Hospital-based health technology assessment of emerging medical devices: A socio-technical approach for multicriteria evaluation of emerging biomarkers for HER2+ breast cancer

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Abstract

Health systems are facing significant challenges, with new medical devices and technologies constantly entering the market. Consequently, there is an increasing need to assess their quality, safety, effectiveness and inform decision-makers on the adoption of these technologies. In this context, Health Technology Assessment (HTA), combined with innovative Multicriteria Decision Analysis (MCDA) models and tools, have the potential to face some of these challenges.

Biomarkers are a good example of an innovative medical device. However, despite the current progress with the discovery of multiple new biomarkers, many of them are still not used in clinical practice and are yet to be approved by international guidelines.

Thus, and within the scope of Hospital-based HTA, this thesis has the core objective of developing and implementing an innovative socio-technical approach, combining the MACBETH approach for multicriteria evaluation with a rapid review of evidence and with specially designed participatory processes, using the WisedOn software as a decision support system. The approach will enable the multicriteria evaluation of emerging biomarkers, for HER2+ breast cancer, to assist decision-making at Hospital do Espírito Santo de Évora (HESE).

With this methodology it was possible to obtain a comprehensive evaluation of the emerging biomarkers. Despite the initial challenge of lack of information, the results show the approach was useful to achieve a consensus among the several key-actors, which resulted in a model with six criteria for the evaluation of eleven emerging biomarkers. The model also has the potential to be reused in other contexts in HESE, for other health technologies.

Keywords: Hospital-based Health Technology Assessment • Multicriteria Decision Analysis • Socio-technical approach • MACBETH • Emerging biomarkers • HER2+ breast cancer

1. Introduction

Technology has globally changed health care systems and has increasingly become a dominant force. New medical and clinical technologies are currently being developed, introduced into international markets, and consequently health care systems, at a rate never seen before [1]. Moreover, the development of personalized drugs used in precision medicine therapeutics, nanotechnology, artificial intelligence, or stem cells is steadily, and already, shaping the future of healthcare [1].

In 2017, the Organization for Economic Cooperation and Development (OECD) published a report regarding new health technologies [2] and stated that many new biomedical technologies are approved in the market with small evidence of their effectiveness and safety, claiming that the assessment of these devices, under real-world conditions, is scarce [2]. Other studies similarly conclude that there is a lack of transparency regarding clinical evidence for medical devices worldwide, and consequently, having healthcare professionals using medical devices without real knowledge or data regarding them [3].

Consequently, this thesis intends to develop methods and tools to provide healthcare professionals, in hospital and clinical context, with synthesized medical-device evidence of its benefits, risks, and costs and to explore healthcare professionals' interpretation and need of further evidence and information. This thesis is inserted in the Developing HTA tools to consensualise MEDIcal devices' VALUE through multicriteria decision analysis (MEDI-VALUE) project [4], based on Health Technology Assessment (HTA) to assess the overall value of medical devices, valuable information that can

improve the current health systems, promoting both innovation and sustainability, not only for clinical care and overall population health, but also for research and development.

Thus, and within the scope of HB-HTA, the main goal of this project is to develop and implement a socio-technical approach to construct a multicriteria model. This approach combines the use of the MACBETH approach with a rapid review and participatory methods (results from a prior Web-Delphi process, interviews, Workshops and Decision Conferences) allied to the WisedOn decision support system to create a multicriteria evaluation of biomarkers for breast cancer, more specifically, for the HER2+ breast cancer subtype.

Consequently, it is expected that this thesis can fulfill the need for evidence synthesis and also provide relevant information and data to the HESE healthcare professionals, in order to aid the decision-making process. Additionally, the model can be reused since it can be used by HESE to assess other emerging biomarkers, not only for breast cancer In fact, emerging biomarkers for other diseases can be assessed to be used in future clinical practise.

2. Literature Review

2.1. Health Technology Assessment

To understand which technologies have value and are relevant to the current health systems, a variety of jurisdictions, driven by policy-makers and clinicians, is becoming more interest HTA. According to the World Health Organization (WHO), HTA is "*the systematic evaluation of properties, effects and/or impacts of health technologies and interventions. (...) The approach is used to inform policy and decision-making in health care, especially on how best to allocate limited funds to health interventions and technologies (...)*" [5]. It is, undoubtedly, of multidisciplinary nature, bringing together scientific evidence and policy-making to assess the overall value of new or existing technology. Despite being well developed in the pharmaceutical industry, the HTA of medical devices is still in development [5].

