Developing tools to evaluate genomic testing strategies at IPO Lisboa: A multi-methodological approach

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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.

Introduction

During the last decades, the paradigm of cancer treatment has been shifting from a "one size fits all" approach to the application of personalised methods focused on the genetic, physiological and even social characteristics of the patient and his disease [1]. The increasing popularity and usage of precision medicine was mostly propelled by the recent development and dissemination of genomic technologies such as next generation sequencing (NGS) techniques, which allow for massively parallel gene sequencing [2]. Such methods are particularly relevant for oncological diseases, as despite there being 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 [3]. Therefore, NGS techniques emerge as a powerful tool for the prevention, diagnosis, treatment and monitorization of cancer.

On the other hand, the growing offer of different genomic tests creates the need for hospitals to revaluate the currently applied technologies and compare them with the available alternatives in the market. This might prove challenging, as the health technology assessment (HTA) of genomic biomarkers and technologies is a relatively recent field, with concomitant challenges and significant gaps in the literature [4-6]. Even though there is not a standardised framework for the hospital-based HTA [7] of emerging genomic technologies, the use of suitable decision analysis methods and the involvement of several stakeholders in the process can contribute to a more thorough and relevant assessment of alternative genomic testing strategies [8, 9].

For instance, the use of multicriteria decision analysis (MCDA) has already proved to be successful in many scenarios, as it allows to consider multiple criteria when comparing several options, increasing the transparency, efficiency, and objectivity in healthcare decision-making [10]. Furthermore, simulation techniques and artificial intelligence (AI) are also powerful tools to overcome the multiple sources of uncertainty present in the healthcare context [11, 12].

This paper presents a multi-methodology [13] developed to assist the decision-makers (DM) of Instituto Português de Oncologia de Lisboa Francisco Gentil (IPO Lisboa) in the evaluation of different genomic testing strategies for patients suffering from acute myeloid leukemia (AML). After undergoing a series of interviews to understand the decision context and the needs of the hospital, a socio-technical approach [14] was implemented to guide the process and guarantee the use of appropriate techniques and the involvement of all relevant stakeholders. Besides mapping the clinical pathways of AML patients, the MACBETH approach for value measurement was applied to build a multicriteria model to comprehensively assess the value of each strategy considering the opinion of several health professionals, and a Monte Carlo simulation model was implemented to estimate the associated costs. These modelling components generated information to be combined into a three-dimensional graph ("strategy landscape" graph) to

inform the added value and added cost of the strategies. In sum, the proposed multi-methodology combines several methods in a novel way, contributing to hospital-based HTA and to genomic biomarker's literature.

Methods

The developed multi-methodology [13], which is socio-technical by nature [14] and combines several modelling techniques within a common frame, was divided in three main steps, as illustrated in Figure 1. The first step was focused on understanding the decision context, the second step included the development of methods to inform the evaluation of genomic testing strategies considered in the analysis, and the last step was aimed at combining the results in a way that generated solid and relevant recommendations for the DM.

Step 1. Problem Identification

With the purpose of better understanding the problem at hands and the needs of the institution, five meetings were held over the course of one month involving six stakeholders from IPO Lisboa, including a board member, physicians and laboratory technicians. 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.

Therefore, three genomic testing strategies were selected for this analysis. Strategy 1, which can be considered 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. [15]. This panel targets a full or partial exon region of 54 DNA genes frequently mutated in myeloid malignancies, including AML. On the other hand, strategy 2 requires the patient's blood and/or bone marrow samples to be sent to Roche Foundation Medicine, a company specialised in comprehensive genomic profiling, to perform the *FoundationOne Heme* test [16]. 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. Finally, strategy 3 involved the acquisition of new equipment to study a larger and more personalised NGS gene panel than the current one. This would guarantee IPO Lisboa would maintain their current access to all the patients' genetic data.

Even though the DM are the members of IPO Lisboa Board of Administration, most of the work was developed in close collaboration with a medical doctor and two laboratory technicians from the haematology department, hereby called the "evaluators". In fact, working with a smaller group focused on haematological pathologies was considered an advantage in terms of time management and the quality of the information.

Step 2.1. Clinical Pathway Mapping

Mapping the clinical pathways (CP) of AML patients was deemed 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.

