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REVIEW

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Are we properly evaluating genetic and genomic testing? A systematic review of health technology assessment reports

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Abstract

Background Despite advances in precision medicine, the translation of genetic and genomic technologies into routine practice is hampered by a heterogeneous and limited evidence base and the absence of standardized evaluation methodologies. Health Technology Assessment (HTA) plays a critical role in bridging this gap, yet assessment approaches and comprehensiveness vary widely. This systematic review aims to map the landscape of the assessment reports on genetic and genomics applications, analyze their methodological aspects and identify gaps.

Methods PubMed, Scopus, Web of Science, and the international HTA database, were searched for assessment reports of genetic/genomic technologies. Information on reports general characteristics, assessment domains and their components, consulted sources of evidence and reported gaps was extracted. Findings were synthesized narratively.

Results Out of 27,331 screened records, 41 reports were included, predominantly from Canada, the United Kingdom, and Australia, mainly aimed at informing policy making for single or multiple gene tests for cancer patients. Most reports used a generic HTA methodology and assessment domains varied across reports. Key clinical aspects, such as clinical accuracy and safety, suffered from evidence gaps (39.0% and 22.0%), while personal and societal aspects were the least investigated assessment domain (48.8-78.0%). Overall, lack of evidence and limited generalizability of findings were the most commonly reported gaps across multiple domains.

Conclusions The review highlighted significant fragmentation in current evaluation methodologies of genetic and genomic applications, with underassessment of analytical/clinical accuracy, safety, and non-health outcomes, alongside evidence gaps and limited generalizability. These issues compromise both evaluation and decision-making

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process, underscoring the urgent need for alternative study designs and standardized, comprehensive assessment frameworks to facilitate the successful implementation of emerging genetic and genomic technologies.

Keywords Health technology assessment, Genetic and genomic technologies, Genetic and genomic applications, Systematic review

Background

Advances in genetic and genomic medicine hold the promise of significantly transforming various aspects of the healthcare landscape, from deepening our understanding of the physiological and pathological processes underlying disease development to improving the management of multiple diseases [1]. This is particularly relevant to the fields of Personalized Medicine (PM) and Public Health Genomics (PHG), that aim to leverage genetic and genomic applications to enable tailored health interventions at individual and population levels, respectively [2, 3]. However, despite successful examples like BRCA1/2 testing for predicting ovarian and breast cancer risk [4], many other interventions based on these technologies, including Precision Oncology applications [5], remain far from real-world practice, even as the availability and variety of genetic and genomic tests continue to grow [6, 7].

This gap may be partly attributed to the challenges of translating genetic and genomic applications from research to real-world practice, among which the generation and assessment of scientific evidences are critical for successful implementation [8]. Indeed, both these processes are not streamlined processes in this context. First, building evidence is challenging due to the inherent complexity of these applications, their rapid development and commercialization, widespread societal impact, and, above all, the lack of flexibility of conventional study designs [9]. This may results in a limited and heterogeneous body of evidence that ultimately hinders effective evaluation [2]. Second, there is currently no standardized methodology for assessing genetic and genomic applications, although several assessment frameworks have been proposed over the past decades. While the ACCE model (named after its principals evaluations domains: Analytic validity, Clinical validity, Clinical utility, Ethical, Legal, and Social implications), and its variations have been widely used, they overlook key aspects such as economic, personal, and societal factors [10]. To overcome these limitations, Health Technology Assessment (HTA)-based frameworks for evaluating genetic and genomic applications have been recently increasingly developed [10]. Nevertheless, these frameworks may lack validation, implementation, and widespread adoption [11].

Given the fragmentation and heterogeneity in the assessment of genetic and genomics applications and their slow-pacing implementation in the clinical and prevention practice, we herein present a systematic review of evaluation reports of genetic and genomic applications. The aims of this review are to: (i) map the current landscape and scope of the current corpus of evaluation reports on genetic and genomics applications; (ii) analyze their methodological aspects; and (iii) identify any barriers or gaps that have emerged during the assessment process and may ultimately hinder the evaluation itself.

Methods

This study was performed according to the Cochrane Handbook for systematic reviews [12] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [13]. The review protocol was registered at PROSPERO (identifier: CRD42023435433). Since this study did not involve primary data collection, the protocol was not submitted for institutional review board approval.

Search strategy and study selection

PubMed, Scopus, Web of Science and the international HTA database [14] were searched from inception to 30/06/2023, using the following key terms, adapting the research string to fit the search criteria of each database (see Supplementary Table 1): genetic and genomic testing and application, evaluation, assessment, report. As the international HTA database provides a single point of access to assessment reports produced by national agencies [14] and its authority in the field is widely recognized, other grey literature sources were deemed not necessary.

Duplicate items were removed, and the title and abstract of all collected records were screened by two reviewers to identify all articles that potentially met the inclusion criteria. Records that clearly did not meet the inclusion criteria were excluded. Full texts of potentially relevant reports were retrieved and independently assessed for eligibility by two review-team members. The reference lists of retrieved records were also searched to identify other potentially relevant reports. Disagreements were resolved through discussion or by a third reviewer and the reasons for exclusion were recorded.

As for inclusion criteria, the review included any report that (i) was expressly produced to assess new or existing genetic/genomic technologies on human specimens and for human conditions [15], including molecular tests (i.e., single gene tests, multiple gene tests, whole exome/whole genome sequencing), chromosomal tests and gene expression tests [16]; (ii) was complete, i.e. considered at least three of the following evaluation domains: disease/condition of interest, application aspects, clinical aspects, personal and societal aspects and economic/organizational aspects; (iii) was reported in English or Italian; (iv) was available as a full-text. Conversely, the review excluded articles that (i) did not assess new or existing genetic/genomic technologies for human conditions (i.e. not assessment reports, such as clinical practice guidelines, systematic reviews, protocols, commentaries, letters); (ii) were incomplete, i.e. considered fewer than three evaluation domains; (iii) were reported in languages other than English or Italian; (iv) were not available as full-texts.

