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Systematic Literature Review

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

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ABSTRACT

Objectives: 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 to harmonize definitions and identify additional criteria and or subcriteria. Based on this analysis, we extracted a comprehensive, evidence-based list of criteria and subcriteria to be considered in the design of a NGS/CGP VF.

Results: A total of 42 additional VFs were compared with 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; and 15 (6%) were new. Clinical benefit and economic aspects were the most common criteria. VFs oriented to genomic testing showed significant overlap with other VFs. Considering all criteria and subcriteria, a total of 18 criteria and 36 individual subcriteria were identified.

Conclusions: Our study provides an evidence-based set of criteria and subcriteria for healthcare decision making useful for NGS/CGP as well as other health technologies. The resulting list can be beneficial to inform decision making and will serve as a foundation to co-create a multistakeholder 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: CGP, diagnostic, HTA, NGS, systematic review, value framework.

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Highlights

- 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.
- 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 health technology assessment stakeholders in Latin America.
- In this article, we report a systematic review to update the previous framework and develop a comprehensive evidence-based list of criteria and subcriteria that could be considered for creation of a next-generation sequencing/comprehensive genomic profiling-targeted value framework, as well as a starting point for value frameworks targeted to other health technologies.

Introduction

Value frameworks, or value assessment frameworks (VFs), 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 have been highly variable. Although 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 National Institute for Health and Care Excellence,[1] Medical Services Advisory Committee[2] or the ICER[3,4] VF). Because of the complexity and specificities of different contexts, VFs have been increasingly developed in the last decade or two. 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 (eg, oncology) or in specific settings (eg, patient-centered decisions).[5,6]

Collaborative and multistakeholder frameworks (with participation of regulatory and HTA bodies, academia, patient organizations, and pharmaceutical companies) could expedite and standardize evidence gathering for the purpose of evaluating potential benefits, risks, and economic value, among other criteria, in the context of health.[7]

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 or whole

genome sequencing. 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).[8] 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 VF 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 because these technologies are becoming more numerous and increasingly integrated into medical care (eg, in oncology care pathways). Thus, constructing or adapting a precise VF for implementing NGS/CGP becomes crucial. To accomplish this objective, resource allocation decisions concerning NGS/CGP must be strongly evidence based, ensuring that they align with the principles of evidence-based medicine. Because of 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 (LA) decision makers.[5] The IECS VF 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 subcriteria or subdomains (defined as different aspect or components "nested" within a criterion or domain, in cases which 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; therefore, it may not address the particular needs of genetic testing, and particularly NGS/CGP. Appendix Figure 1 in Appendix S1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.02.002 shows LA VFs (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 VF for NGS/CGP technologies for decision makers. In the IECS diagnostic VF, the value was mainly focused on assessing the information gains or the changes that can be made to an existing treatment after a more accurate diagnosis. However, a VF for NGS/CGP demands a broader approach. For example, dealing with the value of changes in a range of treatments, and also additional value, arising from the treatment possibilities for potential patients in the future by identifying the patients with the gene alterations that future treatments might target. Therefore, because 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 and further VF development. Therefore, we used the recent IECS framework as a starting VF, and we performed a systematic review to define an updated exhaustive list of potential criteria or subcriteria.

The project was co-led by IECS and the London School of Economics. In this article, we present the results of the first stage of the project, which includes a systematic review of VFs used for the evaluation of NGS/CGP, a mapping of their criteria and subcriteria, and the development of a comprehensive list of nonoverlapping value criteria and subcriteria (nonoverlapping in this case is understood in a non restrictive way, as criteria or subcriteria that could be evaluated individually, although 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 VF but also provides an important reference for future endeavors to develop VFs for these or other health technologies.[9] Although 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 (ie, Delphi panel) with key stakeholders.

