluate genomic technologies, as was highlighted in the literature review.

3.3. Limitations and Future Work

Being intertwined with different sources of complexity, uncertainty, and subjectivity, the work developed has a certain number of limitations which should be acknowledged to promote a critical analysis of the results and to inspire better practices in the future.

First of all, AML is fortunately not as common as other types of cancer [43], but this implies that data on this disease can be sparse, which is further aggravated by its genetic complexity. Although the use of NGS techniques and other technologies has been helping unravel the mysteries of this condition [37], it also gives rise to some controversial opinions on which new genomic findings are truly relevant for the treatment of the patients. This can reflect, for example, on the relative importance a healthcare stakeholder gives to the use of larger gene panels, since the connection between some of the included genes and their repercussions on the development of the disease have not yet been totally confirmed. Other evident sources of uncertainty in this study were the somehow broad definition of strategy 3, the intrinsic subjectivity of the value model and the assumptions made when building the cost model.

Another limitation which should be addressed is that the value model was built specifically for this particular decision context, with value scales directly reflecting the characteristics of the three genomic testing strategies considered, although it can be adapted to other circumstances. Furthermore, only a small number of people participated in the online survey, consequence of the reduced number of IPO professionals which are familiar with the AML pathology and their availability. Regarding the Monte Carlo simulation model, varied assumptions were established from the beginning to simplify the collection and treatment of the available data. Some of these, for instance imposing a time horizon of only five years or considering only the direct costs of the strategies, should not be overlooked when assembling recommendations for the DM [116].

Even though the developed work was seen by the IPO DM as a good starting point for the decision at hands, some future work should be done not only to improve the methods applied but also to extend them to other areas. Suggested improvements to the methodology are: further specifying

strategy 3 by searching for specific products available in the market and consulting experts in the area, involving a greater number of stakeholders when assessing the value of each alternative, and conducting a more detailed cost analysis with a longer time horizon. Moreover, it would be interesting to try to adjust and replicate the developed multi-methodology for other pathologies at IPO Lisboa, as feedback from the participants confirmed it was a relevant and useful approach for the decision-making process.

4. Conclusion

Considering the rapid spread and adoption of precision medicine, particularly in the oncology field, there is a need to develop appropriate tools and methods to properly evaluate emerging genomic technologies. This thesis aimed at helping the decision-makers of IPO Lisboa, a renowned cancer research centre and hospital, to assess the value and costs of adopting different next generation sequencing (NGS) tests for the care of acute myeloid leukemia (AML) patients. Therefore, a multi-methodology was implemented, with social and technical components, which involved studying the clinical pathways of different groups of patients, building a multicriteria value model to measure the value of each strategy for different stakeholders and estimating the monetary cost of each alternative for the institution.

The currently used NGS test, which consists of a panel with 54 DNA genes frequently mutated in AML, obtained the lowest score in the value model, but was also estimated to have the lowest mean cost for IPO Lisboa. On the other hand, the second strategy to be considered, in which the patients' samples are sent to an external laboratory to be tested using a larger gene panel, obtained the highest score in the value model, as well as the highest mean cost for IPO Lisboa. Finally, strategy 3, in which IPO Lisboa would acquire new equipment to implement a larger gene panel in-house, was in between the other two strategies both in the value model and the cost model. In addition, mapping the CP of patients belonging to different risk groups allowed to better understand the decision context and to conclude that neither of the considered strategies would have a direct impact in the patients care.

Overall, the developed multi-methodology provided IPO Lisboa with comprehensive and insightful information regarding the costs and benefits of the three genomic testing strategies considered in the analysis and elicited positive feedback from all stakeholders. Even though it was focused on a specific type of cancer, AML, this multi-methodology shows potential to be adjusted and replicated for other pathologies and in different settings. Furthermore, it combines several methods in a novel way, contributing to hospital-based HTA and to genomic biomarkers' literature. Despite some limitations, this work demonstrates the advantages of applying a multi-methodology to tackle more complex problems in the healthcare context, without failing to incorporate possible sources of uncertainty and the opinions of the involved stakeholders. More studies should be developed in this area to help DM assess the multitude of healthcare technologies available nowadays, since this will ultimately impact the wellbeing of many patients all over the world.

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Appendix A – Data and Calculations for the Cost Model

Table A.1. UIPM accounting data regarding the reagents and other laboratory expenses from years 2018 to 2020.

Costs (UIPM)	2018	2019	2020	**Mean**	**Stand. Dev.**
Reagents	600 075,02 €	554 157,98 €	612 109,16 €	588 780,72 €	24 970,06 €
Other lab expenses	24 017,79 €	21 227,85 €	15 220,01 €	20 155,22 €	3 670,89 €

Table A.2. Annual costs of reagents, other laboratory expenses and salary for 5 years, based on the average of the costs from years 2018 to 2020 and the government issued salary tables for 2021 [109]. For the reagents and other laboratory expenses, minimum and maximum values were estimated by subtracting and adding the standard deviation to the mean costs, respectively. The present value formula was applied, and a discount rate of 4% was considered [106].

	Groups of costs	**Years**					**Present Value**
		1	2	3	4	5	
Expected Value	Reagents	588 780,72 €	588 780,72 €	588 780,72 €	588 780,72 €	588 780,72 €	2 621 147,16 €
	Other lab expenses	20 155,22 €	20 155,22 €	20 155,22 €	20 155,22 €	20 155,22 €	89 727,44 €
	Salary/Superior Technician	38 773,52 €	38 773,52 €	38 773,52 €	38 773,52 €	38 773,52 €	172 612,84 €
Minimum Value	Reagents	563 810,66 €	563 810,66 €	563 810,66 €	563 810,66 €	563 810,66 €	2 509 984,89 €
	Other lab expenses	16 484,33 €	16 484,33 €	16 484,33 €	16 484,33 €	16 484,33 €	73 385,30 €
	Salary/Superior Technician	17 299,01 €	17 299,01 €	17 299,01 €	17 299,01 €	17 299,01 €	77 012,13 €
Maximum Value	Reagents	613 750,78 €	613 750,78 €	613 750,78 €	613 750,78 €	613 750,78 €	2 732 309,42 €
	Other lab expenses	23 826,11 €	23 826,11 €	23 826,11 €	23 826,11 €	23 826,11 €	106 069,59 €
	Salary/Superior Technician	58 458,53 €	58 458,53 €	58 458,53 €	58 458,53 €	58 458,53 €	260 247,01 €