Data collection and synthesis

For each eligible report, two reviewers independently extracted the following information: (i) identification (i.e. authors, year of publication, country of publication, institution/organization responsible for the report); (ii) general information (i.e. report purpose, healthcare field, target population, clinical setting, technology to be assessed, type of test, test purpose); (iii) methodological characteristics (i.e. framework/methodological guidance, assessment of quality of evidence, reporting of research priorities, recommendations), including assessment domains and their components: "disease/condition of interest" (epidemiology, etiopathogenesis, natural history, current management), "application" (analytic accuracy), "clinical aspects" (clinical accuracy, efficacy, effectiveness, safety, patient-reported outcomes, post-test clinical pathways), "personal and societal aspects" (non-health-related outcomes, ethical aspects, legal aspects, social aspects) and "organizational aspects" (burden of disease, professional resources need, material resources need, financial resources need, budget impact analysis, equity in access, economic evaluations); (iv) outcomes/measures and sources of evidence used for component assessment, and assessment gaps reported within each domain and component. A narrative synthesis approach was used to analyze the information presented in the reports.

Results

Overall, 42,801 records were identified by database searching. After removal of duplicates, 27,331 records resulted from the systematic search. Screening by title and abstract yielded 140 documents and a total of 41 reports were included after screening by full text (Fig. 1) [17–57].

General characteristics of reports

Most reports were produced in Canada (34.1%), followed by the United Kingdom (29.3%) and Australia (12.2%), with two reports (4.9%) coming from EUnetHTA (Fig. 2). General characteristics of the reports are shown