For this purpose, patients were divided into three groups according to the ELN Risk Stratification [17], that is, whether they belonged to the favorable-, intermediate- or adverse-risk group, and their CP were described and schematized as a process flowchart. This was done in collaboration with the evaluators, over the course of three meetings.

Step 2.2. Value Modelling

As part of the applied multi-methodology, a multicriteria decision model was structured and built over the course of several months in order to assess the value of each strategy for the stakeholders of IPO Lisboa, considering several criteria. For this purpose, the MACBETH approach [18], which makes use of qualitative judgements to measure the attractiveness of the existing alternatives and has been used in multiple health settings [19-24], was applied.

First, the evaluators participated in three workshops which culminated in the selection of the five criteria to be included in the model. Furthermore, a descriptor of performance was associated with each criterion, composed of two or three levels of performance, and each strategy was classified according to those levels, as represented in Table 1.

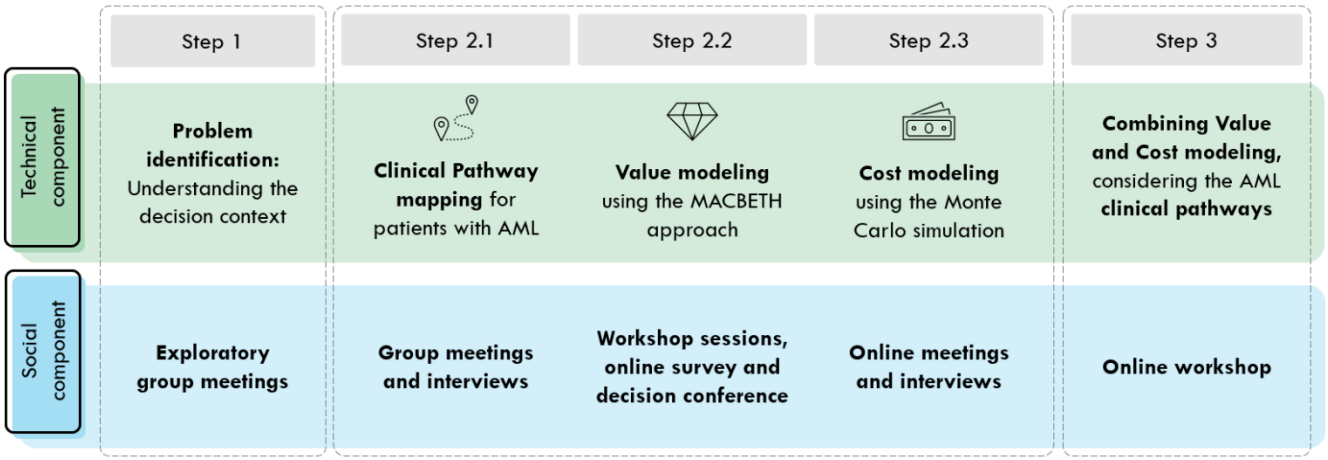

Figure 1. Socio-technical approach developed to implement the proposed multi-methodology.

Table 1. Criteria selected to assess the value of different genomic testing strategies at IPO Lisboa using a MCDA model, and associated descriptors of performance. Furthermore, each strategy's performance on each criterion is presented (S1 = Strategy 1; S2 = Strategy 2; S3 = Strategy 3).

	Criteria	Descriptor of performance	Strategies' Performance		
			S1	S2	S3
Value 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 haematologic malignancies.		X	
		Level 2: The panel detects variations in the DNA of a personalised number of genes, focusing on myeloid pathologies.			X
		Level 3: The panel detects variations in the DNA of 54 genes mutated frequently in myeloid malignancies.	X		
	Time to access the results	**Level 1:** The time interval between collecting the sample and obtaining the results is 2 weeks.		X	
		Level 2: The time interval between collecting the sample and obtaining the results is 3 weeks.			X
		Level 3: The time interval between collecting the sample and obtaining the results is 4 weeks.	X		
Value for IPO and its stakeholders	*Usability for the health professional*	**Level 1:** The process is easy and simple to interpret. No training is needed.		X	
		Level 2: The process is easy and simple to interpret. Some initial training is needed.			X
		Level 3: The process is easy, albeit sometimes difficult to interpret. Some occasional training is needed.	X		
	Resource optimization	**Level 1:** No infrastructures are needed. At least two people are involved in the process.		X	
		Level 2: Requires using the currently available infrastructures. At least four people are involved in the process.	X		
		Level 3: Requires using more infrastructures than the ones currently available. At least four people are involved in the process.			X
	Knowledge improvement	**Level 1:** The institution has total access to the information (access to the sample, the raw data and the final results).	X		X
		Level 2: The institution cannot access all the information (only the final results).		X	

