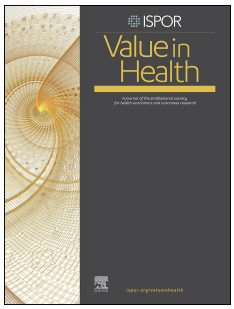
# Journal Pre-proof




A Systematic Review of Value Criteria for Next-Generation Sequencing/ Comprehensive Genomic Profiling to Inform Value Framework Development

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**TITLE**

# A Systematic Review of Value Criteria for Next-Generation Sequencing/Comprehensive Genomic Profiling to Inform Value Framework Development

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**Highlights section:**

- Value frameworks play a crucial role in enhancing transparency and facilitating informed decision-making within the healthcare system. They serve as valuable guides, highlighting key dimensions that need evaluation when assessing various healthcare technologies.
- IECS (Institute for Clinical Effectiveness and Health Policy) recently developed a value framework for diagnostic technologies, based on a targeted systematic review and a participatory process with HTA stakeholders in Latin America.

- In this paper we report a systematic review to update the previous framework and develop an comprehensive evidence based list of criteria and subcriteria that could be considered for creation of a NGS/CGP targeted value framework as well as a starting point for value frammeworks targeted to other health technologies

**TITLE**

# A Systematic Review of Value Criteria for Next-Generation Sequencing/Comprehensive Genomic Profiling to Inform Value Framework Development


## Abstract

**Objective:** To comprehensively identify and map an exhaustive list of value criteria for the assessment of Next-Generation Sequencing/Comprehensive Genomic Profiling (NGS/CGP), to be used as an aid in decision making.

**Methods:** We conducted a systematic review to identify existing Value Frameworks (VFs) applicable to any type of healthcare technology. VFs and criteria were mapped to a previously published Latin American -LA- VF (Augustovski et al., VIH 2021) to harmonize definitions and identify additional criteria and or subcriteria. Based on this analysis, we extracted a comprehensive, evidence-based list of criteria to be considered in the design of an NGS/CGP VF.

**Results:** A total of 42 additional VFs were compared to the LA VF, 88% were developed in high-income countries, 30% targeted genomic testing and 16% specifically targeted oncology. A total of 242 criteria and subcriteria were extracted; 227 (94%) were fully/partially included in the LA VF; 15 (6%) were new. Clinical benefit and economic aspects were the most common criteria. VFs oriented to genomic testing showed greater overlap with the previous VFs. Considering all criteria and subcriteria, a total of 18 criteria and 36 individual sub-criteria were identified.

**Conclusion:** Our study provides an evidence-based set of criteria and subcriteria for healthcare decision-making useful for NGS/CGP. The resulting list can be beneficial to inform decision making and will serve as a foundation to co-create a multi-stakeholder NGS/CGP VF that is aligned with the needs and values of health systems and could help to improve patient access to high value technologies.


**Keywords: Value framework, HTA, Systematic Review, Diagnostic, NGS, CGP**

## Introduction

Value frameworks, or value assessment frameworks (VF) transparently and explicitly define the individual dimensions and criteria that are important in a decision-making process and often reflect the preferences or values of the different actors involved in their construction and use. In the context of healthcare, they provide an indication of which factors are most important, and by extension less important, in assessing the value of a health intervention. The scope, role, and application of VFs in healthcare has been highly variable. While drugs and therapeutic technologies have been the primary target of VFs, there are numerous examples of "generic" VFs used for the evaluation of a range of different health technologies (such as the Genetic testing Evidence Track Tool [GETT][1], UK Genetic Testing Network [UKGTN][2], ACCE model[3] framework among others). Due to the complexity and specificities of different contexts, VFs have been increasingly developed in the last one or two decades. Some VFs have been developed on a worldwide scale, but there are also regional or country-specific VFs, or even frameworks aimed at decision-making in specific health conditions (e.g. oncology) or in specific settings (e.g.patient-centred decisions).[4,5]

Collaborative and multi-stakeholder frameworks (encompassing regulatory bodies, academia, patient organizations, and pharmaceutical companies) could expedite and standardize data collection for the purpose of evaluating potential benefits, risks, economic value, among other criteria, in the context of health.[6]

Next-Generation Sequencing/Comprehensive Genomic Profiling (NGS/CGP) are high-throughput sequencing technologies that enable rapid analysis of DNA and RNA. These tests allow for broad genomic profiling evaluations, whole exome sequencing (WES) or whole genome sequencing (WGS). NGS/CGP technologies have transformed the way we use genetic data in healthcare by allowing the rapid generation of large amounts of sequence data. This has spurred developments in various domains, including genetics, genomics, transcriptomics, epigenetics, metagenomics, and personalized medicine (PM).[7] In the latter domain, PM has enabled the detection of somatic driver mutations, allowed resistance mechanisms to be defined, facilitated quantification of mutational burden, and detected germline mutations. In the context of PM, there is a need to build or adapt a value framework for the specificities of NGS/CGP to inform resource allocation decisions using evidence-based principles and values.

Previous studies have already emphasized the difficulty of evaluating diagnostic technologies, such as how to view them in the context of the patient's treatment pathway, or to be able to assess direct benefits at such an early stage within this context. NGS/CGP not only does not escape these difficulties, but new ones are also encountered, such as the real relationship between genetic alterations and diseases, simultaneous diagnosis of multiple diseases or the incidental finding of diseases and their possible impact. This is important, as these technologies are becoming more numerous and increasingly integrated into medical care (e.g. in oncology care pathways).Thus, constructing or adapting a precise value framework for implementing NGS/CGP becomes crucial. To accomplish this objective, resource allocation decisions concerning NGS/CGP must be strongly evidence-based, ensuring they align with the principles of evidence-based medicine Due to the dynamic nature of the field and the continuing emergence of new diagnostic tests and medicines, together with the infrastructure investment decisions that these technologies often require, there is growing uncertainty associated with the decision-financing point for NGS/CGP technologies. In this context, technology assessments can play an important role in facilitating informed coverage decisions. Taking into account that many generic VFs have been developed for specific diseases/conditions, they may not necessarily address the proper use of NGS/CGP.