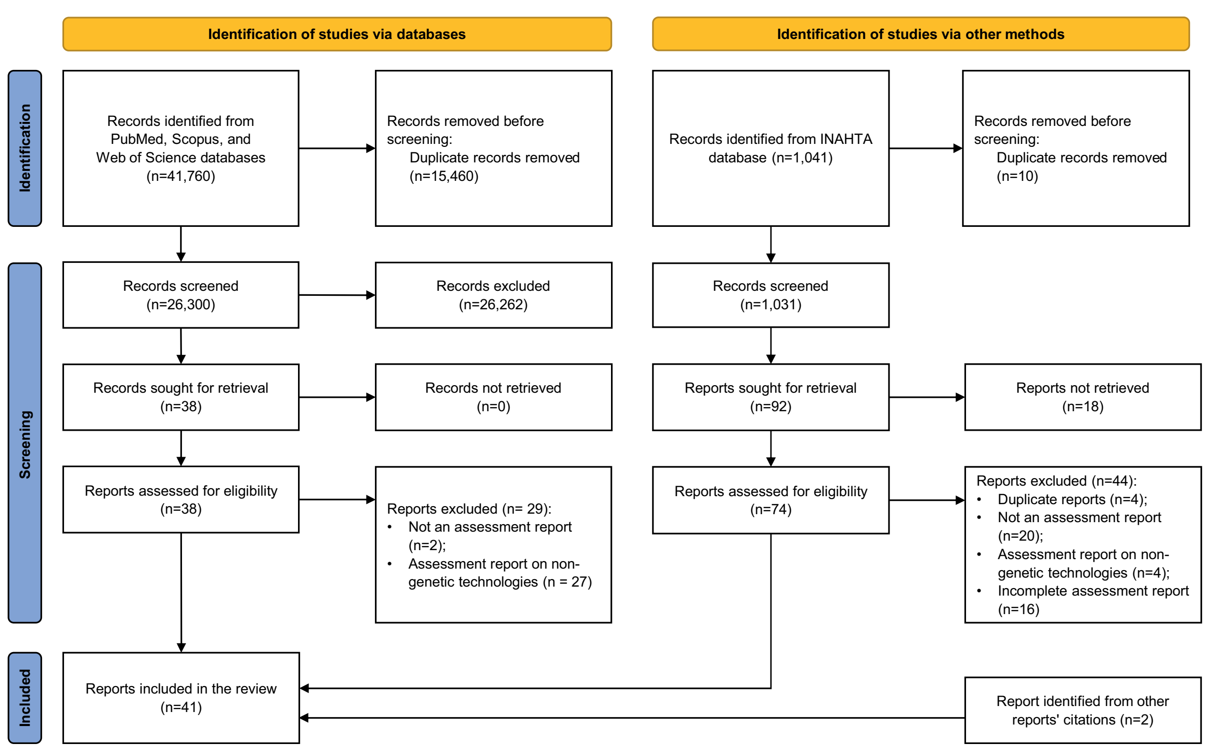

Fig. 1 PRISMA flow diagram of the review process

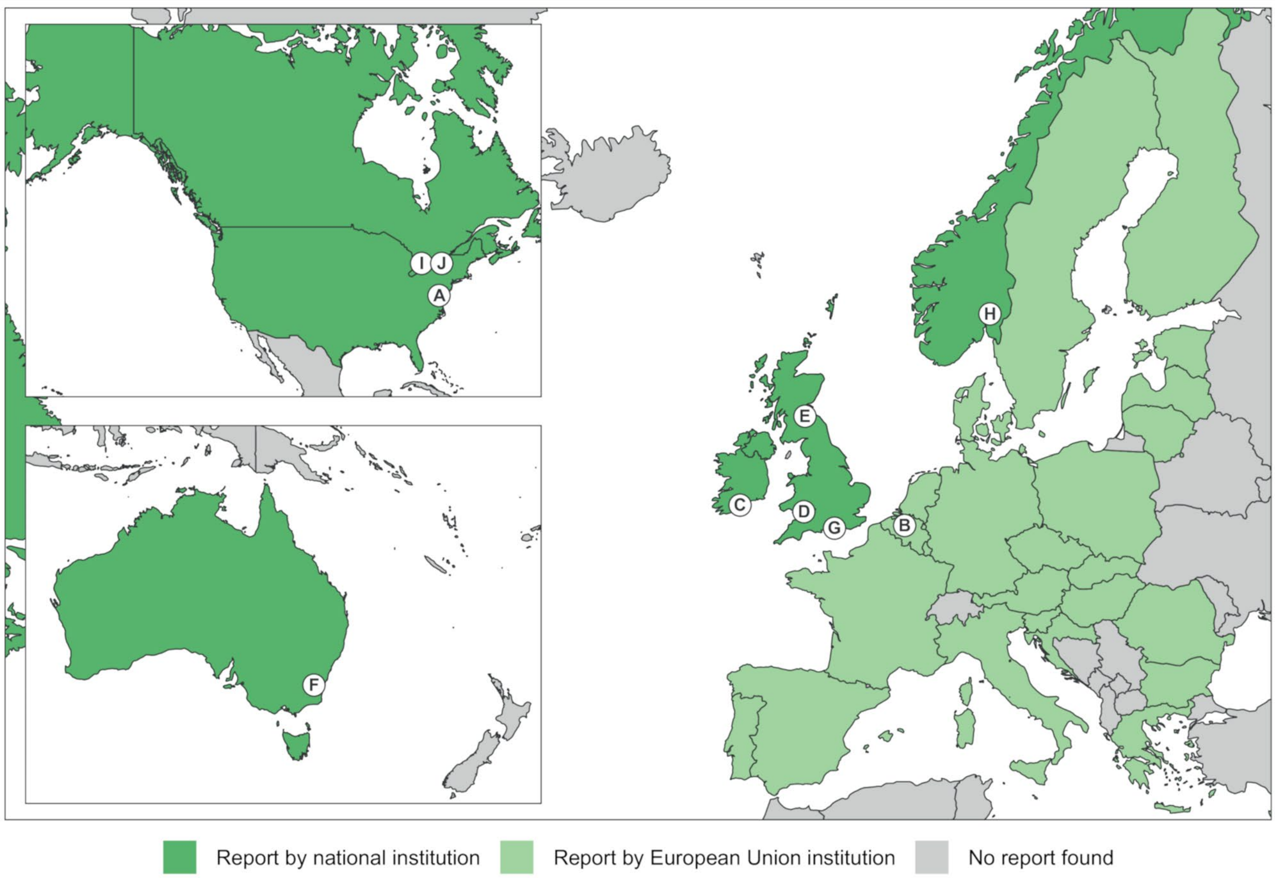

Fig. 2 Country and institution of assessment reports included in the systematic review (*N*=41). **A**: AHRQ, United States of America (*N*=2, 4.9%); **B**: EUnetHTA, European Union (*N*=2, 4.9%); **C**: HIQA, Ireland (*N*=1, 2.4%); **D**: Health Technologies Wales, Wales (*N*=1, 2.4); **E**: Healthcare Improvement Scotland, Scotland (*N*=1, 2.4%); **F**: MSAC, Australia (*N*=5, 12.2%); **G**: NIHR, United Kingdom (*N*=2, 29.3%); **H**: NIPH, Norway (*N*=3, 7.3%); **I**: Ontario Health, Canada (*N*=13, 31.7%); **J**: SickKids, Canada (*N*=1, 2.4%). AHRQ: Agency for Healthcare Research and Quality; EUnetHTA: European Network for Health Technology Assessment; HIQA: Health Information and Quality Authority; MSAC: Medical Services Advisory Committee; NIHR: National Institute for Health Research; NIPH: Norwegian Institute of Public Health; SickKids: The Hospital for Sick Children Technology Assessment Task Force

in Table 1. In terms of purpose, 58.5% of the reports aimed to inform policy making, 31.7% were intended to guide funding decisions, and 9.8% seek to provide clinical guidance.

The most common field of the reports was cancer (70.7%), followed by congenital disorders (14.6%), metabolic/cardiovascular disorders (7.3%), neurology/psychiatry (4.9%) and obstetrics (2.4%). Patients were the main target population (78%), while pregnant women (9.8%), newborns (2.4%) and healthy subjects (2.4%) were less represented. The most common clinical setting was staging or treatment (58.5%), followed by diagnosis (22.0%) and screening (12.2%), with 3 reports investigating both diagnosis and screening (7.3%). Finally, the most frequent test purposes were diagnostic (34.1%), pharmacogenetic (34.1%), and prognostic (19.5%), and the majority of reports evaluated multiple (43.9%) or single (39.0%) gene tests, with assessments covering either all available technologies (53.7%) or specific ones (46.3%).

Methodological characteristics of reports

As shown in Table 2, most reports (78.0%) referred to a generic HTA methodology, while three reports followed the HTA Core Model® (7.3%), and two reports each (4.9%) used the ACCE framework and the EGAPP/Sapienza framework as guidance. Nearly all reports (95.1%) included an assessment of the evidence quality, with only one report omitting this step due to its focus on primary analyses only. Most reports (68.3%) identified evidence gaps and research priorities, and only one report (2.4%) formulated recommendations on the application implementation.

The following subparagraphs describe the reports characteristics regarding the evaluation domains and components covered, the outcomes and measures used (when feasible), and the sources from which data were retrieved.

Assessment domains and components

Figure 3 illustrates the specific components of each assessment domain (see also Supplementary Table 2).