HTA can also be conducted in the hospital context, for managerial decisions, *i.e.*, Hospital-based Health Technology Assessment (HB-HTA) [6]. According to the literature, the number of hospitals performing HB-HTA is increasing, which calls for the need to improve its quality and efficiency and develop guidelines and tools to support it [7]. The final products of a HB-HTA consist of HTA assessment reports, technical queries, and quick response services. HB-HTA can be performed in multiple ways, with different levels of complexity, and with multidisciplinary teams [6].

Besides the more traditional evaluations (such as effectiveness and economic evaluations), there are new assessment approaches which use different evaluation dimensions. As a consequence, MCDA has been considered extremely useful in HTA, due to its alignment with value-based healthcare, its transparency and ability to account for the different stakeholders values and preferences, its contribution to aid decision-makers to understand the technology value, among many others [8].

There are several examples regarding the use of MCDA in healthcare, including the assessment of health technologies regarding its benefits, risks and costs. Typically, decision-makers, in cases of multidimensional healthcare problems, are faced with very complex problems and so, in order to simplify them, they tend to opt for more intuitive or heuristic approaches. As a direct consequence, important information can be neglected: usually, evidence from economic evaluations tends to be the one that is more used, with social values and context being under-used, little analysed and sometimes even excluded from the decision-making process. This can ultimately lead to decision-makers not being adequately equipped to make rational and well-informed decisions and diminished credibility related with the decision outcomes [9]. That is why the use of specific frameworks is so important, since it brings a more detailed, structured and transparent way of assessing and choosing healthcare technologies, leading to better and trustworthy decisions and solutions.

2.2. Breast cancer and the HER2+ breast cancer subtype

Breast cancer consists of cancer that is formed in the breast tissues, typically in the ducts or in the lobules and it considered the most common carcinoma in women [10]. It can be categorized as non-invasive, in case it corresponds to a pre-malignant lesion, or invasive, if the cancer has already spread outside the place in which it developed [10].

Despite being referred to as a single disease, breast cancer is very heterogeneous, with a large spectrum of different diseases. Different breast cancer subtypes have varied morphological characteristics and distinct clinical outcomes. One of the most common classifications is associated with the expression of four biomarkers (Estrogen Receptor (ER), Progesterone Receptor (PR), Human Epidermal Growth Factor Receptor 2 (HER2), and Ki-67), which divides breast cancer into five distinct subtypes: Luminal A, Luminal

B-like (HER2-), Luminal B-like (HER2+), HER2-enriched and Triple negative [11] [12].

In this thesis, the focus will be on HER2+ breast cancer, i.e., cancers in which the HER2+ biomarker is expressed (in both Luminal B-like (HER2+) and HER2-enriched).

HER2+ breast cancer is associated with the overexpression of HER2, a transmembrane glycoprotein, coded by the ERBB2 gene [13]. It is part of the Human Epidermal Growth Factor (HER) family receptors, which are associated with pathogenesis in a variety of cancers [13]. Additionally, they are also responsible for the regulation of cell functions, namely growth, survival, proliferation, and differentiation. The amplification or overexpression of HER2 occurs in approximately 15-30% of all breast cancers [13]. Its presence is associated with facilitating excessive and/or uncontrolled cell growth as well as tumorigenesis. HER2+ cancer cells possess around 2 million HER2 proteins on their surface, which is around 100 times more than a normal cell, leading to tumour cells growing and dividing more rapidly [14].

As a result, HER2+ breast cancer tends to be more aggressive than the other subtypes, correlating with poorer prognosis and unfavourable tumour characteristics, such as tumour size, high nuclear grade, and high proliferation index [14]. HER2 is considered an important and reliable biomarker for the diagnostic, prognostic, and prediction of drug/therapy response in HER2+ breast cancer. In fact, it is currently the only biomarker approved to guide HER2-targeted therapy [15].

Due to new and improved anti-HER2 targeted agents, the patients' prognostic has increased considerably [16]. Nevertheless, and despite the improved prognostic, more than 60% of patients experience resistance to the treatment in the first year, which is associated with heterogeneity sources, namely with causes related with genetic expression, DNA mutations and immune micro-environment [16] [17].

Understanding these sources of heterogeneity can eventually lead to new biomarkers for HER2+ breast cancer, expanding the current treatments and, gradually optimize the situation of HER2+ breast cancer patients [16]. With a larger number of biomarkers for this breast cancer subtype, it might be possible to decrease the current percentage of patients that are resistant to the therapy and to increase the patient's life expectancy, with personalized therapies, adjusted to their conditions. Having this in mind, it is also important to understand that there is a generalized lack of information in the literature for emerging biomarkers, due to their relatively recent discovery and its absence in the clinical practise. Thus, to try to overcome this limitation, it is important to gather experts and stakeholders in order to develop a methodology to assist HESE in the evaluation of emerging biomarkers for HER2+ breast cancer.