In 2020, the Institute for Clinical Effectiveness and Health Policy (IECS) developed a Diagnostic Technology Value Framework aimed broadly at diagnostic test technologies for Latin American (Latam) decision-makers.[4] The IECS value framework consists of 15 criteria or domains (defined as a set of criteria or attributes that assist in defining the global value of particular health technologies) and a total of 21 sub-criteria or sub-domains (defined as different aspect or components “nested” within a criterion or domain, in cases where a dimension includes several different aspects) for assessing the value of a diagnostic technology. The previous targeted literature review and the specificity of this framework focused on diagnostic tests, as well as the wide variety of criteria and subcriteria- led us to consider this framework as a starting or reference VF. However, the framework addresses all types of diagnostic technologies, so it may not address the particular needs of genetic testing, and particularly NGS/CGP. Appendix Figure 1 shows Latam VF (IECS) criteria and subcriteria. Given the growing use of genomic testing worldwide, this project was undertaken to review and describe an extensive list of criteria and subcriteria for the further development of a new value framework for NGS/CGP technologies for decision-makers. In this diagnostic value framework, the value was mainly focussed on assessing the changes that

can be made to an existing treatment following a more accurate diagnosis. However, a VF for NGS/CGP demands a broader approach. For example, dealing the value of changes in a range of treatments, and also additional value, arising from the treatment possibilities for other potential patients in the future, by identifying the patients with the gene alterations that future treatments might target. Therefore, since NGS/CGP may be associated with more aspects of value it was necessary to approach the generation of a VF in a more comprehensive way. Using this broad approach it may also be relevant to a wider range of health technologies. So, we using the recent IECS framework as a starting VF, we performed a systematic review to define an updated exhaustive list of potential criteria or subcriteria.

The current project was co-led by IECS and the London School of Economics (LSE). In this paper, we present the results of the first stage of the project, which includes a systematic review of value frameworks used for the evaluation of NGS/CGP, a mapping of their criteria and subcriteria, and the development of a comprehensive list of non-overlapping value criteria and subcriteria (non-overlapping in this case is understood in a non-restrictive way, as criteria or subrcriteria that could be evaluated individually, even though some of them could be related to a lesser or greater extent.). This proposed list can not only serve as the starting point for the further development of a collaborative NGS/CGP value framework but also provides an important reference for future endeavors to develop value frameworks for these or other health technologies.[8] While this work provides a list of criteria that could be further contextualized to any jurisdiction, the next step of this project will include, using this exhaustive list as a starting point, to develop a NGS/CGP VF for Europe through a collaborative process that will include several consensus building rounds (i.e Delphi panel) with key stakeholders.

**Methods**

The methodology employed in this study consisted of three distinct stages. The initial stage encompassed a systematic literature review, during which various VFs were identified. Subsequently, in the second stage, a mapping exercise was conducted to ascertain the alignment of criteria and subcriteria between the identified VFs through the systematic literature review (SLR) and the original Latam VF.

In the last stage, the entire author team collaboratively addressed the discrepancies that arose during the mapping, leading to the final integration and inclusion of the new criteria/sub-criteria in the original IECS VF. A detailed explanation of each step is presented below. The outcome of this study was the development of a comprehensive list of potentially relevant and mutually exhaustive criteria and sub-criteria.

***First stage: Systematic review***

Contemplating that many domains of interest can be addressed not only by value frameworks targeting genetic testing but also by generic frameworks, our systematic review employed a threefold approach to comprehensively identify available value frameworks, without any language restriction. Firstly, we updated the previous SLR search strategy applied to the original IECS´s VF[4], extending the search from 2018 to October 2022. This step aimed to capture more recent value frameworks associated with diagnostic technologies, encompassing both genetic and non-genetic diagnostics. Secondly, we added an extensive literature search across MEDLINE and EMBASE, also until October 2022. This was a tailored-sensitive search strategy, focusing on value frameworks and genomic tests, specifically Next-Generation Sequencing (NGS) and Comprehensive Genomic Profiling (CGP) technologies. In this component, we did not include an initial publication date. Thirdly, in order to identify any value frameworks possibly overlooked by the previous two components, we performed a specific search using the term value framework without date restriction. More detail of the search strategy can be seen in the Supplementary Material (S1).

To augment our search, we supplemented it by exploring grey literature, with the aim of detecting VFs from key health technology assessment agencies from diverse countries, and scientific societies, and embraced the utilization of general search engines.

Study screening and selection were performed independently by two reviewers from the research team. Disagreements were resolved by consensus of the entire review team. All phases of study selection were performed using COVIDENCE®[9,10], a web-based platform designed for the systematic review process. The eligibility criteria were defined to capture both generic and targeted frameworks that could be used to assess NGS/CGP technologies. This included: a) generic value frameworks aimed at health technologies; b) value frameworks aimed more specifically at

genomic tests; c) value frameworks aimed more specifically at diagnostic tests (genomic or otherwise); and d) value frameworks specifically targeting NGS or CGP technologies. Studies were considered if they included at least two value criteria.

Data extraction was performed independently by reviewers from the research team and discrepancies were resolved by consensus of the entire team. In the case of studies with several publications, the main study was considered as the main reference and the evidence was supplemented with data from the grey literature for completeness. For each of the frameworks surveyed, the criteria and sub-criteria that make up the framework, the reference framework, the region, the area of use, the scope, and the perspective (the recommended context of use) were extracted.

***Second stage: Mapping***

Once data from all included VFs had been extracted, the similarities and differences between these frameworks and the IECS framework were assessed. In order to perform this mapping, we assessed the degree of inclusion of each criterion and subcriteria of all included value frameworks, using a four-category scale: fully included (criteria or subcriteria that were considered to be fully captured by the IECS framework), partially included, not included, and methodological criteria (those that are part of the methodology for conducting an evaluation, but not as a particular final criterion or subcriterion that can be used to assess value - one example can be how to determine the population to be included in the assessment). The mapping was performed by two researchers and any discrepancies were discussed with the research team. Criteria and sub-criteria were considered as separate units and were matched against the IECS value framework independently. In turn, a comparative analysis of the criteria-subcriteria included according to the scope of application of VF, the perspective of VF, and the therapeutic area of VF was performed.

***Third stage: Integration of the criteria/subcriteria***

Upon completion of the search for value frameworks and the execution of criteria/sub-criteria mapping, the selection process encompassed those elements that exhibited partial overlap or no overlap at all with the criteria/sub-criteria of the IECS VF. This set of criteria/sub-criteria underwent independent evaluation by two distinct working groups—the IECS researchers and the LSE researchers' team—with the aim of discerning which among them should be included in the

value framework designed for the assessment of NGS/CGP. Any discrepancies were collectively resolved through a series of successive meetings involving the entire working team. Finally, those criteria/sub-criteria judged to be potentially relevant were incorporated into the final mutually exclusive list of criteria and subcriteria to be further assessed in a following step of the project by a panel of experts.

## Results

The review of peer-review literature yielded a total of 2067 non-duplicate records, of which 31 articles were identified for full-text review. Following full-text review, 18 articles were excluded: nine for not being value frameworks, three for the wrong outcome, three due to inadequate study design (e.g., systematic reviews, case studies), three for being a value framework out of scope (e.g., frameworks with only one criterion, non-health-oriented framework). A total of 13 studies were included from the grey literature, a further 16 studies were identified, of which, after evaluation, 13 met the inclusion criteria. Two of the grey literature studies surveyed were used to supplement the evidence extracted from two studies of VF in the literature from indexed journals, leading to a final 11 VF from the grey literature. An additional 19 studies were included from the previous literature search of the Augustovski *et al.* study, in which a total of 20 studies were identified.[4] One of the studies (a methodological manual) was excluded as the team considered that it did not meet the inclusion criteria for the present review. See Figure 1 for more information.