Table 1 General characteristics of assessment reports included in the systematic review ($N=41$)

Author, year	Country	Institution	Purpose	Field	Target population	Clinical setting	Type of genetic test	Genetic test purpose
Grimshaw, 2003 [17]	United Kingdom	NIHR	Policy making	Congenital disorders	Pregnant women	Screening	Chromosomic	Diagnostic
Bryant, 2009 [18]	United Kingdom	NIHR	Policy making	Metabolic disorders/cardiovascular diseases	Patients	Diagnosis	Single	Presymptomatic
Buckley, 2009 [19]	Australia	MSAC	Funding decision	Cancer	Patients	Diagnosis	Single	Diagnostic
Simpson, 2009 [20]	United Kingdom	NIHR	Policy making	Metabolic disorders/cardiovascular diseases	Patients	Staging or treatment	Multiple	Predictive/susceptibility
Donnan, 2010 [21]	Canada	SickKids	Policy making	Cancer	Patients	Staging or treatment	Single	Pharmacogenetic
Fleeman, 2010 [22]	United Kingdom	NIHR	Policy making	Cancer	Patients	Staging or treatment	Multiple	Pharmacogenetic
Medical Advisory Secretariat, 2010 [A] [23]	Canada	Ontario Health	Policy making	Cancer	Patients	Staging or treatment	Multiple	Prognostic
Medical Advisory Secretariat, 2010 [B] [24]	Canada	Ontario Health	Policy making	Cancer	Patients	Staging or treatment	Single	Prognostic
Medical Advisory Secretariat, 2010 [C] [25]	Canada	Ontario Health	Policy making	Cancer	Patients	Staging or treatment	Single	Pharmacogenetic
Fleeman, 2011 [26]	United Kingdom	NIHR	Policy making	Cancer	Patients	Staging or treatment	Single	Pharmacogenetic
Morona, 2011 [27]	Australia	MSAC	Funding decision	Cancer	Patients and families/partners	Diagnosis	Single	Presymptomatic
Meleth, 2013 [28]	United States of America	AHRQ	Clinical guidance	Cancer	Patients	Diagnosis	Multiple	Diagnostic
Newton, 2013 [29]	Australia	MSAC	Funding decision	Cancer	Patients and families/partners	Diagnosis	Single	Presymptomatic
Meleth, 2014 [30]	United States of America	AHRQ	Clinical guidance	Cancer	Patients	Staging or treatment	Mixed	Prognostic
Snowsill, 2014 [31]	United Kingdom	NIHR	Funding decision	Cancer	Patients	Diagnosis and screening	Multiple	Diagnostic
Westwood, 2014 [A] [32]	United Kingdom	NIHR	Policy making	Cancer	Patients	Staging or treatment	Single	Pharmacogenetic
Westwood, 2014 [B] [33]	United Kingdom	NIHR	Funding decision	Cancer	Patients	Staging or treatment	Single	Pharmacogenetic
Huxley, 2015 [34]	United Kingdom	NIHR	Policy making	Cancer	Patients	Staging or treatment	Multiple	Prognostic
Kessels, 2015 [35]	Australia	MSAC	Funding decision	Congenital disorders	Patients and families/partners	Diagnosis and screening	Single	Carrier
Snowsill, 2017 [36]	United Kingdom	NIHR	Funding decision	Cancer	Patients	Diagnosis	Multiple	Diagnostic
Zierler, 2017 [37]	Canada	Ontario Health	Policy making	Cancer	Patients	Staging or treatment	Multiple	Prognostic
Varela-Lema, 2018 [38]	European Union	EUnetHTA	Funding decision	Congenital disorders	Pregnant women	Screening	Chromosomic	Diagnostic
Elston, 2019 [39]	Wales	Health Technologies Wales	Policy making	Neurology/psychiatry	Patients	Staging or treatment	Multiple	Pharmacogenetic
Fagerlund, 2019 [40]	Norway	NIPH	Funding decision	Cancer	Patients	Staging or treatment	Multiple	Prognostic
Harnan, 2019 [41]	United Kingdom	NIHR	Clinical guidance and funding decision	Cancer	Patients	Staging or treatment	Multiple	Prognostic
McKane, 2019 [42]	Canada	Ontario Health	Policy making	Congenital disorders	Pregnant women	Screening	Chromosomic	Diagnostic

Table 1 (continued)

Author, year	Country	Institution	Purpose	Field	Target population	Clinical setting	Type of genetic test	Genetic test purpose
Stürzlinger, 2019 [43]	European Union	EUnetHTA	Policy making	Cancer	Adult healthy subjects	Screening	Multiple	Diagnostic
Berg, 2020 [44]	Scotland	Healthcare Improvement Scotland	Funding decision	Cancer	Patients	Staging or treatment	Single	Pharmacogenetic
Betsch, 2020 [A] [45]	Canada	Ontario Health	Policy making	Cancer	Patients	Staging or treatment	Single	Pharmacogenetic
Betsch, 2020 [B] [46]	Canada	Ontario Health	Policy making	Congenital disorders	Patients	Diagnosis	Genomic	Diagnostic
Maguire, 2020 [47]	Canada	Ontario Health	Policy making	Cancer	Patients	Staging or treatment	Multiple	Prognostic
Zierler, 2020 [48]	Canada	Ontario Health	Funding decision	Obstetrics	Pregnant women	Staging or treatment	Single	Diagnostic
Betsch, 2021 [49]	Canada	Ontario Health	Clinical guidance and funding decision	Neurology/psychiatry	Patients	Staging or treatment	Multiple	Pharmacogenetic
Maguire, 2021 [50]	Canada	Ontario Health	Policy making	Cancer	Patients	Staging or treatment	Single	Pharmacogenetic
Stinton, 2021 [51]	United Kingdom	NIHR	Funding decision	Cancer	Patients	Diagnosis and screening	Multiple	Diagnostic
Flodgren, 2022 [52]	Norway	NIPH	Policy making	Cancer	Patients	Staging or treatment	Single	Pharmacogenetic
Hamidi, 2022 [53]	Norway	NIPH	Policy making	Cancer	Patients	Staging or treatment	Mixed	Pharmacogenetic
Maguire, 2022 [54]	Canada	Ontario Health	Policy making	Metabolic disorders/cardiovascular diseases	Patients	Diagnosis	Mixed	Diagnostic
McKane, 2022 [55]	Canada	Ontario Health	Policy making	Cancer	Patients	Diagnosis	Multiple	Diagnostic
Newton, 2022 [56]	Australia	MSAC	Funding decision	Cancer	Patients	Staging or treatment	Multiple	Pharmacogenetic
Comber, 2023 [57]	Ireland	HIQA	Policy making	Congenital disorders	Newborns	Screening	Multiple	Diagnostic