Afterwards, an online survey was sent to several IPO professionals to gather the qualitative judgements necessary to build the value model. Therefore, to create the value scales of 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". On the other hand, to estimate the weight coefficient of each criterion, participants were asked to order the criteria as well as to indicate the attractiveness of improving from their lowest to their highest level of performance, using the abovementioned categories. Their opinions were then inserted into the MCDA software M-MACBETH in order to build a prototype value model which was later adjusted and validated during a decision conference. In this decision conference, only two of the three evaluators were present.

Step 2.3. Cost Modelling

Afterwards, the cost of each strategy was estimated by means of a Monte Carlo simulation model. To simplify the process, indirect costs were not calculated, due to the added complexity they would introduce in the model, and only costs which would differentiate the strategies were included, as suggested in the literature [25, 26]. Prior to building the simulation model, it was necessary to identify the relevant groups of costs to be considered (Figure 2).

It is important to mention that, since IPO Lisboa 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. Therefore, after consulting with the DM, it was decided that 70% of the fixed costs of strategy 1 would be included in the second strategy.

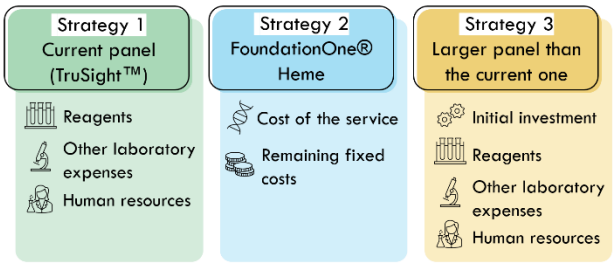

Figure 2. Main costs identified for each strategy.

Afterwards, a triangular distribution was assigned to each of these input variables, in order to better describe the associated costs in light of the limited data available [27]. Being so, minimum, maximum and expected values were estimated for each input variable of the model (Table 2), using 2018 to 2020 accounting reports from UIPM (Unidade de Investigação em Patobiologia Molecular [28]), the unit where the haematology laboratory is included, government sources and consulting with experts whenever data was lacking. The number of human resources involved in the genomic testing process, as well as the annual number of NGS reports, were also estimated.

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 [25]. In this case, however, since only direct costs were evaluated and there was access to limited data, a shorter time period was considered, 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) [29].

Table 2. Expected, minimum and maximum value of each input variable, used to build the triangular functions for the Monte Carlo simulation model.

Input variable	Expected Value	Minimum Value	Maximum Value
Reagents [(1)]	2 621 147 €	2 509 985 €	2 732 309 €
Other expenses [(1)]	89 727 €	73 385 €	106 070 €
Salary [(2)]	172 613 €	77 012 €	260 247 €
FoundationOne [(3)]	5 526 €	4 452 €	27 643 €
Initial Investment	200 000 €	160 000 €	240 000 €
Haematology HR	7	6	8
Annual AML reports	50	40	60
Annual UIPM reports	2300	1800	2800

[(1)]Present cost, considering a period of 5 years; [(2)]Present cost per Superior Technician, considering a period of 5 years; [(3)]Present cost of purchasing one test per year, for a period of 5 years.