Methods

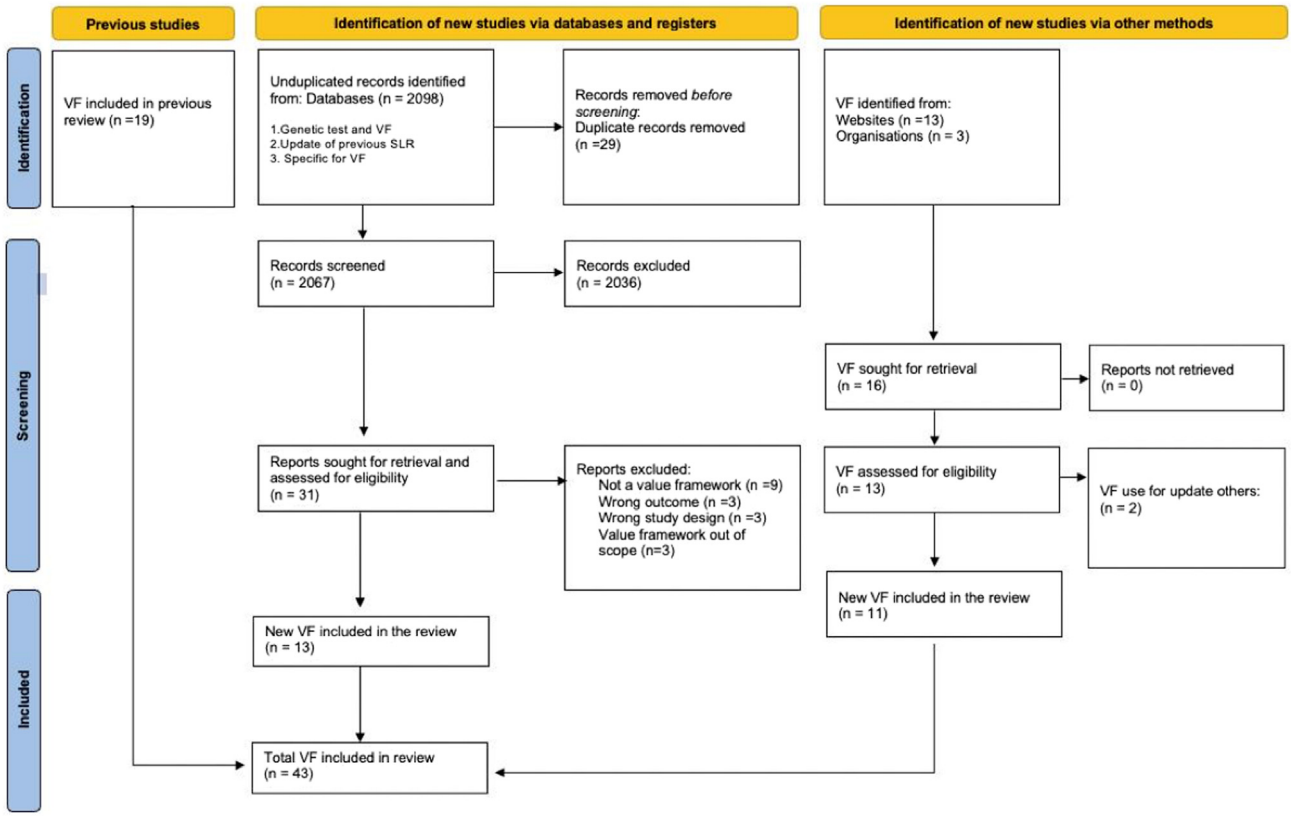
The methodology used in this study consisted of 3 distinct stages. The initial stage encompassed a systematic literature review, during which various VFs were identified. Subsequently, in the second stage, a mapping exercise was conducted to ascertain the alignment of criteria and subcriteria between the identified VFs through the systematic literature review and the original LA VF.

In the last stage, the entire team collaboratively addressed the discrepancies that arose during the mapping, leading to the final integration and inclusion of the new criteria/subcriteria in the original IECS VF in order to propose a new updated list of criteria and subcriteria. 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 subcriteria (ie, that could be operationally assessed independently, knowing there can oftentimes be some overlap among several criteria or subcriteria).

First Stage: Systematic Review

Contemplating that many domains of interest can be addressed not only by VFs targeting genetic testing but also by generic frameworks, our systematic review used a 3-fold approach to comprehensively identify available VF, without any language restriction. First, we updated the previous systematic literature review search strategy applied to the original IECS's VF,[5] extending the search from 2018 to October 2022. This step aimed to capture more recent VFs associated with diagnostic technologies, encompassing both genetic and nongenetic diagnostics. Second, we added an extensive literature search across MEDLINE and Excerpta Medica Database, also until October 2022. This was a tailored-sensitive search strategy, focusing on VFs and genomic tests, specifically, NGS and CGP technologies. In this component, we did not restrict by initial publication date. Third, to identify any VFs possibly overlooked by the previous 2 components, we performed a specific search using the term VF without date restriction. More detail of the search strategy can be seen in the

Figure 1. Study flow diagram. PRISMA 2020 flow diagram.[12]



PRISMA indicates Preferred Reporting Items for Systematic Reviews and Meta-Analyses; VF, value framework.

Appendix S2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.02.002.