AHRQ: Agency for Healthcare Research and Quality; EUnetHTA: European Network for Health Technology Assessment; HIQA: Health Information and Quality Authority; MSAC: Medical Services Advisory Committee; NIHR: National Institute for Health Research; NIPH: Norwegian Institute of Public Health; SickKids: The Hospital for Sick Children Technology Assessment Task Force

Table 2 Methodological characteristics of assessment reports included in the systematic review (*N*=41)

	N (%)	Reference
Framework/methodological guidance		
ACCE	2 (4.9)	[18, 22]
Ad hoc framework	1 (2.4)	[30]
Diagnostic technologies framework by Fineberg et al. 1977	1 (2.4)	[17]
EGAPP and Sapienza framework	2 (4.9)	[52, 53]
HTA Core Model®	3 (7.3)	[38, 43, 57]
Generic HTA framework	32 (78.0)	[19–21, 23–29, 31–37, 39–42, 44–51, 54–56]
Assessment of quality of the evidence		
Reported	39 (95.1)	[18–43, 45–57]
Not reported	1 (2.4)	[44]
Not applicable	1 (2.4)	[17]
Reporting of evidence gaps/research priorities		
Reported	28 (68.3)	[17, 18, 20–23, 26, 28, 30–34, 36–43, 46–48, 51–53, 57]
Not reported	13 (31.7)	[19, 24, 25, 27, 29, 35, 44, 45, 49, 50, 54–56]
Recommendations		
Reported	1 (2.4)	[21]
Not reported	40 (97.6)	[17–20, 22–57]

ACCE: Analytic validity, Clinical validity, Clinical utility, Ethical, legal, and social implications; EGAPP: Evaluation of Genomic Applications in Practice and Prevention; HTA: Health Technology Assessment

In the "disease/condition of interest" domain, all reports that investigated components found evidence. Specifically, every report investigated and found evidence on the epidemiology of the disease or condition of interest. High proportions of reports also explored natural history (90.2%) and current management (97.6%), while only 63.4% looked for evidence on etiopathogenesis.

In contrast, in the "application" domain only 39.0% of the reports investigated and found evidence on analytical accuracy, with the remainder not investigating this component at all.

Regarding the "clinical aspects" domain, no report provided an exhaustive investigation, and apart from the "post-test clinical pathways" component, reports that investigated the other components found evidence inconsistently. Specifically, "efficacy" was the most investigated component (85.3%, but only less than a half found out any evidence), followed by "post-test clinical pathways" (82.9%, all finding evidence), "effectiveness" (78.0%, evidence found in 18.8%), "clinical accuracy" (61.0%, evidence found in the 88.0%), "safety" (61.0%, evidence found in 56.0%), and "patient-reported outcomes" (34.2%, evidence found in 64.3%).

Within the "personal and societal aspects" domain, all reports that investigated specific components found evidence. However, only about half of the reports (51.2%) investigated the "non-health-related outcomes" component, and even fewer addressed the ethical, social and legal aspects components (26.8%, 22.0% and 4.9%, respectively).

Finally, in the "organizational aspects" domain, most reports investigated and found evidence on burden of disease (90.2%), financial resources need (82.9%), economic evaluations (82.9%), and material resources need (78.0%). Fewer reports examined professional resources need (58.5%), budget impact analysis (53.7%) and the equity in access (29.3%). Only for the "economic evaluation" component three reports (7.3%) searched but did not find any evidence on the application of interest.

Outcomes/measures used for component assessment

Table 3 summarizes the outcomes or measures used by the reports that found evidence for specific components within each assessment domain.

In the "application" domain (16 reports), the most frequently used outcomes/measures were accuracy/concordance and sensitivity and specificity (both 56.2%), followed by test failure rate (50.0%), and positive predictive values (PPV) and negative predictive value (NPV) (37.5%).

In the "clinical aspects" domain, 22 reports investigating the "clinical accuracy" component most often used sensitivity and specificity (90.9%), followed by PPV and NPV (63.6%), while diagnostic yield and test failure rate were each used in 22.7% of reports. For the "efficacy" component (16 reports), disease recurrence/progression was the most frequently assessed outcome (68.8%), followed by early response to treatment (50.0%) and all-cause mortality (56.2%). Among 26 reports exploring the "effectiveness" component, common outcomes included all-cause mortality (50.0%), disease recurrence/progression (50.0%), and change in patient management (53.8%). "Safety" components (14 reports) predominantly focused on false negative and false positive rate (57.1%) and procedure-related adverse events (42.9%). Lastly, in the 9 reports examining the "patient-reported outcomes"