3. Methodology

To meet the objectives, a socio-technical approach based on MACBETH method was designed. The socio-technical approach (Figure 1) used can be divided into four distinct stages: evidence synthesis, model structuring, model construction, and model testing and validation. Each one of these phases can also be divided in its technical and social component.

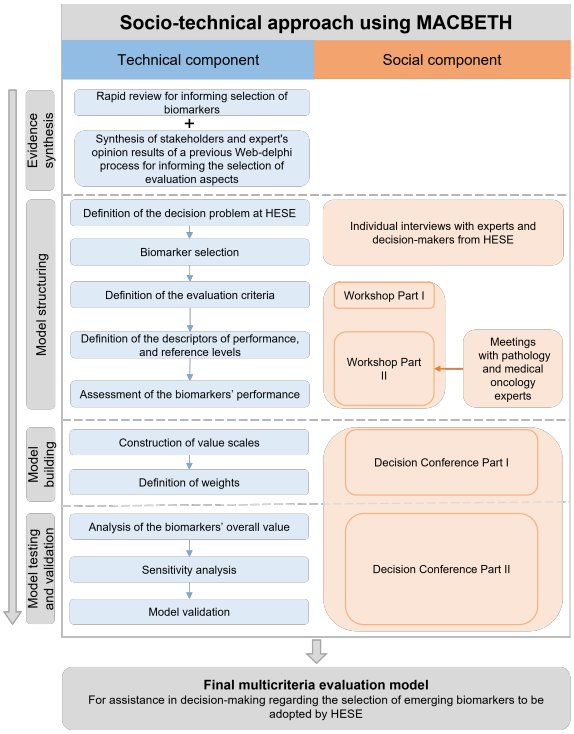

Figure 1: Socio-technical approach that describes this thesis methodology. The left arrow indicates the flow of time, from top to bottom, culminating in the final multicriteria evaluation model.

The technical component includes the definition of the problem at HESE, the selection of the biomarkers, and the use of MACBETH. The MACBETH approach was chosen for this thesis since it uses qualitative judgements of difference in attractiveness not only to generate the value scores for the options but also to weight the criteria [18]. By doing so, this tool becomes very intuitive for the decision-maker when compared with other approaches and models that can, oftentimes, be more confusing. The MACBETH approach is used in multiple contexts, not only in the field of health and health technology such as this thesis, but also in other sectors namely

energy, military and industry sectors, among others [19].

MACBETH (Measuring Attractiveness by a Category-Based Evaluation Technique) is an MCDA technique, described as a "*decision-aid approach for multicriteria value measurements*" [18] that uses qualitative judgements to assess the difference in attractiveness to compare options in a set.

This approach is based on the additive value model, used to prioritize and select the distinct options available, and can be described through the following equation:

$$V(a) = \sum_{j=1}^{n} w_j v_j(a), \; with \; \sum_{j=1}^{n} w_j = 1, w_j > 0 \quad (1)$$

where $V(a)$ represents the overall value of alternative a, $v_j(a)$ translates the partial value of alternative a in terms of the criterion j and w_j is defined as the weight of the criterion j [18] [20].

Besides, the additive model must also have two reference levels associated with each criterion w_j, typically the *neutral* (*i.e.*, minimally acceptable) and *good* reference levels, with a score of 0 and 100, respectively [18]. These were the chosen reference levels since this formulation allows the model to not depend on the options. Without dependence on the options, the model presents a clear advantage as it can be replicated and reused, with other options, and also in other contexts.

On the other hand, besides the technical component based on MACBETH, the social component uses input provided by the participants (in this case, the experts and decision-makers from HESE) to build the multicriteria model. In this way, the social component acts as a supporter of the technical component, providing in the specific case of this thesis, individual interviews with experts and decision-makers, a Workshop, and a Decision Conference.

Using this methodology represented in Figure 1, it is expected to construct a decision support tool to assist in the evaluation of biomarkers for the specific case of HER2+ breast cancer, that can later be used for *in vitro* tests. Due to its universality in the world of biomarkers, any biomarker can be assessed using this tool. This can be extremely advantageous since it will be possible to use this multicriteria evaluation model for any new emerging biomarkers that might appear in the literature with potential to be used in clinical practice.