Figure 1. Study flow diagram. PRISMA 2020 flow diagram[11]

### *First stage: Systematic review*

43 VFs were extracted (including the IECS VF), all of which are listed in Table 1 below (more detailed information on the criteria/sub-criteria can be found in Supplementary Material (S3 Table 1).

Fifteen were developed in the USA, followed by five developed for all of Europe, four developed worldwide, four in Canada, four in the United Kingdom, three in Australia, two in Germany, and two in Latin America. One framework was developed in Spain, Brazil, and Iran. One framework did not refer to its country/region.

In terms of scope, fourteen (32.5%) of the frameworks were designed to evaluate general diagnostic tests, thirteen (30.2%) frameworks were developed to evaluate genomic tests, twelve (27.9%) were general frameworks, and only four (9.3%) frameworks were designed for the evaluation of medicines.

In terms of therapeutic area, twenty-nine (67.4%) of the frameworks were developed for any health condition, seven (16.3%) for oncology, and two (4.7%) for rare diseases. Only one framework was developed strictly for genetic diseases, independent of any disease area. Two frameworks (4.7%) did not specify the target therapeutic area, while the other two focused on other areas of use.

Thirty-five VF (81.4%) were *de novo* developed frames where no other frameworks were considered as a reference. Only eight VF (18.6%) remarked that they used other frameworks as references. The ACCE, EGAPP, and USPSTF frameworks were referenced most frequently.[3,12,13]

The perspective of the use of the frameworks was mainly for use in technology assessment agencies, with twenty-four VF developed in this context (55.8%), followed by seven (16.3%) for use in professional societies, five (11.6%) for use in ministries of health, two (4,7%) for hospitals and only one framework was designed for use from a patient perspective. Table 1 shows the total number of studies per category extracted.

***Second stage: Mapping***

Mapping of criteria and subcriteria was undertaken following completion of data extraction. We used the IECS VF as the reference framework and we mapped the rest of the VFs to find commonalities and differences. When including all criteria and subcriteria from each of the 42 frameworks (excluding the IECS VF), a total of 242 individual criteria and subcriteria were retrieved. Of these, 200 criteria and subcriteria were fully captured within the IECS framework, 8 were partially captured, 15 were new, and 19 were non-final criteria or values and referred to methodological aspects (See Figure 2).

**Figure 2.** Scheme of the methodology and general results of the mapping (non-overlapping criteria and subcriteria).

When we mapped the forty-two VFs with the IECS VF, they had at a minimum 2 shared criteria and a maximum of 10 shared criteria. The most frequently included criteria within the 43 VF were clinical benefit (n=40) and economic aspects (n= 34). Other commonly occurring criteria included non-clinical benefit (n=22), safety (n=19) and organizational impact (n=17). Less frequently included criteria were absence of alternative diagnostic technologies (n=3), environmental impact (n= 2) and priority in the health system (n=1). Table 2 displays the 42 FVs categorized by scope,

denoting their respective application areas and the intended perspectives they were designed for. Each criterion aligning with the IECS FV is marked with a checkmark, while those criteria not aligning are marked with a hyphen.

Sub-analysis on the criteria included within identified VFs was conducted based on VF scope, perspective, and therapeutic area (See Figure 3). In terms of scope, both similarities and differences in the criteria included are present between generic frameworks, diagnostic frameworks, genomic frameworks, and medicines frameworks. Most of the frameworks assessed included clinical benefit and economic aspects criteria, regardless of VF scope. Medicines frameworks had a high frequency of including safety (100%) and disease burden (≈75%) relative to other framework scopes (25-30%). However, nonclinical benefits were included less frequently in drug frameworks. Value frameworks with a genomic scope had a higher frequency of including legal and ethical criteria (≈50% compared to ≈25% for other scopes) and organizational impact (≈50% compared to ≈0-12% for other scopes).

When examining the perspectives of the VFs, the findings revealed that they were developed for application in Health Technology Assessments (n=23), Ministry of Health (MoH) standpoint (n=4), professional societies (n=7), while a subset (n=8) did not specify their perspective.

There were no major differences between the criteria included across VF perspectives. Organizational impact was the most frequently included criteria within HTA frameworks (≈50% vs ≈12.5-25%). Non-clinical benefits were less frequently included in scientific society frameworks compared to the rest ≈12% vs. ≈50-60%).

In terms of therapeutic area, categories for sub-analysis included frameworks for all health conditions (n= 28), frameworks for oncology (n= 7) and frameworks for others (n= 7). Frameworks designed for a specific therapeutic area that is not oncology were grouped into a single “other” category given small sample size. Inclusion of criteria was generally similar across the three therapeutic area groups. However, the oncology-oriented frameworks generally evaluated fewer criteria (mainly clinical benefit, safety, economic evaluation, and to a lesser degree, disease burden). Frameworks for all health conditions and frameworks for non-oncology therapeutic areas (“others”) included other criteria at a higher frequency, such as organizational impact (≈15% vs ≈40%-60%) and non-clinical benefits (0% vs ≈40-70%).

**Figure 3.** Analysis of the criteria considered according to different VF categories (scope, perspective, and area)

***Third stage: Integration of the criteria/subcriteria***

A total of 15 criteria/sub-criteria were identified that did not overlap with any of the criteria/sub-criteria in the original IECS framework (See Supplementary Material S4. Table 2 contains more information about these criteria/subcriteria). Out of these, 4 were deemed irrelevant for this study after reaching consensus with the entire team. Finally, 2 were included as additional criteria ('Public health/population benefit', 'Quality assurance/quality improvement program'), and 7 as sub-criteria ('Technical aspects', 'Fear of contagion', 'Real option value', 'Research priorities', 'Risk of overutilization', 'External pressures', 'Degree of investment in research and development'). On the other hand, out of the 9 criteria/sub-criteria that partially matched the original IECS value framework criteria, after team consensus, it was decided to include 8 as sub-criteria ('Test for disadvantaged or underserved communities', 'Test for rare diseases', 'Equity in health financing', 'Impact on education', 'Impact on career', 'Impact on stigma', 'Effective access to the test and subsequent treatment').

It's important to highlight that after team discussion, a consensus was reached to add the sub-criterion 'Safety and Data Governance', given the significance of patients being owners of their own information. Additionally, a criterion labeled 'Other' was introduced to encompass certain sub-criteria that weren't well-defined under other main criteria but hold importance within this context.

Table 3 shows the final list of non-overlapping and potentially relevant criteria and subcriteria, proposed for further contextualization exercises such as the upcoming next phase of the project consisting of a VF co-creation for Europe with consensus building activities with key stakeholders , or other VF design initiatives. This final list ontains 18 criteria and 36 sub-criteria.