To further augment our search, we supplemented it by exploring selected gray 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 2 reviewers from the research team. Disagreements were resolved by consensus of the entire review team. All phases of study selection were performed using COVIDENCE,[10,11] 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: (1) generic VFs aimed at health technologies, (2) VFs aimed more specifically at genomic tests, (3) VFs aimed more specifically at diagnostic tests (genomic or otherwise), and (4) VFs specifically targeting NGS or CGP technologies. VFs were considered if they included at least 2 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 gray literature for completeness. For each of the frameworks surveyed, the criteria and subcriteria 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 in the reference VF of each criterion and subcriteria of all included VFs, using a 4-category scale: fully included (criteria or subcriteria that were considered to be fully captured), 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 2 researchers, and any discrepancies were discussed with the research team. Criteria and subcriteria were considered as separate units and were matched against the IECS VF 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 VFs and the execution of criteria/subcriteria mapping, the selection process encompassed those elements that exhibited partial overlap or no overlap at all with the criteria/subcriteria of the IECS VF. This set of criteria/subcriteria underwent independent evaluation by 2 distinct working groups—the IECS researchers and the London School of Economics researchers' team—with the aim of discerning which

Table 1. Value frameworks identified.

Author	Year	Region	Scope	Target area of use	Reference framework	Perspective
Augustovski et al[5]	2021	Latin America	Diagnostic technology	All health conditions	No	HTA
CDC[15]	2000-2004	USA	Diagnostic technology	All health conditions	No	Professionals Society
Angelis et al[16]	2017	UK	General framework	All health conditions	No	HTA
Pearson et al/ICER[3,4]	2018/2020-2023	USA	General framework	All health conditions	No	HTA
ASCO[17]	2016	USA	Drugs framework	Oncology	No	Professionals Society
Campolina et al[18]	2022	Brazil	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[2]	2021	Australia	General framework	All health conditions	USPSTF	HTA
Anonychuck et al[28]	2012	Australia	Diagnostic technology	All health conditions	No	Hospital
NICE[1]	2022	UK	General framework	All health conditions	No	HTA
Teutsch et al[29]	2009	USA	Genetic test	All health conditions	No	MoH
INESS[30]	2022	Canada (Quebec)	Diagnostic technology	All health conditions	No	HTA
IQWIG[31]	2017	Germany	General framework	All health conditions	No	HTA
AdvaMed[32]	2017	USA	Diagnostic technology	All health conditions	No	HTA
Medtech[33]	2019	Europe	Diagnostic technology	Other	No	Other
Frueh et al[34]	2014	USA	Diagnostic technology	All health conditions	No	HTA
Palmetto GBA[35]	2011	USA	Genetic test	All health conditions	No	Other
Mann et al[36]	2010	UK	Diagnostic technology	Other	No	Professionals Society
Canestaro et al[37]	2015	International	Diagnostic technology	Oncology	No	HTA
Lee et al[38]	2010	International	Diagnostic technology	All health conditions	No	HTA
EUnetHTA[39]	2015	Europe	Diagnostic technology	All health conditions	No	HTA

continued on next page

Table 1. Continued

Author	Year	Region	Scope	Target area of use	Reference framework	Perspective
Blancquaert et al[40]	2007	Canada	Genetic test	All health conditions	ACCE	HTA
Calonge et al[41]	2003	USA	Genetic test	Rare diseases	ACCE y EGAPP	Professionals Society
Rousseau et al, GETT[13]	2010	International	Genetic test	All health conditions	ACCE y UKGTN	HTA
Severin et al (Eurogentest Evaluation Model)[42]	2015	Europe	Genetic test	All health conditions	No	Other
UKGTN (The United Kingdom Genetic Testing Network)[14]	2002	United Kingdom	Genetic test	All health conditions	ACCE	HTA
Fryback and Thornbury[43]	1991	USA	Diagnostic technology	All health conditions	No	Professionals Society
Annemans et al[44]	2017	Europe	Drugs framework	Rare deseases	No	HTA
Garrison et al[45]	2016	Europe	Diagnostic technology	All health conditions	No	HTA
InformedDNA[46]	2019	USA	Genetic test	Genetic conditions	EGAPP/USPSTF	HTA
Krahn et al[47]	2007	Canada	General framework	Unspecified	No	HTA
Harris et al[48]	2001	USA	Diagnostic technology	All health conditions	No	Professionals Society
Shah-Manek[49]	2017	USA	General framework	Oncology	No	HTA
AHRQ[50]	2011	USA	Genetic test	All health conditions	EGAPP	HTA
Calderón et al[51]	2006	Spain	Genetic test	All health conditions	UK Genetic Testing Network	HTA
Memorial Sloan Katherine Hospital[52]	NM	USA	Drugs framework	Oncology	No	Other