Finally, an output function was defined for every strategy, to combine all the existing inputs into the result of the simulation. The output functions for the three strategies are as follows:

$$Cost_1 = \frac{AML\ reports}{UIPM\ reports} \times lab\ expenses + salary \times HR \times 0{,}15 \quad (1)$$

$$Cost_2 = FoundationOne \times AML\ reports + Remaining\ FC \quad (2)$$

$$Cost_3 = Invest.\ capital + \frac{AML\ reports}{UIPM\ reports} \times lab\ expenses + salary \times HR \times 0{,}15 \quad (3)$$

where $Cost_i$ is the present cost of strategy i considering a time horizon of five years. Besides that, *AML reports* is the annual number of NGS reports for AML patients, *UIPM reports* corresponds to the annual number of NGS reports at UIPM, *lab expenses* refers to the cost of reagents and other laboratory expenses at UIPM, *salary* refers to the salary of a superior technician, *HR* is the number of human resources from the haematology laboratory working at UIPM, *Invest. capital* includes the initial costs of purchasing new equipment and *Remaining FC* corresponds to 70% of the current fixed costs. A factor of 0,15 was applied to the salaries considering that only approximately 15% of a haematology technician's time is spent with AML NGS related tasks.

Following the choice of the statistical distributions and the definition of the output functions, the software @RISK, from Palisade [30], was used to perform a Monte Carlo simulation for the three genomic testing strategies. In each iteration, random samples are drawn from the input distributions, from which an output is calculated. After several runs, we obtain an output distribution representing possible cost scenarios and the corresponding probability [31]. A statistical analysis can then be performed and used to make decisions regarding the best course of action. In this case, 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 be available in the form of graphs and tables with the corresponding statistics report.

In addition, a sensitivity analysis was performed to understand the effect of each input distribution in the output, which is vital considering the uncertainty surrounding most of the data [25]. Consequently, one can easily identify the most critical inputs and concentrate on them when deciding between alternative plans of action.

Step 3. Combining the results

At this point, the most relevant aspects of AML patients' clinical pathways had been mapped, and all strategies had been compared using a value model and a cost model. Consequently, there was a need to combine the results in a clear way which would provide the DM with 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 results from the Monte Carlo simulation model were combined with the scores obtained with M-MACBETH and represented in a 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 patients care.

Results

Clinical Pathway Mapping

To better compare the three genomic testing strategies, it was first necessary to understand and map the clinical pathways of AML patients at IPO Lisboa, which often include performing one or more NGS tests. The process flowcharts built for each pathway can be consulted in this link, and will be described in this section.

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. After being referred to IPO Lisboa 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.

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 [17]. 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 might be offered the option to receive a haematopoietic cell transplant, as long as they are deemed fit to undergo this therapy [17]. 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 needed.

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 to be further studied.

Value Modelling

A MCDA model was developed using the MACBETH approach, to assess the value of each genomic testing strategy considering a five criteria. In order to build this model, an online survey was sent to several IPO professionals, including a laboratory technician, two haematology doctors, one research manager and a member of the Board of Administration.

To generate the partial value scales for each criterion, the most consensual judgments among the five participants, that is, those with the highest number of votes, were selected and inserted into the software. Furthermore, to obtain the weight coefficients, the criteria were first ordered by the most consensual order, estimated using the Borda voting system [32]. Afterwards, the required judgements were inserted in a judgement matrix to obtain the weight of each criterion.

However, for a MCDA model to be complete it must be adjusted and validated by the involved stakeholders. Therefore, a decision conference was held with the evaluators, who made some modifications to the model according to their opinion and expertise, which resulted in minor changes to the weighs of the criteria.

Figure 3 shows the overall score obtained for each strategy, highlighted in yellow. According to these results, strategy 2 is the most attractive one, with an overall score of 72.00, followed by strategy 3 and strategy 1 with a respective score of 49.80 and 35.00.

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.

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 3. Table of scores for the three strategies, obtained using software M-MACBETH.

Results indicate that 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 4). Changes in the weight of the remaining criteria would not produce significant changes in the results of the model.

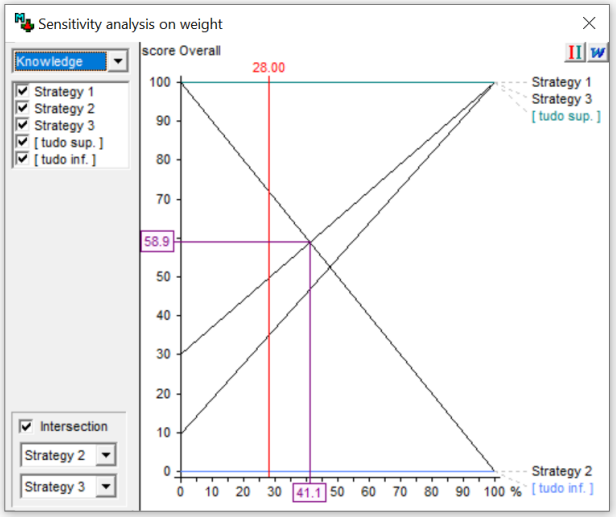

Figure 4. Sensitivity analysis on the weight of the "Knowledge Improvement" criterion. The red line represents the current weight and the purple line shows the intersection between strategies 2 and 3.