The first phase in this methodology was to synthesise the available evidence regarding emerging biomarkers for HER2+ breast cancer and to select the most promising ones, based on the information available in the literature. To do so, a rapid review on this area was performed (using academic research databases and other search engines), to select a list of emerging biomarkers for HER2+ breast cance. Parallel to this step, the results from a previous study consulting medical devices' stakeholders and experts in Portugal on which value aspects are relevant to evaluate biomarkers were used, which served as a starting point for the model.

Next, the model was structured, *i.e.*, the decision problem was defined, which allowed the selection of the biomarkers to be evaluated. This was possible due to the input provided by eight experts and decision-makers from HESE, during the exploratory individual interviews. The evaluation aspects, descriptors of performance, and reference levels were also created and, for that, a Workshop was conducted with the decision-makers (two healthcare professionals from HESE). Regarding the performance of biomarkers in the various aspects, it was advised by the decision-makers to consult other professionals, namely from the Pathology and Medical oncology services from HESE, given the deeper knowledge of these professionals in the area. For that, two meetings with these two professionals were conducted.

After the structuring of the model, it was then possible to advance to the next stage: model building. During this stage, value scales were built, and weights were defined to the criteria. To do so, a Decision Conference was held with the decision-makers, in which the WisedOn software [21], a decision support system, was chosen to aid with the process.

As a result, a provisional multicriteria evaluation model is created. Thus, the next step was to test and validate the model with the decision-makers, which was also done during the Decision Conference. First, and using the value scales previously build, the biomarker options were evaluated, for each criterion, so that the performance of the options in each criterion could be converted into (1) a partial value score; and then (2) a global score, for the evaluation of the options, *i.e.*, add the partial value scores of the biomarkers across the criteria. After obtaining the overall scores for each biomarker, several sensitivity analysis were conducted, based on the results obtained.

Only after the phase of model testing and validation, the final multicriteria model is constructed, and it was possible to obtain the performance profile for each one of the options, as well as the ordered list of biomarkers, ranked by

their respective scores. The most relevant biomarkers were presented to the decision-makers as the most promising biomarker options to be adopted in the near future by HESE to handle HER2+ breast cancer patients.

Lastly, and as the final and last contact with HESE, it was asked, also during the Decision Conference, for the decision-makers to provide some feedback regarding the distinct stages of the socio-technical approach in which they participated, to gather general thoughts and opinions that arose during the process, as a way to validate the approach.

To develop such methodology, it was important to establish a facilitation team, a group of people responsible to manage all the processes and activities associated with the MCDA methodology, and that would establish direct contact with the participants and the decision-makers during the individual interviews, the Workshop, and the Decision Conference (*i.e.*, in the social component of the process). The facilitator team for this methodology consisted of two persons.

4. Results

4.1. Evidence synthesis

A rapid review was conducted to select the emerging biomarkers for HER2+ breast cancer that would be evaluated, using the keywords *breast cancer*, *biomarkers*, *diagnostic*, *prognostic*, and *drug response*, in the PubMed [22] and ScienceDirect [23] databases, with the searchflow depicted in Figure 2.

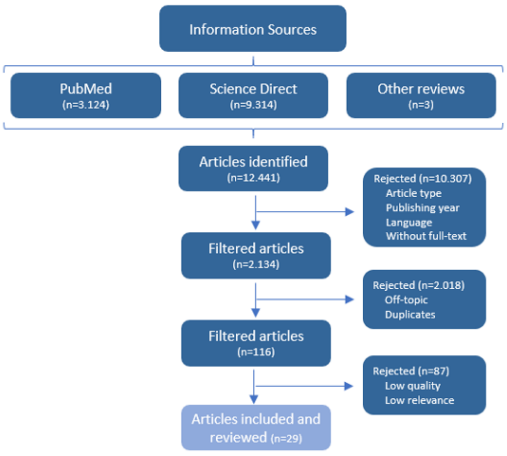

Figure 2: Literature review search flow, resulting in 29 articles to be fully analysed. The resulting pool of articles served as a base for the rapid review with the focus on emerging biomarkers for HER2+ breast cancer.

In Table 1, the final list of the distinct biomarkers found through evidence synthesis, after the approval of the healthcare professionals at HESE, is presented. During this first stage, the biomarkers were grouped into four distinct categories, according to their characteristics. The categories served only as an organization of the biomarkers, for a better presentation to the healthcare professionals and did not interfere with the consequent results obtained.