AHRQ, Agency for Healthcare Research and Quality; ASCO, American Society of Clinical Oncology; CDC, Centers for Disease Control and Prevention; EGAPP, Evaluation of Genomic Applications in Practice and Prevention; EUnetHTA, European Network for Health Technology Assessment; GETT, Genetic testing Evidence Tracking Tool; HTA, health technology assessment; ICER, Institute for Clinical and Economic Review; INESS, Institut National d'excellence en santé et en services sociaux; IQWIG, Institute for Quality and Efficiency in Health Care; MSAC, Medical Services Advisory Committee; NICE, National Institute for Health care Excellence; NM, not mentioned; UK, United Kingdom; UKGTN, UK Genetic Testing Network; USA, United States of America; USPSTF, U.S Preventive Services Task Force.

ones among them could be included in the value criteria and subcriteria considered 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/subcriteria 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: 9 for not being VFs, 3 for the wrong outcome, 3 because of inadequate study design (eg, systematic reviews and case studies), 3 for being a VF out of scope (eg, frameworks with only 1 criterion, or a non-health-oriented framework). A total of 13 studies were included from the gray literature (16 studies were identified, of which, after evaluation, 13 met the inclusion criteria). Two of the gray literature studies surveyed were used to supplement the evidence extracted from 2 studies of VF in the literature from indexed journals, leading to a final 11 VF from the gray literature. An additional 19 studies were included from the previous literature search of the study by Augustovski et al,[5] in which a total of 20 studies were identified. One of the studies (a methodological manual) was excluded because the team considered that it did not meet the inclusion criteria for this review. See Figure 1[12] in a PRISMA diagram for more information.

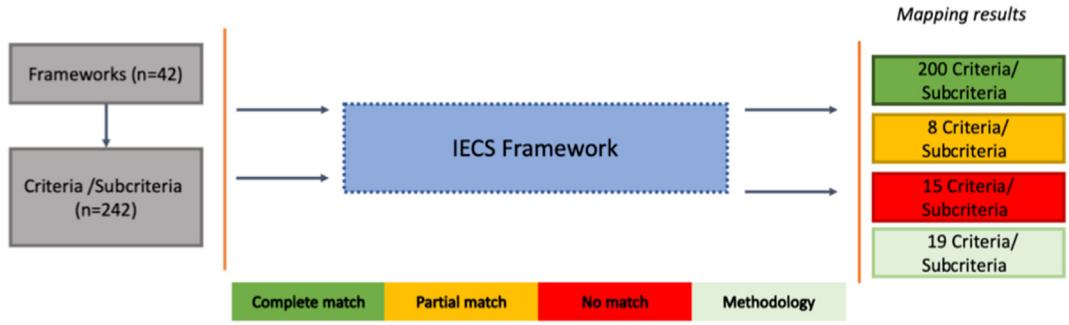
First Stage: Systematic Review

A total of 43 VFs were extracted (including the IECS VF), all of which are listed in Table 1[1-5,13-52] below (more detailed information on the criteria/subcriteria can be found in Appendix Table 1 in Appendix S3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.02.002).

Fifteen VF were developed in the United States of America, followed by 5 developed for all of Europe, 4 developed worldwide, 4 in Canada, 4 in the United Kingdom, 3 in Australia, 2 in Germany, 2 in Latin America, and 1 each in Spain, Brazil, and Iran. One framework did not refer its country/region.

In terms of scope, 14 (32.5%) of the frameworks were designed to evaluate general diagnostic tests, 13 (30.2%) were developed to evaluate genomic tests, 12 (27.9%) were general

Figure 2. Scheme of the methodology and general results of the mapping (nonoverlapping criteria and subcriteria).



IECS indicates Institute for Clinical Effectiveness and Health Policy.

frameworks, and only 4 (9.3%) were designed for the evaluation of medicines.

In terms of therapeutic area, 29 (67.4%) of the frameworks were developed for any health condition, 7 (16.3%) for oncology, and 2 (4.7%) for rare diseases. Only 1 framework was developed strictly for genetic diseases, independent of any disease area. Two frameworks (4.7%) did not specify the target therapeutic area, whereas 2 focused on other disease.

Thirty-five VF (81.4%) were de novo developed frames in which no other frameworks were considered as a reference. Only 8 VF (18.6%) stated that they used other frameworks as references. The ACCE, Evaluation of Genomic Applications in Practice and Prevention, and US Preventive Services Task Force frameworks were the most frequently referenced.[53]

The perspective of the use of the frameworks was mainly for use in technology assessment agencies, with 24 (55.8%) VF developed in this context, followed by 7 (16.3%) for use in professional societies, 5 (11.6%) for use in ministries of health, 2 (4.7%) for hospitals, and only 1 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 Fig. 2).

When we mapped the 42 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 nonclinical 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, whereas those criteria not aligning are marked with a hyphen.