Cost Modelling

After building the Monte Carlo simulation model, an output distribution was obtained for every strategy, representing different cost scenarios and the probability associated with each of them. Table 3 shows a summary of the most relevant statistics obtained for each strategy and Figure 5 conjugates the three output distributions in one picture, providing a visual comparison of the results.

Table 3. Output statistics obtained for each genomic testing strategy using a Monte Carlo simulation model.

Output statistics	Strategy 1	Strategy 2	Strategy 3
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
Stand. Dev. (€)	42 118,52	278 292,80	44 140,32

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.

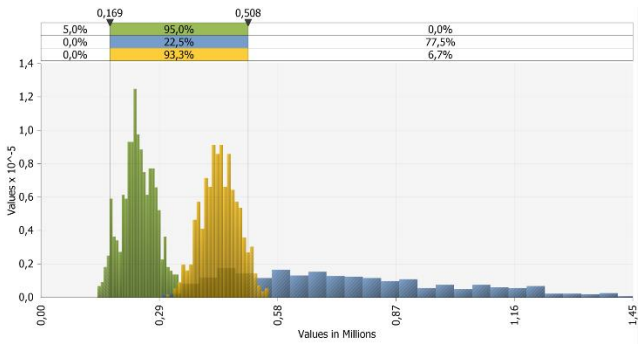

Figure 5. Combined output distributions obtained for the costs of the three genomic testing strategies using a Monte Carlo simulation model (strategy 1 in green, strategy 2 in blue and strategy 3 in yellow).

Finally, a sensitivity analysis was performed to understand the impact of each input variable in the results of the cost model. Results show that 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 mean cost is the price of each *FoundationOne Heme* test, followed by the expected number on annual AML reports. Lastly, for strategy 3 the salary is once again the variable with the highest potential impact, followed by the estimated initial investment.

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 considered genomic testing strategies, 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.

Figure 6 shows an XY plot which combines the overall score of each strategy, obtained with the MACBETH model, with its 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.

A strategy landscape graph was also generated to allow a better visualization of the aforementioned results (Figure 7). Once again, one can see that although strategy 2 was given the highest score in the value model, its cost function shows a greater deviation from the mean value when compared to the other strategies.

Finally, Table 4 describes the impact which the implementation on each strategy is expected to have on the AML patients' current CP, according to early interviews with the group of evaluators involved in the study.

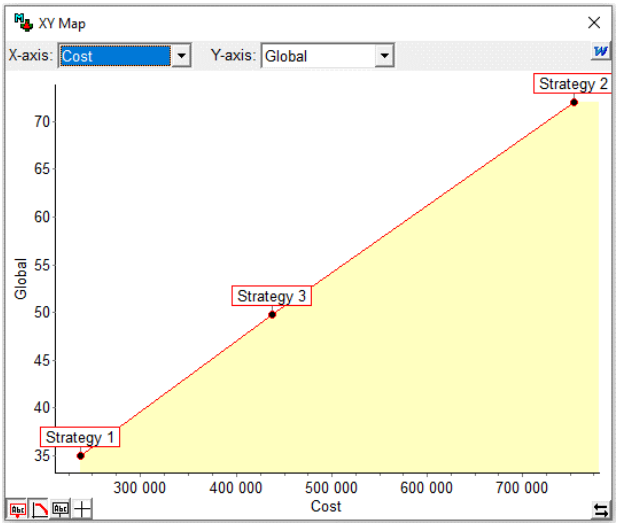

Figure 6. XY plot representing the mean cost and the global score of each strategy. The red line shows the efficient frontier, and the inefficient area is highlighted in yellow.