4.2. Model structuring

Individual interviews with experts and decision-makers

With the results from the MEDI-VALUE project's Web-Delphi serving as a base, individual exploratory interviews with the two decision-makers and other six healthcare professionals from HESE were conducted, to assess which aspects are considered relevant to evaluate biomarkers for HER2+ breast cancer.

Regarding the results from this initial phase, it is necessary to mention that, in some aspects, it was not possible to reach conclusions, since some healthcare professionals considered the aspect relevant, while others considered it irrelevant. These aspects were re-analysed at an advanced stage, during the Workshop session with the decision-makers. In addition, some general comments made by the healthcare professionals regarding the questions asked during the interviews were also made. Regarding question "*Do you consider that the aspects presented are easy to understand, concerning the knowledge you have in the area? If not, what do you think could be improved?*", most professionals referred that the set of aspects was too general and that a focus should be made to specify it for the context of biomarkers for HER2+ breast cancer. In addition, a healthcare professional reported that most aspects were very technical and that a greater focus on the clinical part would also be important. Regarding this question, there was some confusion among the healthcare professionals when assessing aspects, since some professionals considered the initial list of aspects to be very general for the specific case of in vitro tests based on biomarkers for HER2+ breast cancer. This fact can be considered as a limitation in the individual exploratory interviews and the consequent classification of the aspects concerning their relevance. Regarding question "*Within the mentioned aspects, do you consider that there is a missing aspect that should be included?*", all professionals considered the list to be quite exhaustive and complete, touching on all the points that they considered relevant. Note that the initial list of aspects was considered too long, according to some healthcare professionals. Finally, for the question "*Do you approve the list of potential biomarkers for HER2+ breast cancer?*", all of the eight participants provided their

Table 1: List of the emerging biomarkers' options to be used for HER2+ breast cancer, grouped in distinct categories, after approval from the healthcare professionals at HESE.

Category	Biomarker	Reference
HER2 and HER3	HER2 levels	[16], [24]
	HER2 mutations	[25]
	HER2 heterogeneity	[16]
	HER3	[16]
Gene expression	Intrinsic subtype (PAM50)	[16], [26]
	PTEN	[27], [28]
DNA mutations	PIK3CA mutations and PI3K pathway inhibitors	[16], [17], [25], [24], [27], [28], [29], [30]
Immune micro-environment	TILs	[16], [25], [31], [32]
	PD-L1	[16], [33], [34]
	FcγRs	[16], [25]
	Liquid biopsy (ctDNA, ct-miRNA, CTC)	[25], [35]

feedback. In fact, one of them showed particular enthusiasm for: HER2 mutations, PIK3CA mutations and PI3K pathway inhibitors, PD-L1, and Liquid biopsy. Additionally, two of the health professionals did not feel comfortable giving their approval regarding the list sent, as they considered that they did not have enough information about these emerging biomarkers.

Workshop (Part I)

During the first part of the Workshop, it was clarified with the decision-makers which was the focus of the study. After some discussion, the participants decided that, despite being an ambitious focus, it was possible and appropriate to compare the different biomarkers with each other, despite the distinct functions that they might present (of diagnosis, prognosis, and prediction of drug/therapy response). Thus, the initial and provisional list of biomarkers was once again analysed and reformulated, resulting in the final list, presented in Table 1. After the focus was defined, it was then possible for the decision-makers to classify the aspects according to their relevance, for the context of HESE. After the classification, and out of the 34 initial aspects, the list was reduced, with only 18 aspects considered relevant at this stage.

Workshop (Part II)

The first activity proposed to the two decision-makers for Workshop Part II was to identify potential overlaps, redundancies, and inter-dependencies between the different aspects. For that, a value tree was presented, in which the aspects were organized in different dimensions of evaluation. It was also mentioned during this exercise that the costs associated with the biomarker were only going to be considered afterwards, following a logic of *Value for Money*. At this stage, the decision-makers were asked to analyse the value tree and, if necessary, to suggest changes in its organization. They referred that the evaluation dimensions considered, and the aspect organization were coherent, which allowed proceeding to the validation/discussion in greater detail regarding some characteristics of the value tree. Then, the performance scales developed, based on the available literature and scientific evidence, were presented to the decision-makers, for each of the aspects that were represented in the value tree. With the following exercise, it was intended that the decision-makers gave their opinion, based on their experience in the area, regarding the performance scales previously built. As mentioned, besides the input provided during Workshop Part II, it was also necessary to speak with other two healthcare professionals (directors of the Pathology and Medical oncology services, at HESE) to have further insight to build the value tree and the performance scales. As a result, some of these scales did not undergo any changes and remained the same as those initially proposed. However, in the majority, proposals for improvement and alteration were mentioned by these two healthcare professionals, including grouping aspects due to redundancies between them; removing some aspects; and consider some aspects only at a later stage, from the perspective of *Value for Money*, and for a future cost-benefit analysis. The contribution of these two professionals, expressed after Workshop Part II, was of extreme importance, since it provided further insight and their inputs were an excellent addition to the results obtained from the Workshop (both Part I and Part II). After this, it was possible to decide which were the aspects that were going to be considered for the evaluation of the biomarkers' options (and thus, be considered as criteria - Table 2), and to build the descriptors and performance scales for the criteria (Table 4), as well as a final value tree (Figure 3).