Subanalysis on the criteria included within identified VFs was conducted based on VF scope, perspective, and therapeutic area (see Fig. 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. VFs with a genomic scope had a higher frequency of including legal and ethical criteria (≈50% compared with ≈25% for other scopes) and organizational impact (≈50% compared with ≈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 standpoint (n = 4), professional societies (n = 7), whereas 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 health technology assessment frameworks (≈50% vs ≈12.5%-25%). Nonclinical benefits were less frequently included in scientific society frameworks compared with the rest ≈12% vs ≈50%-60%).

In terms of therapeutic area, categories for subanalysis 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 the small sample size. Inclusion of criteria was generally similar across the 3 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 nononcology therapeutic areas (“others”) included other criteria at a higher frequency, such as organizational impact (≈15% vs ≈40%-60%) and nonclinical benefits (0% vs ≈40%-70%).

Third Stage: Integration of the Criteria/Subcriteria

A total of 15 criteria/subcriteria were identified that did not overlap with any of the criteria/subcriteria in the original IECS framework (see Appendix Table 2 in Appendix S4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.02.002.

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	Prior	Burd	Equi	EthL	Sever a	Alter	Non-C	Envi	Soc	Inno	Other
Diagnostic technology																		
Fryback et al[43]	All conditions*	PS	✓	✓	-	✓	-	-	-	-	-	-	-	✓	-	-	-	-
ACCE[15]	All conditions	PS	✓	✓	✓	✓	-	-	✓	-	✓	-	-	-	-	✓	-	-
Canestaro et al[37]	Oncology	HTA	✓	-	-	✓	-	-	✓	-	-	-	-	-	-	-	-	-
EUnetHTA[39]	All conditions	HTA	✓	✓	-	✓	✓	-	✓	✓	-	✓	-	✓	✓	-	-	-
Frueh et al[34]	All conditions	HTA	✓	-	-	✓	-	-	-	-	-	-	-	-	-	-	-	-
Garrison et al[24]	All conditions	HTA	✓	-	-	✓	-	-	-	-	-	-	-	✓	-	-	✓	-
Harris et al[48]	All conditions	PS	✓	✓	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Harris et al[20]	Oncology	PS	✓	-	-	✓	-	-	-	-	-	-	-	-	-	-	-	-
Lee et al[38]	All conditions	HTA	✓	-	-	-	-	-	-	-	-	-	-	✓	-	-	-	-
Mann et al[36]	Other	PS	✓	-	-	✓	✓	-	-	✓	-	-	-	-	-	-	-	-
Anonychuck et al[28]	All conditions	Hospital	✓	✓	-	✓	✓	-	-	-	✓	-	-	✓	✓	✓	-	-
Medtech[33]	Other	Other	-	-	-	✓	✓	-	-	-	-	-	-	✓	-	-	-	-
Drugs framework																		
Annemans et al[44]	Rare diseases	HTA	✓	✓	✓	✓	✓	-	✓	-	-	✓	-	✓	-	✓	✓	-
ASCO[17]	Oncology	PS	✓	✓	-	✓	-	-	-	-	-	-	-	-	-	-	-	-
Campolina et al[18]	Oncology	Hospital	✓	✓	-	✓	-	-	✓	-	-	-	-	-	-	-	-	-
MSK[52]	Oncology	Other	✓	✓	-	✓	-	-	✓	✓	-	-	✓	-	-	✓	✓	✓
General framework (drugs and other)																		
NICE[1]	All conditions	HTA	✓	-	-	✓	-	-	-	-	-	-	-	✓	-	-	-	-
IQWIG[31]	All conditions	HTA	✓	-	-	✓	✓	-	-	-	✓	-	-	✓	-	✓	-	-
AdvaMed[32]	All conditions	HTA	✓	✓	-	✓	✓	-	-	-	-	-	-	✓	-	-	-	-
Krahn et al[47]	Unspecified	HTA	✓	✓	-	✓	-	-	-	✓	✓	-	-	-	-	-	-	-
Angelis et al[16]	All conditions	HTA	✓	✓	-	✓	-	-	✓	✓	-	-	✓	✓	-	✓	✓	-
MSAC[2]	All conditions	HTA	-	-	-	✓	✓	-	-	-	-	-	-	-	-	-	-	-
DosReis et al[19]	All conditions	Patients	✓	✓	-	✓	-	-	✓	-	-	✓	-	✓	-	✓	✓	-
ICER[3,4]	All conditions	HTA	✓	-	-	✓	-	-	-	-	-	-	-	✓	-	✓	✓	-
Lakdawalla et al[25]	All conditions	HTA	✓	-	-	✓	-	-	-	✓	-	✓	-	✓	-	✓	✓	✓
NCCN[49]	Oncology	HTA	✓	✓	✓	-	✓	-	-	-	-	-	-	-	-	-	-	-
Pichon-Riviere et al[26]	All conditions	HTA	✓	✓	✓	✓	✓	✓	✓	✓	-	✓	-	-	-	-	✓	-
Shams et al[22]	All conditions	MoH	✓	-	-	✓	-	-	-	✓	-	-	-	✓	-	-	-	✓
Teutsch et al[29]	All conditions	MoH	✓	-	✓	-	-	-	-	-	-	-	-	-	-	-	-	-
Genetic test																		
AHRQ[48]	All conditions	HTA	✓	✓	-	-	✓	-	-	-	✓	-	-	-	-	-	-	-
Blancquaert[40]	All conditions	HTA	✓	-	-	-	✓	-	-	-	-	-	-	✓	-	-	-	-
INESS[30]	All conditions	HTA	✓	-	-	✓	✓	-	-	-	✓	-	-	✓	-	-	-	-
Calderón et al[51]	All conditions	HTA	✓	✓	-	✓	-	-	-	✓	✓	-	-	-	-	-	-	-
Calonge et al[41]	Rare deseases	PS	✓	-	-	-	-	-	-	-	-	-	-	-	-	✓	-	-
Eurogentest [...][42]	All conditions	Other	✓	-	-	✓	-	-	✓	-	-	-	-	✓	-	-	-	-
GETT[13]	All conditions	HTA	✓	-	-	✓	✓	-	✓	-	✓	-	-	✓	-	-	-	✓
Giacomini et al[27]	All conditions	MoH	✓	-	-	✓	✓	-	-	-	-	-	-	✓	-	✓	-	-