## Discussion

The systematic review unveiled a total of 42 value frameworks, encompassing a collective sum of 242 individual criteria and subcriteria (when including overlap). Among these, 15 criteria were not encompassed in the original lECS framework. Most of these frameworks were conducted from a health technology assessment (HTA) perspective and targeted all health conditions and technologies. The vast majority of the frameworks adequately addressed both clinical benefit and economic endpoints. Safety, another very common criterion, was not universally addressed in the frameworks evaluated. This may be in part because the search was oriented to value frameworks for diagnostic/genomic tests, technologies in which it may be less important compared to frameworks oriented towards medicines evaluation.

There are inherent tensions and trade-offs among the usefulness, applicability, and precision of different value frameworks. For rapid and general decision-making, generic VF are probably preferred by decision-makers, but they have the downside of being less fit for purpose when targeting more specific technologies such as diagnostic tests, genetic/genomic tests, or particular disease populations such as oncology patients.

As previously stated, the evaluation of diagnostic tests presents inherent complexities compared to other medical technologies. Amongst diagnostic health technologies genomic panel tests, such as Next-Generation Sequencing, introduce additional intricacies. Frequently, there is a significant gap between the utilization of these tests and the subsequent emergence of their derived benefits. This situation makes it intricate to ascertain their genuine advantages.

Despite our review having identified thirteen frameworks specifically designed for the evaluation of genomic profiling, none of them were explicitly tailored to technologies like NGS/CGP, which facilitate the simultaneous assessment of numerous genes.

Within the criteria and subcriteria of genomic testing value frameworks, we found specific criteria that warrant further consideration, such as analytical validity or penetrance. While these criteria could conceivably be taken into account within the patient's clinical pathway, it is pertinent to explicitly contemplate the potential importance of incorporating these types of criteria and subcriteria. However, frameworks like ACCE and EGAPP, some of the earliest frameworks and foundations for subsequent frameworks, fail to address the unique challenges posed by broad

genomic panels such as Whole Exome Sequencing (WES) or Whole Genome Sequencing (WGS).[12,54] This raises the question of whether specific genomic testing criteria suffice in this context. Another interesting aspect to highlight is that these frameworks pay more attention to ethical and legal aspects relative to other frameworks. One issue that necessitates consideration in these cases pertains to incidental findings. Such findings hold relevance in the context of NGS/CPG, as large-scale genomic testing may reveal genomic alterations associated with diseases unrelated to the specific pathology for which the tests were conducted, thereby having substantial clinical ramifications.[55,56] In many instances, it becomes necessary to determine what information should be communicated to patients and how it ought to be conveyed. While the incorporation of these specific considerations may not suffice in conferring complete value to these technologies, it nevertheless represents a step in the right direction.

Although in this study we do not consider how each of the criteria of the framework is technically evaluated, and if and how are they weighted in a deliberative or quantitative way, it is important to understand that NGS/CPG may present particular difficulties.[57] For example, for economic evaluation, the choice of comparator, the time and type of analysis, and the structure of the model may be particularly challenging. Additional challenges are present for the evaluation of clinical benefit in the clinical (PICO) question. Normally, in the evaluation of a diagnostic technology, the relationship of a test to its treatment can be established, while in this case there may be multiple associated therapeutic interventions.[58]

This review serves as an initial step in the development of a value framework specifically adapted to CGP/NGS . Additionally, our study, which provides a unique evidence base set of non overlapping value criteria and subcriteria, can also help to inform future value framework initiatives. Despite the identification of numerous value frameworks, none are expressly designed for wide-range gene panels, and only thirteen of these are designed for general genomic testing. Consequently, our understanding of the specific areas requiring evaluation in the context of NGS/CGP technology remains limited. Nevertheless, we strongly believe that this study serves as a starting point for establishing criteria values for these novel and innovative technologies.

This paper has strengths and limitations. Some limitations that warrant consideration. Notably, the initial process of mapping criteria and sub-criteria of all included VF was undertaken by the research team, drawing from the LATAM value framework. Such a process involved qualitative

research methods and it inherently involves an element of interpretation. Although we followed a rigorous qualitative process and the final decision regarding the inclusion, definition and grouping of criteria and subcriteria involved all the researchers from both institutions, there exists the potential for the omission of criteria that could hold substantial significance for others. Moreover, the act of mapping, inherently tied to a specific framework, can limit the distinctions among the appraised frameworks. For instance, while two distinct frameworks assessing different facets of clinical benefit, they were subsumed under the overarching criteria of clinical benefit, and their individual disparities were not delineated and carried forward. Regarding our study strengths, foremost among these is the comprehensive incorporation of diverse scopes, perspectives, and domains for which the frameworks under study were formulated. This inclusive approach affords a more comprehensive and holistic understanding of the intrinsic values attributed to healthcare technologies. Furthermore, while the principal focus of this study pertains to NGS/CGP technologies, the search strategy extended beyond this domain, thereby encompassing criteria germane to alternative technological realms, including general diagnostic technologies. The resultant synthesis of these broader criteria lends added relevance to the assessment of NGS/CGP technologies.

## Conclusion

Our study establishes a robust set of evidence-based criteria and subcriteria to inform healthcare decision-making in the realm of NGS/CGP genomic testing. This set of criteria will form the cornerstone for the multi/stakeholder collaborative development of NGS/CGP Value Framework in Europe, and can also help to inform future value framework initiatives. This holds the potential to drive meaningful advances in patient health outcomes and access and help to address some of the current healthcare system challenges.

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**Table 1.** Value frameworks identified