Table 2: Criteria, criteria relevance and description

Criteria	Relevance	Description
Clinical relevance	Critical	Biomarker's capacity to identify subtypes of the disease, and its expected impact on clinical practice.
Existence of clinical guidelines and quality of evidence	Complementary	Robustness of the evidence sources and quality of the evidence with regard to the target population and the intended clinical course, and recommendation of the biomarker by national and/or international clinical guidelines.
Usability for the healthcare professional	Complementary	Extent to which the procedures for using the biomarker are defined and clear, and the result is easy to interpret. The need for training the healthcare professional, and the learning curve are also taken into account.
Impact on the form of work and workload	Fundamental	Extent to which the biomarker can be implemented without drastic changes in the current form of work and in the workload of healthcare professionals.
Agreement of key-actors in the decision	Fundamental	Agreement between key-actors (stakeholders) in the hospital context, that is, the extent to which the adoption of the biomarker is aligned with common objectives.
Public health concern	Complementary	Ability to use the biomarker as a tool for diagnosis, prognosis, or prediction of drug/therapy response.

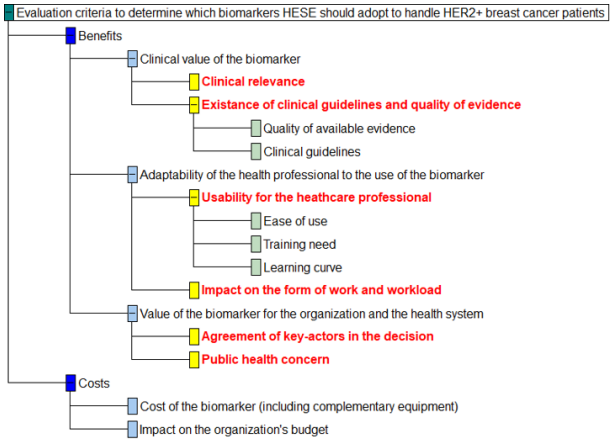

Figure 3: Final value tree. The red nodes correspond to the evaluation criteria considered. [source: M-MACBETH software]

4.3. Model building

Decision Conference Part I

During this phase, two activities were conducted: the construction of value scales for each criterion and the weighting of the criteria. Regarding the first activity, it was asked for the decision-makers to make pairwise comparisons, with the MACBETH qualitative judgements, between the levels of each criterion. For that, comparisons between two levels of the descriptor of performance were presented and it was asked the decision-makers to judge the difference in attractiveness between the pairs. By doing so, it was possible to construct a judgement matrix for each criterion that would result in the final value scales (Figure 4).

Afterwards, the second and last activity of this session was to assign the weights to the different criteria. To do so, the swings between the neutral and good levels were ranked, by the decision-makers. With this ranking, the criteria were organized according to its importance, meaning that the swing, from neutral to good, associated with the criterion placed first (or on top) was more important for the decision-makers than the other swings, associated with the other criteria, placed last (or at the bottom).

After this organization, it was then possible to compare the swings (with the neutral reference level or with another criterion), to build the weighting matrix of judgements, that provides the relative weights for each criterion. Following the 21 questions asked to fill every cell of the matrix, the weights were obtained.

The obtained weights were then presented to the decision-makers and the results were discussed. It was referred that the weights should be rounded up to the nearest unit, for a simpler and evidence presentation of the results. In Table 3 the partial scores associated with each biomarker, as well as the global scores of each biomarker option are presented.