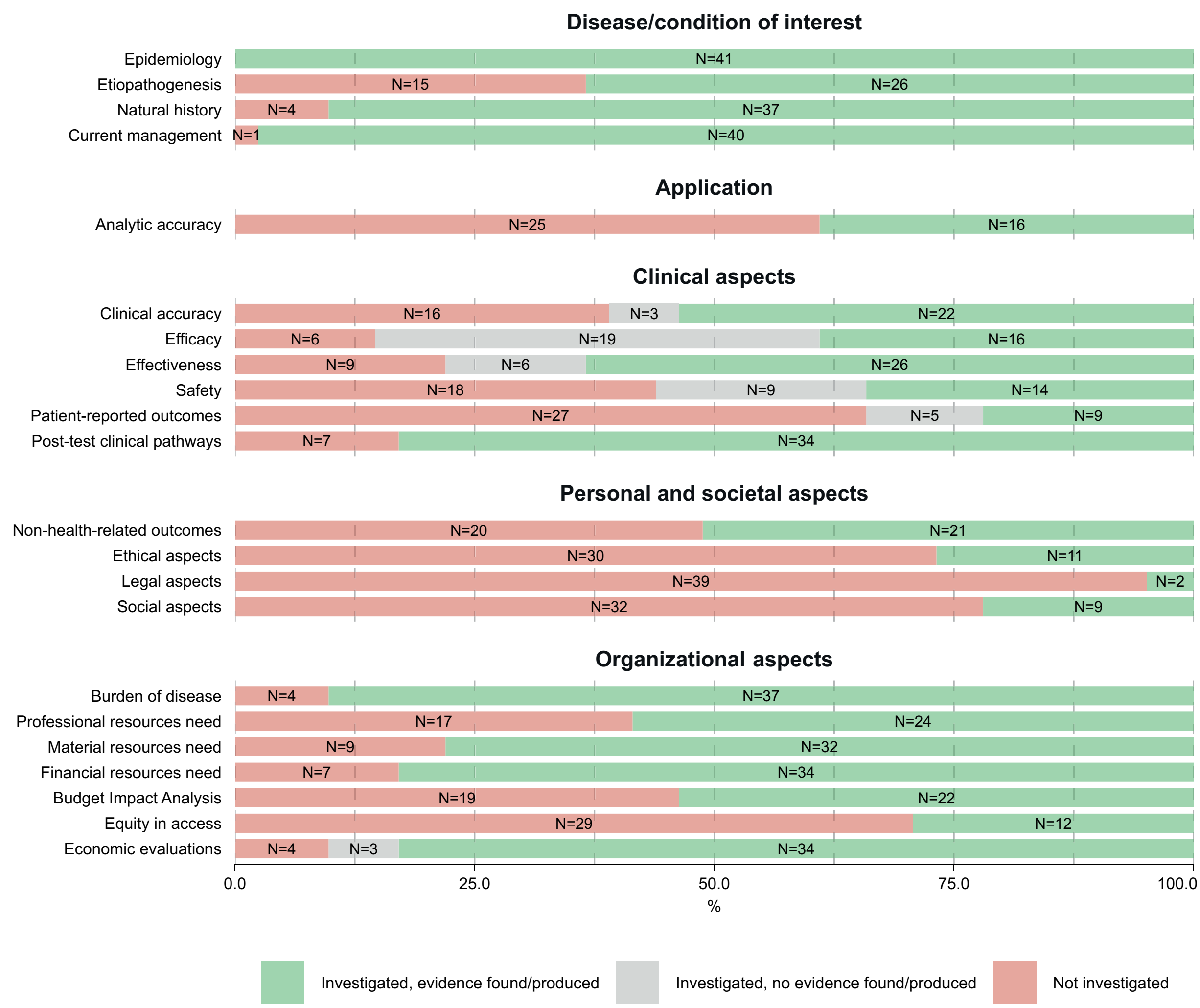

Fig. 3 Assessment components of reports included in the systematic review, by domain (*N* = 41). See Supplementary Table 2 for references

component, health-related quality of life (77.8%) and patients' anxiety/depression (66.7%) were the only outcomes reported.

For the "personal and societal aspects" domain (21 reports), the outcomes most often considered were patients' preferences and values (66.7%), healthcare professionals' preferences and values (42.9%), psychological impact on patients and their families (23.8%), and non-health-related quality of life (4.8%).

Finally, in the "organizational aspects" domain (34 reports), the dominant economic evaluation outcome was cost-utility (70.6%), followed by cost-effectiveness (44.1%).

Sources of evidence used for component assessment

Table 4 details the sources of evidence used or generated for assessing components within each domain. In the "disease/condition of interest" domain, clinical practice guidelines were most frequently used (87.8%), followed by disease/death registries and government/regulatory agencies data (both 75.6%), and narrative reviews (46.3%).

In the "application" domain, the evaluation of the "analytical accuracy" component primarily relied on diagnostic test accuracy studies (56.2%) and analytic studies (37.5%).

Within the "clinical aspects" domain, the approach varied by component. For the "clinical accuracy" component observational analytic studies were the primary source (59.1%), followed by systematic reviews (22.7%), diagnostic test accuracy studies (27.3%) and randomized clinical trials (RCTs, 18.2%). When assessing the "efficacy" component, randomized controlled trials were most common (68.8%), followed by systematic reviews (37.5%) and non-randomized experimental studies (31.2%). As expected, "effectiveness" component assessments predominantly depended on observational analytic studies (92.3%), while

Table 3 Outcomes/measures used for component assessment, by domain. The denominator (N) is the overall number of reports that both investigated and found/produced evidence on a single component