| Author | Year | Region | Scope | Target area of use | Reference framework | Perspective |
|---|---|---|---|---|---|---|
| Augustovski et al[4] | 2021 | Latin America | Diagnostic technology | All health conditions | No | HTA |
| CDC[3] | 2000-2004 | USA | Diagnostic technology | All health conditions | No | Professionals Society |
| Angelis et al[14] | 2017 | UK | General framework | All health conditions | No | HTA |
| Pearson et al /ICER [15,16] | 2018/ 2020-2023 | USA | General framework | All health conditions | No | HTA |
| ASCO[17] | 2016 | USA | Drugs framework | Oncology | No | Professionals Society |
| CampolinaI et al[18] | 2022 | Brasil | Drugs framework | Oncology | No | Hospital |
| DosReis et al [19] | 2020 | NM | General framework | All health conditions | No | Patients |
| Harris et al [20] | 2015 | USA | Diagnostic technology | Oncology | No | Professionals Society |
| Merlin et al [21] | 2013 | Australia | Genetic test | Oncology | No | MoH |
| Shams et al [22] | 2022 | Iran | General framework | All health conditions | No | MoH |
| Rogowski et al [23] | 2015 | Germany | Genetic test | Unspecified | No | Other |
| Garrison et al Lakdawalla et al [24,25] | 2018 | International | General framework | All health conditions | No | HTA |
| Pichon-Riviere et al[26] | 2019 | Latin America | General framework | All health conditions | No | HTA |
| Giacomini et al[27] | 2003 | Canada | Genetic test | All health conditions | No | MoH |
| MSAC. Medical Services Advisory Committe[28] | 2021 | Australia | General framework | All health conditions | USPSTF | HTA |
| Anonychuck et al[29] | 2012 | Australia | Diagnostic technology | All health conditions | No | Hospital |
| NICE[30] | 2022 | UK | General framework | All health conditions | No | HTA |
| Teutsch et al[12] | 2009 | USA | Genetic test | All health conditions | No | MoH |
| INESS[31] | 2022 | Canada (Quebec) | Diagnostic technology | All health conditions | No | HTA |
| IQWIG[32] | 2017 | Germany | General framework | All health conditions | No | HTA |
| AdvaMed[33] | 2017 | USA | Diagnostic technology | All health conditions | No | HTA |
| Medtech[34] | 2019 | Europe | Diagnostic technology | Other | No | Other |
| Frueh et al[35] | 2014 | USA | Diagnostic technology | All health conditions | No | HTA |
| Palmetto GBA [36] | 2011 | USA | Genetic test | All health conditions | No | Other |
| Mann et al [37] | 2010 | UK | Diagnostic technology | Other | No | Professionals Society |
| Canestaro et al [38] | 2015 | International | Diagnostic technology | Oncology | No | HTA |
| Lee et al [39] | 2010 | International | Diagnostic technology | All health conditions | No | HTA |
| EUnetTHA[40] | 2015 | Europe | Diagnostic technology | All health conditions | No | HTA |

| | | | | | | |
|---|---|---|---|---|---|---|
| Blancquaert et al [41] | 2007 | Canada | Genetic test | All health conditions | ACCE | HTA |
| Calonge et al [42] | 2003 | USA | Genetic test | Rare deseases | ACCE y EGAPP | Professionals Society |
| Rousseau et al, GETT (Genetic testing Evidence Tracking Tool)[1] | 2010 | International | Genetic test | All health conditions | ACCE y UKGTN | HTA |
| Severin et al (Eurogentest Evaluation Model)[43] | 2015 | Europe | Genetic test | All health conditions | No | Other |
| UKGTN (The United Kingdom Genetic Testing Network)[2] | 2002 | United Kingdom | Genetic test | All health conditions | ACCE | HTA |
| Fryback and Thornbury [44] | 1991 | USA | Diagnostic technology | All health conditions | No | Professionals Society |
| Annemans et al[45] | 2017 | Europe | Drugs framework | Rare deseases | No | HTA |
| Garrison et al[46] | 2016 | Europe | Diagnostic technology | All health conditions | No | HTA |
| InformedDNA[47] | 2019 | USA | Genetic test | Genetic conditions | EGAPP/USPSTF | HTA |
| Krahn et al [48] | 2007 | Canada | General framework | Unspecified | No | HTA |
| Harris et al [49] | 2001 | USA | Diagnostic technology | All health conditions | No | Professionals Society |
| Shah-Manek [50] | 2017 | USA | General framework | Oncology | No | HTA |
| AHRQ (Agency for Helathcare Research and Quality) [51] | 2011 | USA | Genetic test | All health conditions | EGAPP | HTA |
| Calderón et al [52] | 2006 | Spain | Genetic test | All health conditions | UK Genetic Testing Network | HTA |
| Memorial Sloan Katherine Hospital [53] | NM | USA | Drugs framework | Oncology | No | Other |

***Abbreviations: HTA:*** *Health Technology Agency,* ***EGAPP:*** *Evaluation of Genomic Applications in Practice and Prevention,* ***USPSTF:*** *U.S Preventive Services Task Force.*

**Table 2.** Characteristics of the frameworks reviewed and their overlap with the IECS framework.

| Source | Target area of use | Perspective | Clin | Safe | Qual | Econ | Org | Priorr | Burd | Equi | EthL | Seve | Alter | Non-C | Envi | Soc | Inno | Other |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Diagnostic technology** | | | | | | | | | | | | | | | | | | |
| Fryback et al [44] | All conditions* | PS | ✓ | ✓ | - | ✓ | - | - | - | - | - | - | - | ✓ | - | - | - | - |
| ACCE[54] | All conditions | PS | ✓ | ✓ | ✓ | ✓ | - | - | ✓ | - | ✓ | - | - | - | - | ✓ | - | - |
| Canestaro et al[38] | Oncology | HTA | ✓ | - | - | ✓ | - | - | ✓ | - | - | - | - | - | - | - | - | - |
| EUnetTHA[40] | All conditions | HTA | ✓ | ✓ | - | ✓ | ✓ | - | ✓ | ✓ | - | ✓ | - | ✓ | ✓ | - | - | - |
| Frueh et al[35] | All conditions | HTA | ✓ | - | - | ✓ | - | - | - | - | - | - | - | - | - | - | - | - |
| Garrison et al[24] | All conditions | HTA | ✓ | - | - | ✓ | - | - | - | - | - | - | - | ✓ | - | - | ✓ | - |
| Harris et al[49] | All conditions | PS | ✓ | ✓ | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Harris et al[20] | Oncology | PS | ✓ | - | - | ✓ | - | - | - | - | - | - | - | - | - | - | - | - |
| Lee et al[39] | All conditions | HTA | ✓ | - | - | - | - | - | - | - | - | - | - | ✓ | - | - | - | - |
| Mann et al[37] | Other | PS | ✓ | - | - | ✓ | ✓ | - | - | ✓ | - | - | - | - | - | - | - | - |
| Anonychuck et al[29] | All conditions | Hospital | ✓ | ✓ | - | ✓ | ✓ | - | - | - | ✓ | - | - | ✓ | ✓ | ✓ | - | - |
| Medtech[34] | Other | Other | - | - | - | ✓ | ✓ | - | - | - | - | - | - | ✓ | - | - | - | - |
| **Drugs Framework** | | | | | | | | | | | | | | | | | | |
| Annemans et al[45] | Rare diseases | HTA | ✓ | ✓ | ✓ | ✓ | ✓ | - | ✓ | - | - | ✓ | - | ✓ | - | ✓ | ✓ | - |
| ASCO[17] | Oncology | PS | ✓ | ✓ | - | ✓ | - | - | - | - | - | - | - | - | - | - | - | - |
| CampolinaI et al[18] | Oncology | Hospital | ✓ | ✓ | - | ✓ | - | - | ✓ | - | - | - | - | - | - | - | - | - |
| MSK[53] | Oncology | Other | ✓ | ✓ | - | ✓ | - | - | ✓ | ✓ | - | - | ✓ | - | - | ✓ | ✓ | ✓ |
| **General framework (drugs and other)** | | | | | | | | | | | | | | | | | | |
| NICE[30] | All conditions | HTA | ✓ | - | - | ✓ | - | - | - | - | - | - | - | ✓ | - | - | - | - |
| IQWIG[32] | All conditions | HTA | ✓ | - | - | ✓ | ✓ | - | - | - | ✓ | - | - | ✓ | - | ✓ | - | - |
| AdvaMed[33] | All conditions | HTA | ✓ | ✓ | - | ✓ | ✓ | - | - | - | - | - | - | ✓ | - | - | - | - |
| Krahn et al[48] | Unspecified | HTA | ✓ | ✓ | - | ✓ | - | - | - | ✓ | ✓ | - | - | - | - | - | - | - |
| Angelis et al[14] | All conditions | HTA | ✓ | ✓ | - | ✓ | - | - | ✓ | ✓ | - | - | ✓ | ✓ | - | ✓ | ✓ | - |
| MSAC[28] | All conditions | HTA | - | - | - | ✓ | ✓ | - | - | - | - | - | - | - | - | - | - | - |