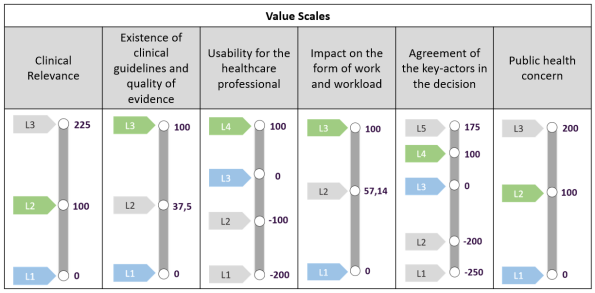

Figure 4: Value scales obtained for each of the criteria, using the MACBETH technique, after adjustments and approval by the decision-makers. The green and blue levels corresponds to the *good* and the *neutral* reference level, respectively. [source: WisedOn software - adapted figure, not represented to scale]

4.4. Model testing and validation

Decision Conference Part II

In the last session with the decision-makers, the overall scores for the biomarkers were presented (Table 3). Regarding the results, the decision-makers considered the biomarkers scores expected. They also considered the 3

Table 3: Partial score for the different biomarkers in each criterion and global score for each one of them, ranked from higher global score to lower global score. [source: WisedOn platform - adapted].

Option (biomarker)	Partial score in each criterion						Global score (#ranking)
	Clinical relevance (25%)	Existence of clinical guidelines and quality of evidence (35%)	Usability for the healthcare professional (3%)	Impact on the form of work and workload (6%)	Agreement of key-actors in the decision (10%)	Public health concern (21%)	
PD-L1	225	100	100	57.14	175	0	**115.18** (#1)
Liquid biopsy (ctDNA, ct-miRNA, CTC)	100	37.5	0	0	100	200	**90.13** (#2)
PIK3CA mutations and PI3K pathway inhibitors	225	0	100	57.14	175	0	**80.18** (#3)
TILs	100	37.5	100	57.14	100	100	**75.55** (#4)
Intrinsic subtype (PAM50)	225	0	0	0	-250	100	**52.25** (#5)
HER2 levels	0	0	100	57.14	-250	200	**23.43** (#6)
HER2 mutations	100	0	0	0	-250	100	**21** (#7)
HER2 heterogeneity	0	0	0	0	-250	100	**-4** (T8)
HER3	0	0	0	0	-250	100	**-4** (T8)
PTEN	0	0	0	0	-250	0	**-25** (#10)
FcγRs	0	0	-200	0	-250	0	**-31** (#11)

biomarkers with the highest scores as the most significant and most discussed according to their experience (PD-L1, Liquid Biopsy, PIK3CA mutations and PI3K pathway inhibitors). In addition to these 3 biomarkers, the 4th biomarker with the highest score (TILs) was also considered by the participants as deserving of attention. Sensitivity analyses were also conducted to understand, to which extent, the criteria weights would interfere with the biomarkers' scores and rank, and in some cases, more than one for each criterion, since in some examples only a subgroup of biomarkers was analysed. Finally, decision-makers were asked to provide feedback on the study in which they had participated. As already mentioned, questions and feedback were asked for the last three phases of the methodology, the phases in which the decision-makers participated.

5. Discussion & Conclusion

Despite being applied in multiple health-related contexts, MCDA, and more specifically the MACBETH approach is still not used in many studies associated with the adoption of biomarkers, for clinical use and application. This project, as part of the MEDI-VALUE project, tries to fill the gap, by providing a structured methodology to evaluate emerging biomarkers for future use in the clinical context. This methodology can be applied, not only for these specific biomarkers but can also be used in other contexts, to analyse different emerging biomarkers for other diseases.

This approach was innovative, as different tools were integrated throughout the process, including a rapid review and Web-Delphi results from a prior MEDI-VALUE project. Besides, the participation of healthcare professionals from multiple backgrounds was extremely advantageous to this project since it allowed this project to be more reliable, contributing to its validation and credibility [36].

The structured methodology allowed to reach a final multicriteria evaluation model, within the scope of HTA, more specifically, HB-HTA to assist decision-making in HESE regarding emerging and promising biomarkers that should be adopted to be used to optimize the current diagnosis, prognosis, and prediction of drug/therapy response in HER2+ breast cancer.

5.1. Future work and the MEDI-VALUE project

As already mentioned, this thesis was inserted in the MEDI-VALUE project and served as a pilot study, since it will become a support for the development of other MEDI-VALUE works. The future developed models will not only be in the field of biomarkers but will also assess other medical devices, namely cardioverters and esophageal/gastric prosthesis, that will be executed with other MEDI-VALUE partners.

In the future, and as a continuity of the work developed, it would be interesting to also perform

Table 4: Descriptors of performance for the criteria (with different levels, L), and its *neutral* and *good* reference levels.