continued on next page

Table 2. Continued

Source	Target area of use	Perspective	Clin	Safe	Qual	Econ	Org	Prior	Burd	Equi	EthL	Seve a	Alter	Non-C	Envi	Soc	Inno	Other
InformedDNA[46]	Genetic	HTA	✓	✓	-	✓	✓	-	✓	✓	✓	✓	-	✓	-	-	-	✓
Merlin et al[21]	Oncology	MoH	✓	-	-	✓	-	-	-	-	-	-	-	-	-	-	-	-
Palmetto GBA[36]	All conditions	Other	✓	✓	-	✓	-	-	-	-	✓	-	-	✓	-	-	-	✓
Rogowski et al[23]	Unspecified	Other	✓	-	-	✓	-	-	✓	-	-	✓	-	-	-	-	-	-
UKGTN[14]	All conditions	HTA	✓	-	-	-	✓	-	✓	-	✓	✓	✓	-	-	-	-	-

AHRQ, Agency for Healthcare Research and Quality; Alter, absence of alternative diagnostic technologies; ASCO, American Association of Clinical Oncology; Burd, disease burden; Clin, clinical benefits and test performance; Econ, economical aspects; Envi, environmental impact; Equi, equity; EthL, ethical and legal aspect;EUnetTHA, European Network for Health Technology Assessment; GETT, Genetic testing Evidence Tracking Tool; HTA, health technology assessment; ICER, Institute for Clinical and Economic Review; IECS, Institute for Clinical Effectiveness and Health Policy; INESS, Institut National d'excellence en santé et en services sociaux; Inno, innovation; IQWIG, Institute for Quality and Efficiency in Health Care; MoH, Ministry of Health; MSAC, Medical Services Advisory Committee; MSK, Memorial Sloan Kettering; NCCN, National Comprehensive Cancer Network; NICE, National Institute for Health care Excellence; Non-C, nonclinical benefits; Org, organizational aspects and feasibility within the clinical path; Prior, health priority of the health system; PS, professional society; Qual, quality of scientific evidence; Safe, safety and unwanted consequences; Seve, severity of the disease; Soc, broader social impact; UKGTN, UK Genetic Testing Network.
*All conditions refer to "All health conditions."

Appendix Table 2 contains more information about these criteria/subcriteria). Out of these, 4 were deemed not relevant for this study after reaching consensus with the entire team. Finally, 2 were included as additional criteria ("Public health/population benefit" and "Quality assurance/quality improvement program"), and 7 as subcriteria ("Technical aspects," "Fear of contagion," "Real option value," "Research priorities," "Risk of overutilization," "External pressures," and "Degree of investment in research and development"). Out of the 9 criteria/subcriteria that partially matched the original IECS VF criteria, after team consensus, it was decided to include 8 as subcriteria ("Test for disadvantaged or underserved communities," "Test for rare diseases," "Equity in health financing," "Impact on education," "Impact on career," "Impact on stigma," and "Effective access to the test and subsequent treatment").