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DosReis et al[19] | All conditions | Patients | ✓ | ✓ | - | ✓ | - | - | ✓ | - | - | ✓ | - | ✓ | - | ✓ | ✓ | - |
| ICER[15,16] | All conditions | HTA | ✓ | - | - | ✓ | - | - | - | - | - | - | - | ✓ | - | ✓ | ✓ | - |
| Lakdawalla et al[25] | All conditions | HTA | ✓ | - | - | ✓ | - | - | - | ✓ | - | ✓ | - | ✓ | - | ✓ | ✓ | ✓ |
| NCCN[50] | Oncology | HTA | ✓ | ✓ | ✓ | - | ✓ | - | - | - | - | - | - | - | - | - | - | - |
| Pichon-Riviere et al[26] | All conditions | HTA | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | - | ✓ | - | - | - | - | ✓ | - |
| Shams et al[22] | All conditions | MoH | ✓ | - | - | ✓ | - | - | - | ✓ | - | - | - | ✓ | - | - | - | ✓ |
| Teutsch et al[12] | All conditions | MoH | ✓ | - | ✓ | - | - | - | - | - | - | - | - | - | - | - | - | - |
| **Genetic test** | | | | | | | | | | | | | | | | | | |
| AHRQ [49] | All conditions | HTA | ✓ | ✓ | - | - | ✓ | - | - | - | ✓ | - | - | - | - | - | - | - |
| Blancquaert[41] | All conditions | HTA | ✓ | - | - | - | ✓ | - | - | - | - | - | - | ✓ | - | - | - | - |
| INESS[31] | All conditions | HTA | ✓ | - | - | ✓ | ✓ | - | - | - | ✓ | - | - | ✓ | - | - | - | - |
| Calderón et al[52] | All conditions | HTA | ✓ | ✓ | - | ✓ | - | - | - | ✓ | ✓ | - | - | - | - | - | - | - |
| Calonge et al[42] | Rare deseases | PS | ✓ | - | - | - | - | - | - | - | - | - | - | - | - | ✓ | - | - |
| Eurogentest [...][43] | All conditions | Other | ✓ | - | - | ✓ | - | - | ✓ | - | - | - | - | ✓ | - | - | - | - |
| GETT [1] | All conditions | HTA | ✓ | - | - | ✓ | ✓ | - | ✓ | - | ✓ | - | - | ✓ | - | - | - | ✓ |
| Giacomini et al[27] | All conditions | MoH | ✓ | - | - | ✓ | ✓ | - | - | - | - | - | - | ✓ | - | ✓ | - | - |
| InformedDNA[47] | Genetic | HTA | ✓ | ✓ | - | ✓ | ✓ | - | ✓ | ✓ | ✓ | ✓ | - | ✓ | - | - | - | ✓ |
| Merlin et al[21] | Oncology | MoH | ✓ | - | - | ✓ | - | - | - | - | - | - | - | - | - | - | - | - |
| Palmetto GBA[36] | All conditions | Other | ✓ | ✓ | - | ✓ | - | - | - | - | ✓ | - | - | ✓ | - | - | - | ✓ |
| Rogowski et al[23] | Unspecified | Other | ✓ | - | - | ✓ | - | - | ✓ | - | - | ✓ | - | - | - | - | - | - |
| UKGTN [2] | All conditions | HTA | ✓ | - | - | - | ✓ | - | ✓ | - | ✓ | ✓ | ✓ | - | - | - | - | - |

***References: PS:*** *Profesional Society,* ***HTA:*** *Health Technology Agency,* ***Clin****: Clinical benefits and test performance;* ***Safe****: Safety and unwanted consequences;* ***Qual****: Quality of scientific evidence;* ***Econ****: Economical aspects;* ***Org****: Organizational aspects and feasibility within the clinical path;* ***Prior****: Health priority of the health system;* ***Burd****: Disease burden;* ***Equi****: Equity;* ***EthL****: Ethical and legal aspect;* ***Seve****: Severity of the disease;* ***Alter****: Absence of alternative diagnostic technologies;* ***Non-C****: non clinical benefits;* ***Envi****: Environmental impact;* ***Soc****: broader social impact;* ***Inno****: Innovation.*
***Note:*** **All conditions refer to ¨All health conditions¨*

Table 3. Final list of value criteria/sub-criteria and their definitions.

| Criteria | Definition | Sub-criteria | Definition |
|---|---|---|---|
| **Clinical Benefit and Test Performance** | Clinical benefits for people undergoing the test (better health or improvement in clinical outcomes derived from the use of this technology considering the perspective of the individual taking the test) and test performance | **Clinical consequences of test use** | Clinical consequences during the diagnostic or therapeutic process of carrying out the test (e.g., a change in the therapeutic approach that is associated to an improvement in the state of health becomes apparent from the test result) |
| | | **Test performance** | Evaluates the diagnostic yield of the test through indicators such as sensitivity, specificity, precision, and reproducibility |
| | | **Technical aspects** | Evaluates the stability and storage form of the reagents used to perform the tests. |
| **Safety and Unintended consequences** | Related to the adverse or unintended effects described for the test being assessed | **Procedure safety** | Unintended consequences in whom the test is being performed secondary to the performance of the test (e.g., injury to neighboring organs during biopsy) |
| | | **Consequences of wrong diagnosis** | Unintended consequences in whom the test is being performed secondary to the misdiagnosis (false positives and false negatives) |
| | | **Safety of test preparation** | Unintended consequences in whom the test is being performed secondary to the preparation for it (e.g., adverse events during bowel preparation for biopsy colonoscopy) |
| | | **Safety for test operators** | Unintended consequences in test operators (e.g. radiation exposure from taking tomography guided biopsies) |
| | | **Risk of overutilization** | Refers to the risk of overuse, or abuse, of genomic testing. (e.g: using the test in an individual, or a population, for reasons not specific to the patient's indication). |
| **Quality of scientific evidence** | How reliable the scientific evidence to be evaluated, as well as its results is; also the potential that different biases or systematic errors would not allow drawing valid conclusions. | | |
| **Economic aspects** | Assess how good the health investment in this diagnostic test (cost-effectiveness) is; what its financial or budget impact are, or other aspects such as impact on the out-of- pocket expenditure of the patient and his family | **Economic evaluation (Clinical effectiveness and/or Budget Impact Analysis)** | Comparison between costs and health results of two or more diagnostic options. Budget impact for the funder when incorporating the test (e.g., includes acquisition costs, maintenance, supplies, training) |
| | | **Other costs** | Patient and family out-of-pocket expenses, costs related to productivity loss, etc |