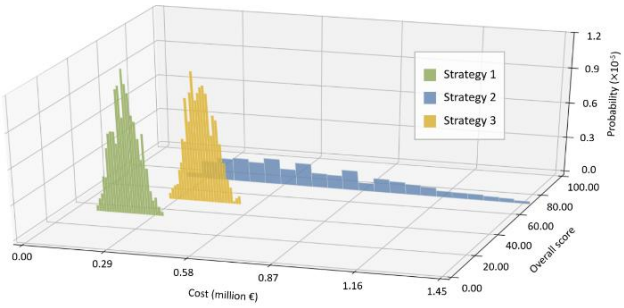

Figure 7. Strategy landscape graph depicting the cost distribution of each strategy and the corresponding score in the value model.

Table 4. 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	Strategy 2	Strategy 3
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)	-	No direct impact	No direct impact

As 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 patient. On a patient level, it is possible the implementation of strategy 2 will provide access to a wider range of clinical trials. Similarly, by sequencing new genes after the implementation of strategy 3, IPO Lisboa would have more complete databases which can be beneficial in the future. However, none of these changes would directly reflect in the general pathways which were mapped for the three different groups of patients, as indicated in the table above.

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 [3, 33]. This transition was only possible due to numerous developments in the field of genomic technologies, which also carry 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 [34]. Therefore, it is essential to develop harmonised methods and tools to assess the impact and value of these technologies for the hospitals and the patients [35].

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 [4, 5, 36]. 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 a hospital level might result in more accurate and relevant recommendations for the DM, and be more beneficial for all the involved stakeholders [7].

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 [37]. 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. Some aspects which were referred are: the relevance of the work for IPO Lisboa, especially considering the everchanging landscape of genetic diseases and constant turnover of genomic technologies; the role of the facilitator, which was seen as crucial in the whole process, working as a bridge between the clinical and the technical fields, and reaching out to different stakeholders; the multi-methodology, which answered the needs of the institution by being carefully personalised accordingly; and the obtained results, that provide a good foundation for IPO Lisboa to better assess and discuss different genomic testing strategies available in the market.

However, participants also mentioned some limitations which should be acknowledged, namely: 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; 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; and more people should have answered the online survey in order to avoid bias and obtain more consensual results.

Main Findings

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.

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 Lisboa, hindering any further analysis (either confirmatory or investigational) from their part. Another topic 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 [2]. Even though the currently used panel already comprises the most common mutations for AML, 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 suitable clinical trials. Finally, one should acknowledge how the vagueness surrounding the definition of strategy 3 might affect 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. Nevertheless, this concern was properly discussed with the DM and the evaluators, who believe this allows more options to be encompassed in the analysis, as long as they correspond to a larger and more personalised gene panel than the currently employed.

After defining the strategies that most interested the DM and describing them with the help of the evaluators, it was important to map the clinical pathways of AML patients and understand how NGS tests impact their care. From the resulting flowcharts, one can understand the intricacy of the whole process, as well as the 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.

NGS tests are usually performed after the patient has already initiated the treatment, and results can take up to four weeks. 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. Therefore, 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.

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. Although MCDA has been increasingly used in the healthcare context [19-24], 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.

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. Looking at the results, it is clear that strategy 2 obtained the highest score, mostly because it performed well in almost every criterion. 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 whole genome sequencing as the standard diagnostic test in oncology [38, 39].

Although there are some published studies in the field of cost estimation of sequencing tests [26, 40], 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, 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.

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, although 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 [25].

Advantages and Limitations of the Methodology

Every step of the implemented multi-methodology 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 [18], 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 [31]. 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. 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.

On the other hand, 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, although NGS techniques and other technologies have been helping unravel the mysteries of cancer, 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. Furthermore, all models were built specifically for this particular decision context, although they can be adapted to other circumstances.

Even though the developed work is 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.

Conclusion

This work aimed at helping IPO Lisboa, a renowned cancer research centre and hospital, to assess the value of implementing three different genomic testing strategies for the care of acute myeloid leukemia patients. Therefore, a multi-methodology was implemented, which involved studying the clinical pathways of different patients, building a multicriteria model to measure the value of each strategy for different stakeholders and estimating the monetary cost of each alternative for the institution.

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 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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