It is important to highlight that after team discussion, a consensus was reached to add the subcriterion "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 subcriteria that were not well defined under other main criteria but can hold importance within this context.

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

Discussion

The systematic review unveiled a total of 43 VF, encompassing a collective sum of 242 individual criteria and subcriteria (when including overlap). Among these, 15 criteria were not encompassed in the original IECS framework. Most of these frameworks were conducted from a health technology assessment 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 VFs for diagnostic/genomic tests, technologies in which safety issues may be less important compared with frameworks oriented toward medicines evaluation.

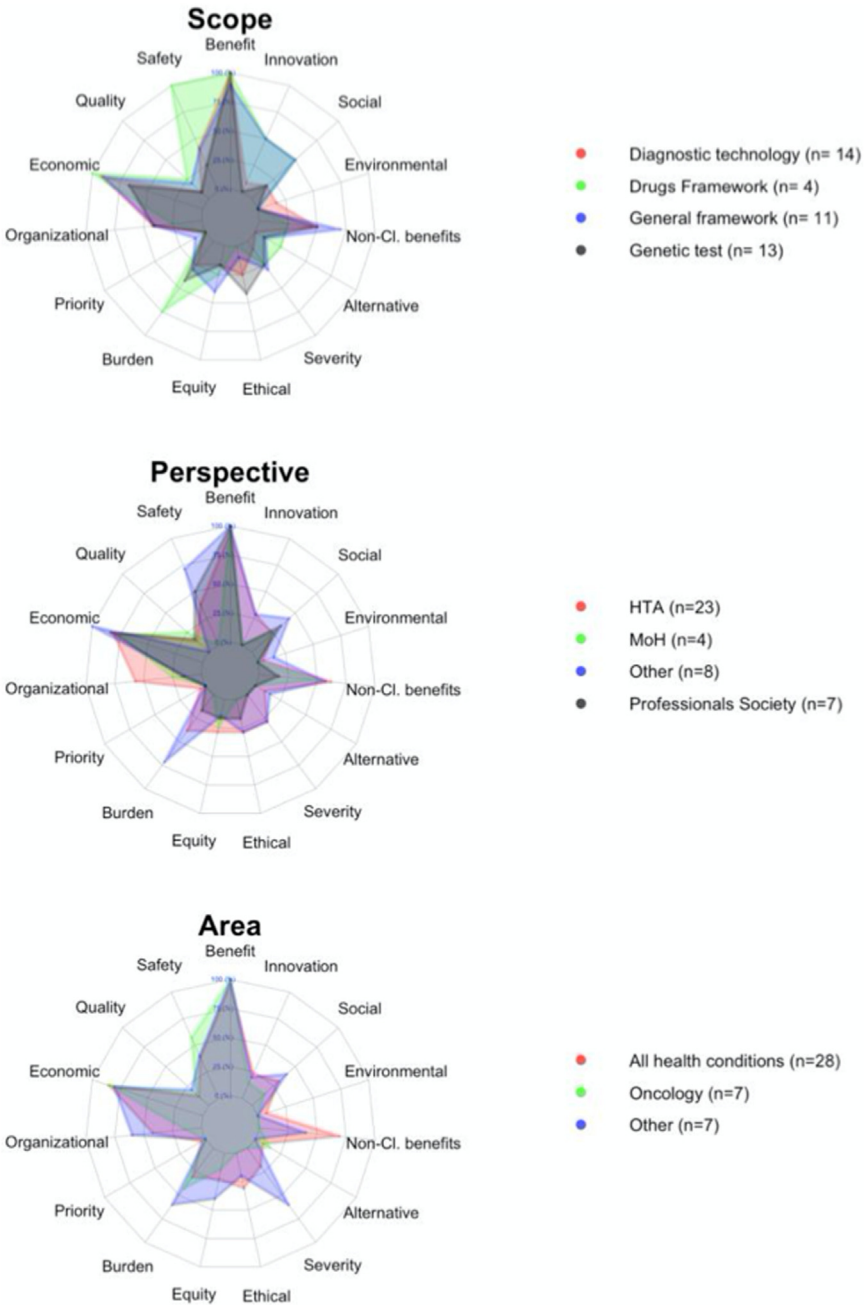
There are inherent tensions and trade-offs among the usefulness, applicability, and precision of different VFs. For rapid and general decision making, generic VF are probably preferred by decision makers, but they have the downside of being less fit for purpose when targeting more specific technologies, 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 with other medical technologies. Among diagnostic health technologies genomic panel tests, such as NGS, 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 13 frameworks specifically designed for the evaluation of genomic profiling, none of them were explicitly tailored to technologies such as NGS/CGP, which facilitate the simultaneous assessment of numerous genes.