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| **Organizational aspects and Feasibility within the clinical path** | Related to the necessary actions taken by the organization of the system to implement the technology being evaluated so that it can reach the target population, also the feasibility of its implementation. It takes into account which place the test being evaluated occupies in the clinical path. | **Impact on the health service provision system** | Implementing the test requires modifications of buildings, processes, logistics, etc. within the organization providing health services |
| | | **Impact on the patient care path** | Implementing the test would be associated with less time in access to the benefit, additional studies, associated practices would be avoided, or the availability of resources would be increased |
| **Health system priorities** | Priority of this health problem (for the country or health system, defined by those who design health policies) | **Health priority within the health system** | Priority of this health problem (for the country or health system, defined by those who design health policies). |
| | | **Research priorities** | Priority for this technology and this disease in the current or future research agenda. |
| **Disease burden** | How important the loss of health, both in mortality and in quality of life is. This includes taking into account the pattern of inheritance, genomic heterogeneity, mutation prevalence, mutation penetrance and neomutation rate. | | |
| **Equity** | What consequences the implementation of the technology being evaluated would have on equity or inequalities in the system and health | **Test for neglected diseases** | Test oriented to the diagnosis of neglected diseases |
| | | **Test for communicable diseases and high prevalence** | Test oriented to the diagnosis of communicable diseases and/or of high prevalence in the region (e.g. HPV/cervical cancer) |
| | | **Test in populations with little access to health services** | Test considered situations where there is poor access to health services |
| | | **Test for disadvantaged or underserved communities** | Test oriented to the diagnosis of disadvantaged or underserved communities defined as those relevant communities that have been historically disadvantaged through discrimination, neglect, reduced research funding, or other factors. |
| | | **Test for rare diseases** | Test oriented to the diagnosis of rare neoplastic diseases. Defined as a disease that affects a small number of people compared to the general population. In Europe, the European Medicines Agency (EMA) considers a disease with a prevalence of less than five in 10,000 people (equivalent to less than one in 2,000) to be rare. |
| | | **Equity in health financing** | Equity in health financing by promoting health, especially in disadvantaged areas, and helping to meet catastrophic health expenditures |

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| **Ethical and legal aspects** | It considers relevant the social and moral norms and values that derive from the technology in question. It implies an understanding of the consequences of implementing or not implementing a sanitary technology in two aspects: with respect to the values that prevail in the society and with respect to the norms and values that the same technology constructs when it is put into use | | |
| **Severity of the disease** | It takes into account the risk of mortality, the risk of disability (and its severity), the quality of life, and the duration of type of cancer. | | |
| **Absence of alternative diagnostic technologies** | There is no diagnostic technology available for that type of cancer, or stage, etc. | | |
| **Non-clinical benefits** | Non-clinical benefits (other benefits) for the people who take the test and other participants, as caregivers, family members, etc. It considers other benefits related to the use of the technology, which improve the experience of the test for those who undergo it and also of other participants, such as family members, caregivers, etc. comfort during preparation implementation practice | **Experience of who takes the test** | Experience of who takes the test / caregivers (comfort, invasiveness, preparation) |
| | | **Value of the information** | Value of the information provided by the test in special situations (e.g., end-of-life diseases, diseases with poor prognosis, diseases that affect offspring) |
| | | **Load on caregivers or family** | The test is associated with a lower burden on caregivers or the family of whom the test is performed (e.g., the result of the test results in a lower number of subsequent controls or avoids other unnecessary tests or associated procedures) |
| | | **Preparation and/or care** | Pre-preparation and / or care after the test (characteristics, need for completion) |
| | | **Number of results associated with the test** | Number of results associated with the sample (amount of information provided by the test with the sample obtained |
| | | **Test processing time** | Sample processing time (suitable for the disease / target population) |
| | | **Self test** | Self-test (whoever takes the test can do it himself or another person without the need for more training) |
| | | **Fear of contagion** | The early and correct diagnosis of an infectious diseases limits the spread the disease to others (e.g. HPV/cervical cancer). |

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| | | **Impact on education** | The impact of the diagnosis and treatment on one's education/schooling |
| | | **Impact on career** | The impact of the diagnosis and treatment on one's career |
| | | **Impact on stigma** | The impact on the person or the family or society of the diagnosis or treatment, generating embarrassment, self-consciousness, rejection by family or rejection by society. |
| **Enviromental Impact** | It is a measure that the production, use or implementation of technology would cause in the environment. Eg, technology is associated with a greater generation of toxic waste | | |
| **Broader Social Impact** | Impact on other sectors beyond health, such as job creation, industrial promotion, technology transfer, and society as a whole. | | |
| **Innovation** | The diagnostic test being evaluated uses new mechanisms or technologies that were not previously available or is a new test not known so far. | | |
| **Quality assurance/ quality improvement program** | Internal: What are the controls (positive or negative, normal or abnormal) and what are their origin (samples banking, cell lines)? Specify internal controls related to the analysis carried out and their limits. Are internal quality control procedures applied to the laboratory as a whole or specific to the test? Provide the rates of errors reported. Provide the type of standards (e.g., molecular weight markers) included in the analysis.<br><br>External: Identify the external quality control programs for this test and specify the type of programs to which you participate. What does this program cover (e.g., analytical aspects of the test or interpretation and reporting)? If no external QC program exists, which type of control do you make (e.g., blind tests, exchanges of various samples between laboratories). | | |

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| **Public health/ population benefit** | The public health/ population that this technology will bring when used for this health problem (e.g: detection of susceptible populations to improve their follow-up, screening uses) | | |
| **Others** | | **Bridge to other future treatments (¨Real option value¨)** | When a health technology extends life, creates opportunities for the patient to benefit from other future advances in medicine. |
| | | **External pressures** | This driver assesses external pressures for test coverage, imposed by providers, members of patient societies, society at large, laboratories and politicians for accelerating unwarranted adoption of tests before solid evidence exists. |
| | | **Degree of investment in research and development** | The number of human subjects enrolled in the approval trials for the first indication, was used as a proxy for the research and development costs necessary to develop the drug. |
| | | **Safety and data governance** | This indicator refers to the extent to which test results and their associated patient data are protected from unauthorized access, use, loss, or corruption. |
| | | **Effective access to the test and subsequent treatment** | Real life effective coverage/access to the test and eventual treatment |