Domain	Component	Outcome/measure	*N* (%)	Reference
Application	Analytic accuracy (*N* = 16)	Accuracy/concordance	9 (56.2)	[22, 28, 31, 36, 37, 45, 52, 53, 56]
		Diagnostic yield	1 (6.2)	[33]
		PPV and NPV	6 (37.5)	[31, 36, 43, 45, 53, 56]
		Sensitivity and specificity	9 (56.2)	[22, 30, 31, 35, 36, 43, 45, 53, 56]
		Test failure rate	8 (50.0)	[17, 23, 31–33, 36, 43, 56]
Clinical aspects	Clinical accuracy (*N* = 22)	Accuracy/concordance	3 (13.6)	[34, 48, 51]
		Diagnostic yield	5 (22.7)	[19, 27, 35, 46, 54]
		Number-needed-to-screen	1 (4.5)	[43]
		PPV and NPV	14 (63.6)	[18, 19, 21, 27, 33, 34, 38, 42, 43, 48, 50, 51, 55, 57]
		Sensitivity and specificity	20 (90.9)	[17–19, 21, 23, 27, 28, 32–35, 38, 40, 42, 43, 48, 50, 51, 55, 57]
		Test failure rate	5 (22.7)	[34, 35, 42, 48, 51]
	Efficacy (*N* = 16)	All-cause mortality	9 (56.2)	[23–25, 32, 41, 45, 47, 50, 56]
		Change in clinical scores/measurements	1 (6.2)	[49]
		Change in invasive/unnecessary procedures	3 (18.8)	[33, 38, 48]
		Change in patient management	5 (31.2)	[45, 47–50]
		Change in procedure/treatment adverse events	3 (18.8)	[21, 38, 44]
		Disease incidence	2 (12.5)	[38, 48]
		Disease recurrence/progression	11 (68.8)	[23–25, 32, 33, 40, 41, 45, 47, 50, 56]
		Disease specific-mortality	1 (6.2)	[23]
		Early response to treatment	8 (50.0)	[24, 25, 32, 33, 45, 49, 50, 56]
		Genetic testing uptake	1 (6.2)	[48]
	Effectiveness (*N* = 26)	All-cause mortality	13 (50.0)	[23, 26–30, 32, 41, 43, 45, 47, 50, 56]
		Change in clinical scores/measurements	3 (11.5)	[22, 54, 57]
		Change in invasive/unnecessary procedures	3 (11.5)	[38, 48, 55]
		Change in patient management	14 (53.8)	[27–30, 35, 37, 41, 45–48, 50, 54, 56]
		Change in procedure/treatment adverse events	6 (23.1)	[22, 27, 38, 42, 44, 57]
		Disease incidence	6 (23.1)	[27, 29, 35, 38, 43, 48]
		Disease recurrence/progression	13 (50.0)	[23, 26, 28–30, 32, 40, 41, 45, 47, 50, 56, 57]
		Disease specific-mortality	3 (11.5)	[23, 30, 43]
		Genetic testing uptake	2 (7.7)	[48, 57]
		Response to treatment	6 (23.1)	[22, 28, 32, 45, 50, 56]
	Safety (*N* = 14)	FN and FP rate	8 (57.1)	[34, 35, 38, 40, 43, 48, 55, 57]
		Procedure-related adverse events	6 (42.9)	[29, 34, 35, 38, 43, 56]
		Rate of secondary/uncertain findings	1 (7.1)	[46]
		Treatment-related adverse events	3 (21.4)	[25, 26, 49]
	Patient-reported outcomes (*N* = 9)	Health-related quality of life	7 (77.8)	[17, 18, 24, 25, 41, 43, 47]
		Patients' anxiety/depression	6 (66.7)	[17, 18, 34, 38, 41, 47]
Personal and societal aspects	Non-health-related outcomes (*N* = 21)	Healthcare professionals' preferences and values	9 (42.9)	[17, 22, 37, 39, 42, 45–48]
		Non-health related quality of life	1 (4.8)	[43]
		Patients' preferences and values	14 (66.7)	[17, 23, 37–39, 42, 45, 47–50, 53–55]
		Psychological impact on patients and their families	5 (23.8)	[20, 35, 43, 47, 57]
Organizational aspects	Economic evaluations (*N* = 34)	Cost-benefit	1 (2.9)	[27]
		Cost-consequence	1 (2.9)	[18]
		Cost-effectiveness	15 (44.1)	[18, 21, 23, 24, 31, 35, 36, 38, 42–44, 46, 48, 56, 57]
		Cost-minimization	4 (11.8)	[18, 27, 29, 50]
		Cost-utility	24 (70.6)	[17, 20, 23–26, 29, 31–34, 36, 39–41, 45, 47–51, 54, 55, 57]

FN: False Negatives; FP: False Positives; PPV: Positive Predictive Value; NPV: Negative Predictive Value

Table 4 Sources of evidence used for component assessment, by domain. The denominator (N) is the overall number of reports that both investigated and found/produced evidence on a single component

Domain	Component	Source of evidence	*N* (%)	Reference
Disease/condition of interest	Epidemiology, etiopathogenesis, natural history, current management (*N* = 41)	Observational analytic studies	7 (17.1)	[17, 18, 20, 27, 38, 44, 48]
		Case report/series	1 (2.4)	[38]
		Clinical practice guidelines	36 (87.8)	[18–22, 24–34, 36–45, 47–55, 57]
		Consensus/position statements, expert opinion/consultation	11 (26.8)	[18, 19, 29, 35, 40, 43, 44, 47, 48, 50, 51]
		Data provided by test/drug manufacturer	1 (2.4)	[43]
		Disease/death registries, government/regulatory agencies data	31 (75.6)	[19–21, 23, 24, 26, 28–38, 40, 41, 43–47, 49, 51, 53–57]
		Genetic association studies	1 (2.4)	[22]
		Narrative reviews	19 (46.3)	[17–20, 23, 27–29, 33, 35, 39, 41, 46, 47, 51–54, 57]
		Previous HTA reports	1 (2.4)	[56]
		RCTs	4 (9.8)	[17, 20, 21, 23]
		Systematic reviews	8 (19.5)	[20, 22, 31, 37, 41, 42, 51, 53]
Application	Analytic accuracy (*N* = 16)	Observational analytic studies	6 (37.5)	[30, 37, 45, 52, 53, 56]
		Clinical practice guidelines	1 (6.2)	[35]
		Data provided by test/drug manufacturer	3 (18.8)	[22, 30, 43]
		Diagnostic test accuracy studies	9 (56.2)	[22, 23, 28, 30, 31, 35, 36, 43, 53]
		Non-randomized experimental studies	1 (6.2)	[52]
		Previous HTA reports	1 (6.2)	[31]
		Primary diagnostic test accuracy study	1 (6.2)	[17]
		Primary laboratory survey	2 (12.5)	[32, 33]
		RCTs	1 (6.2)	[23]
		Systematic reviews	2 (12.5)	[40, 45]
Clinical aspects	Clinical accuracy (*N* = 22)	Observational analytic studies	13 (59.1)	[18, 19, 23, 28, 32, 34, 35, 43, 46, 50, 51, 54, 57]
		Case report/series	2 (9.1)	[19, 27]
		Diagnostic test accuracy studies	6 (27.3)	[21, 27, 34, 38, 42, 55]
		Non-randomized experimental studies	1 (4.5)	[35]
		Primary diagnostic test accuracy study	1 (4.5)	[17]
		RCTs	4 (18.2)	[23, 32, 33, 50]
		Systematic reviews	5 (22.7)	[40, 46, 48, 55, 57]
	Efficacy (*N* = 16)	Non-randomized experimental studies	5 (31.2)	[25, 38, 45, 48, 49]
		RCTs	11 (68.8)	[21, 23–25, 32, 33, 41, 45, 47, 49, 50]
		Systematic reviews	6 (37.5)	[24, 25, 40, 44, 49, 56]
	Effectiveness (*N* = 26)	Observational analytic studies	24 (92.3)	[22, 23, 26–30, 32, 35, 37–39, 41, 43–48, 50, 54–57]
		Case report/series	3 (11.5)	[27, 29, 56]
		Consensus/position statements, expert opinion/consultation	1 (3.8)	[40]
		Diagnostic test accuracy studies	2 (7.7)	[38, 42]
		Non-randomized experimental studies	1 (3.8)	[35]
		Primary analytic study	1 (3.8)	[17]
		Systematic reviews	2 (7.7)	[40, 44]
	Safety (*N* = 14)	Observational analytic studies	7 (50.0)	[26, 29, 34, 35, 38, 43, 57]
		Case report/series	1 (7.1)	[29]
		Clinical practice guidelines	1 (7.1)	[46]
		Diagnostic test accuracy studies	2 (14.3)	[34, 38]
		Non-randomized experimental studies	3 (21.4)	[25, 35, 49]
		RCTs	3 (21.4)	[25, 38, 49]
		Systematic reviews	5 (35.7)	[35, 40, 48, 49, 56]