Within the criteria and subcriteria of genomic testing VFs, we found specific criteria that warrant further consideration, such as analytical validity or penetrance. Although 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 such as ACCE and Evaluation of Genomic Applications in Practice and Prevention, 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 or whole genome sequencing.[15,29] 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.[54,55] In many instances, it becomes necessary to determine what information should be communicated to patients and how it ought to be conveyed. Although 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.

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



VF indicates value framework.

Although in this study we did not consider how each of the criteria of the framework was technically evaluated, and if and how they are weighted in a deliberative or quantitative way, it is important to understand that NGS/CPG may present particular difficulties.[56] For example, for economic evaluation, the choice of comparator, their frequent use for several mutations that could involve several diseases, 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 narrow focused clinical (population, intervention, comparator, outcomes) question. Normally, in the evaluation of a diagnostic technology, the relationship of a test to its treatment can be established, whereas in this case there may be multiple associated therapeutic interventions.[57]

This review serves as an initial step in the development of a VF specifically adapted to CGP/NGS. Additionally, our study, which provides a unique evidence base set of nonoverlapping value criteria and subcriteria, can also help to inform future VF initiatives. Despite the identification of numerous VFs, none are expressly designed for wide-range gene panels, and only 13 of these were designed for general genomic testing. Consequently, our understanding of the specific areas requiring evaluation in the context of

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

Criteria	Definition	Subcriteria	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 (eg, 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 (eg, 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 (eg, adverse events during bowel preparation for biopsy colonoscopy)
		Safety for test operators	Unintended consequences in test operators (eg, radiation exposure from taking tomography guided biopsies)
		Risk of overutilization	Refers to the risk of overuse, or abuse, of genomic testing. (eg: 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 2 or more diagnostic options. Budget impact for the funder when incorporating the test (eg, includes acquisition costs, maintenance, supplies, training)
		Other costs	Patient and family out-of-pocket expenses, costs related to productivity loss, etc

continued on next page

Table 3. Continued

Criteria	Definition	Subcriteria	Definition
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 is, both in mortality and in quality of life. 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 (eg, 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 with the general population. In Europe, the European Medicines Agency considers a disease with a prevalence of <5 in 10 000 people (equivalent to less than 1 in 2000) 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

continued on next page

Table 3. Continued

Criteria	Definition	Subcriteria	Definition
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 2 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	Nonclinical 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, and preparation)
		Value of the information	Value of the information provided by the test in special situations (eg, 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 (eg, 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 (eg, HPV/cervical cancer)
		Impact on education	The impact of the diagnosis and treatment on one's education/schooling

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Table 3. Continued

Criteria	Definition	Subcriteria	Definition
		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
Environmental impact	It is a measure that the production, use or implementation of technology would cause in the environment. For example, 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 (eg, molecular weight markers) included in the analysis. 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 (eg, analytical aspects of the test or interpretation and reporting)? If no external QC program exists, which type of control do you make (eg, blind tests, exchanges of various samples between laboratories).		
Public health/ population benefit	The public health/ population that this technology will bring when used for this health problem (eg: detection of susceptible populations to improve their follow-up, screening uses)		

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Table 3. Continued

Criteria	Definition	Subcriteria	Definition
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 bold are highlighted the criteria/subcriteria that emerged from the systematic review, mapping, and integration as described in the Methods and Results section. HPV indicates human papillomavirus; IECS, Institute for Clinical Effectiveness and Health Policy; QC, quality control.

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 article has strengths and limitations. Some limitations warrant consideration. Notably, the initial process of mapping criteria and subcriteria of all included VF was undertaken by the research team, drawing from the LA VF. Such a process involved qualitative research methods, and it inherently involved elements of interpretation and subjectivity. 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 leading institutions, there still exists the potential for the omission of criteria that could hold substantial significance for others. Moreover, the act of mapping, initially tied to a specific reference framework, can somewhat limit the distinctions among the appraised frameworks. For instance, although distinct frameworks assessing different facets of clinical benefit were found, they were subsumed under the overarching criteria of clinical benefit, and their individual disparities in criteria or subcriteria were not always delineated and carried forward. Regarding our study strengths, foremost among these is the exhaustive systematic review, and 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, although the principal focus of this study pertains to NGS/CGP technologies, the search strategy extended broadly beyond this domain, thereby encompassing criteria germane to alternative technological realms, including general diagnostic technologies and drugs. The resultant synthesis of these broader criteria lends added relevance to the assessment of NGS/CGP technologies.

Conclusions

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 VF in Europe and can also help to inform future VF initiatives in other health technologies. 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.

Author Disclosures

Author disclosure forms can be accessed in the Supplemental Material section.

Supplemental Material

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