***Note:*** *In black colour, the original criteria/sub-criteria of the IECS value framework are mentioned. In yellow are highlighted the criteria/sub-criteria that emerged from the systematic review, mapping; and integration as described in the methods and results section.*

Figure 1. Study flow diagram. PRISMA 2020 flow diagram

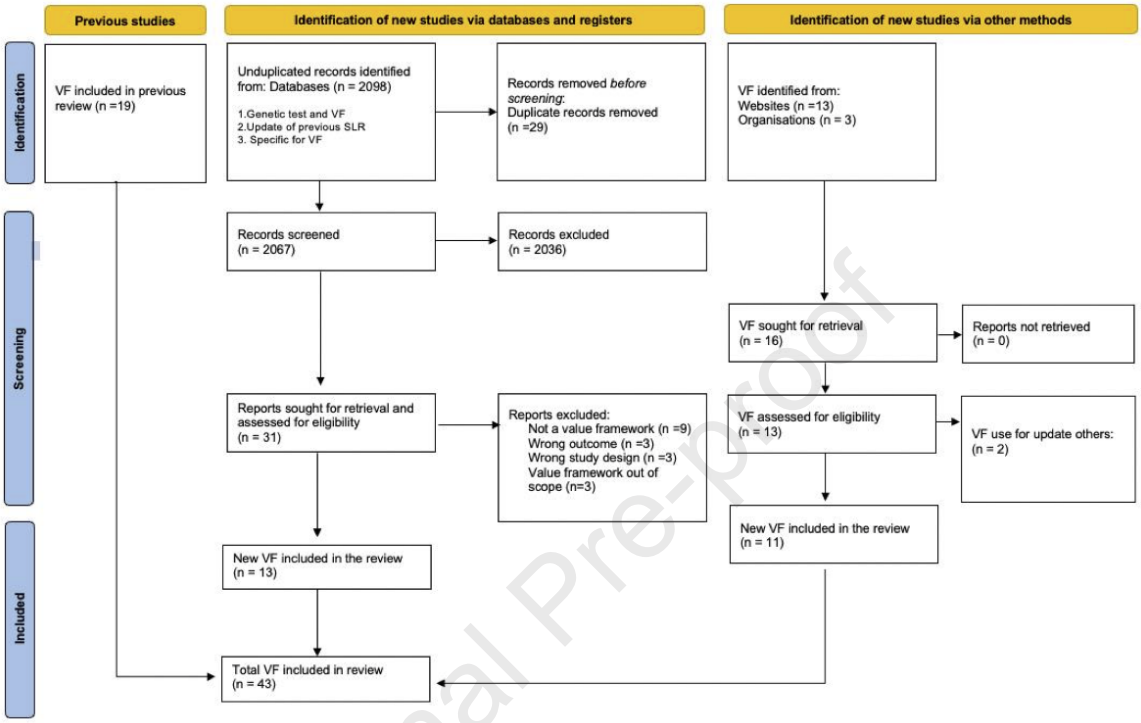


**Figure 2.** Scheme of the methodology and general results of the mapping (non-overlapping criteria and subcriteria).

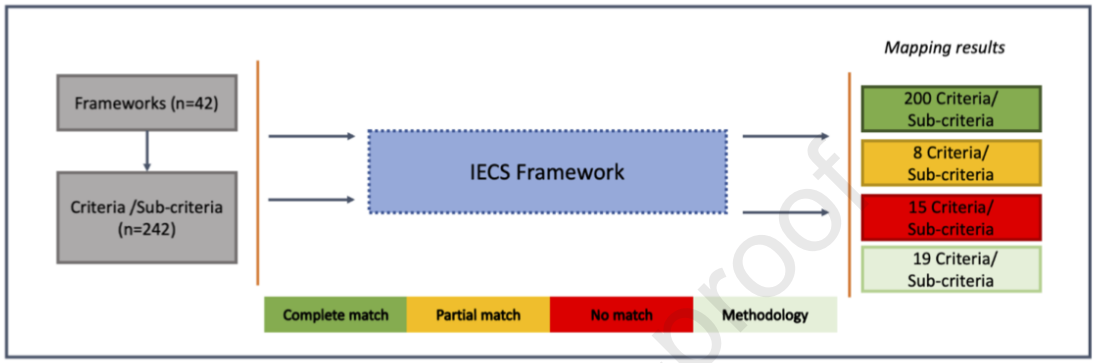
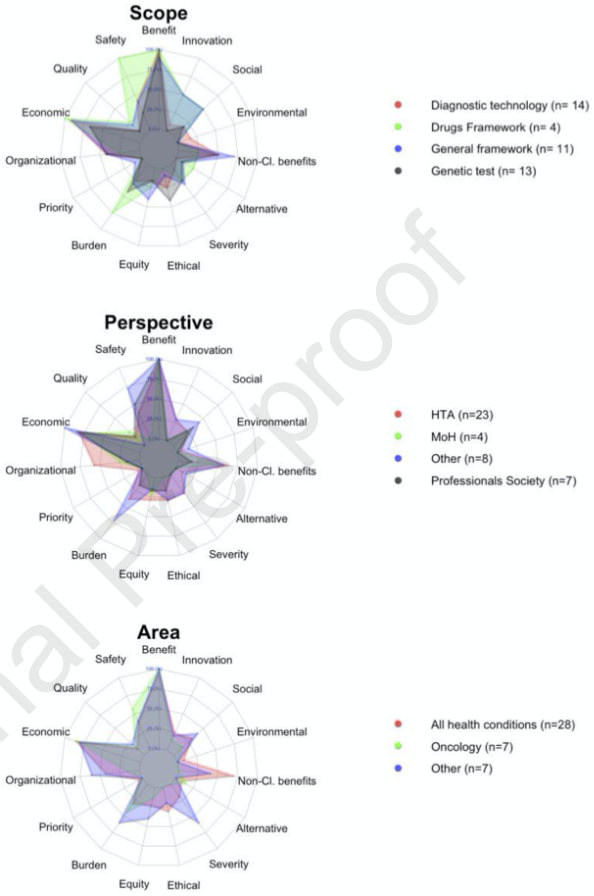


**Figure 3.** Analysis of the criteria considered according to different VF categories (scope, perspective, and area)




*Abbreviations:* ***Benefit****: clinical benefits and test performance;* ***Safety****:Safety and unwanted consequences;* ***Quality****: Quality of scientific evidence;* ***Economics****: Economical aspects;* ***Organizational****: Organizational aspects and feasibility within the clinical path;* ***Priority****: Health priority of the health system;* ***Burden****: Disease burden;* ***Ethical****: Ethical and legal aspect;* ***Severity****: Severity of the disease;* ***Alternative****: Absence of alternative diagnostic technologies;* ***Non-CL benefits****: non clinical benefits;* ***Enviromental****: Enviromental impact;* ***Social****: broader social impact;* ***HTA****: Health technology agency;* ***MoH****: Ministry of Health.*