Criteria	Descriptors of performance
Clinical relevance	**L3-** It is expected the use of the biomarker in clinical practice to be very relevant, since it has the potential to identify different subtypes of the disease and, consequently, allow more effective treatments. It is already available for use in certain cases, in clinical settings. **L2-** It is expected the use of the biomarker in clinical practice to be very relevant, since it has the potential to identify different subtypes of the disease and, consequently, allow more effective treatments. It is not yet available for use in a clinical setting. **[GOOD]** **L1-** It is expected the use of the biomarker in clinical practice to be relevant, with an indirect impact on the treatment of the disease since it is not a crucial biomarker to identify different subtypes of the disease. There are other biomarkers already used in clinical practice that allow for proper diagnosis and treatment. However, it can be used as a complementary instrument. It is not yet available for use in a clinical setting. **[NEUTRAL]**
Existence of clinical guidelines and quality of evidence	**L3-** Biomarker approved at least by one international guideline (*e.g.*, ASCO, NCCN, ESMO, ...) for use in HER2+ breast cancer in a clinical setting **[GOOD]** **L2-** Biomarker approved at least by one local or national scientific group (without recognition by international or national guidelines). **L1-** Biomarker not yet recognized by any international guideline, but with convincing clinical evidence demonstrated in clinical trials. **[NEUTRAL]**
Usability for the healthcare professional	**L4-** The test based on the biomarker requires specific background (through in-house training - training through a hospital colleague) to be handled. The result is easy and simple to interpret (peak proficiency quickly reached by the professional since first use). **[GOOD]** **L3-** The test based on the biomarker requires specific background (through external training - credited training) to be handled. The result of it is easy and simple to interpret (peak proficiency quickly reached by the professional since first use). **[NEUTRAL]** **L2-** The test based on the biomarker requires specific background (through in-house training - training through a hospital colleague) to be handled. However, the result is sometimes difficult to interpret (peak proficiency slowly reached by the professional since the first use). **L1-** The test based on the biomarker requires specific background (through external training - credited training) to be handled. However, the result is sometimes difficult to interpret (proficiency peak slowly reached by the professional since the first use).
Impact on the form of work and workload	**L3-** The implementation of this biomarker in clinical practice will have no impact on the form of work or on the health professional's workload. **[GOOD]** **L2-** The implementation of this biomarker in clinical practice will have no impact on the health professional's workload. However, there will be changes on the form of work. **L1-** The implementation of this biomarker in clinical practice will have an impact on the form of work and the health professional's workload. **[NEUTRAL]**
Agreement of key-actors in the decision	**L5-** Unanimity: all key-actors agree with the adoption of the biomarker (100%). **L4-** Quasi-unanimity: almost all (around 90%) the key-actors agree with the adoption of the biomarker. **[GOOD]** **L3-** Qualified majority: a significant number of key-actors (around 75%) agree with the adoption of the biomarker. **[NEUTRAL]** **L2-** Simple majority: more than half of the key-actors (around 51%) agree with the adoption of the biomarker. **L1-** Non-agreement, among the key-actors in the adoption of the biomarker (below 51%)
Public health concern	**L3-** The use of the biomarker is of high interest to public health, since it can be used to: • Diagnosis, prognosis, and prediction of drug/therapy response for the case of HER2+ breast cancer. **L2-** The use of the biomarker is of interest to public health, since it can be used to: • Diagnosis and prognosis or • Prognosis and prediction of drug/therapy response for the case of HER2+ breast cancer. **[GOOD]** **L1-** The use of the biomarker is of interest to public health, since it can be used to: • Diagnosis or • Prognosis or • Prediction of drug/therapy response for the case of HER2+ breast cancer. **[NEUTRAL]**

a *Value for Money* analysis, which was impossible to perform at this stage, due to lack of information regarding the emerging biomarker's costs. Only with such analysis would it be possible for HESE to adopt a health technology since the economical component is of extreme importance in a hospital adoption process.

Another important improvement for future work will be to streamline and optimize the participatory process, in order to reduce the time gap between meetings and the number of sessions necessary to create. Furthermore, it is also important to improve and develop decision support tools, like the WisedOn software, allowing more functionalities, in order to expedite contact with decision-makers in future studies and works that will use this decision support system.

Besides, and as already mentioned by the decision-makers themselves as a final comment to this project, it would be interesting that, in an upcoming study (an extension of this project), the number of biomarkers under study was reduced, for a more in-depth analysis, where more evidence would be available. Nevertheless, this

project was considered of extreme importance since it served as a first filter to identify the most valuable emerging biomarkers for the HER2+ breast cancer disease.

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