Table 4 (continued)

Domain	Component	Source of evidence	*N* (%)	Reference
	Post-test clinical pathways (*N*=34)	Observational analytic studies	7 (20.6)	[22, 23, 26, 41, 46, 48, 54]
		Clinical practice guidelines	22 (64.7)	[20–22, 24, 25, 27, 33, 34, 36, 39, 41–43, 45, 48–53, 55, 57]
		Consensus/position statements, expert opinion/consultation	4 (11.8)	[17, 40, 43, 51]
		Disease/death registries, government/regulatory agencies data	1 (2.9)	[33]
		Narrative reviews	2 (5.9)	[19, 48]
		Previous HTA reports	1 (2.9)	[56]
		RCTs	4 (11.8)	[21, 23, 25, 34]
	Patient-reported outcomes (*N*=9)	Observational analytic studies	3 (33.3)	[18, 41, 43]
		Clinical practice guidelines	1 (11.1)	[38]
		Consensus/position statements, expert opinion/consultation	1 (11.1)	[38]
		Non-randomized experimental studies	1 (11.1)	[25]
		Primary qualitative interview	1 (11.1)	[43]
		Primary survey	1 (11.1)	[17]
		RCTs	3 (33.3)	[24, 25, 41]
		Surveys	1 (11.1)	[47]
Personal and societal aspects	Non-health-related outcomes, ethical aspects, legal aspects, social aspects (*N*=23)	Observational analytic studies	4 (17.4)	[18, 22, 35, 47]
		Consensus/position statements, expert opinion/consultation	5 (21.7)	[20, 22, 27, 29, 38]
		Narrative reviews	7 (30.4)	[23, 27, 29, 38, 49, 50, 53]
		Primary qualitative interview	12 (52.2)	[17, 37, 42, 43, 45–50, 54, 55]
		Primary survey	1 (4.3)	[17]
		Qualitative studies	7 (30.4)	[23, 35, 38, 39, 46, 49, 50]
		RCTs	1 (4.3)	[47]
		Surveys	12 (52.2)	[35, 38, 39, 42, 45–48, 50, 54, 55, 57]
		Systematic reviews	3 (13.0)	[38, 43, 57]
Organizational aspects	Burden of disease, professional, material, financial resources needs, BIA, equity in access (*N*=37)	Observational analytic studies	2 (5.4)	[48, 51]
		Clinical practice guidelines	7 (18.9)	[18, 22, 31, 36, 37, 43, 53]
		Consensus/position statements, expert opinion/consultation	13 (35.1)	[18, 19, 25, 27, 38, 42, 48–52, 54, 55]
		Cost-effectiveness analyses	1 (2.7)	[23]
		Data provided by test/drug manufacturer	16 (43.2)	[21, 32–35, 37, 38, 40, 41, 43, 45, 47, 49, 53, 56, 57]
		Disease/death registries, government/regulatory agencies data	26 (70.3)	[19–21, 23, 24, 27, 29, 31–33, 35–38, 40–43, 46, 47, 51, 53–57]
		Microcosting analyses	1 (2.7)	[48]
		Narrative reviews	6 (16.2)	[17, 32, 38, 41, 52, 56]
		National health services pricing data	25 (67.6)	[17–20, 22, 24, 25, 27, 29, 31, 33, 34, 37, 41, 42, 45, 49–57]
		Primary laboratory survey	2 (5.4)	[17, 32]
		Surveys	1 (2.7)	[38]
		Systematic reviews	1 (2.7)	[22]
	Economic evaluations (*N*=34)	Consensus/position statements, expert opinion/consultation	1 (2.9)	[31]
		Cost-benefit analyses	2 (5.9)	[27, 34]
		Cost-effectiveness analyses	13 (38.2)	[18, 23, 29, 31, 36, 38, 42–44, 46, 48, 54, 57]

Table 4 (continued)

Domain	Component	Source of evidence	N (%)	Reference
		Cost-minimization analyses	2 (5.9)	[18, 50]
		Cost-utility analyses	15 (44.1)	[20, 26, 31, 32, 36, 39–41, 45, 48, 49, 51, 54, 55, 57]
		Narrative reviews	1 (2.9)	[33]
		Primary cost-consequence analysis	1 (2.9)	[18]
		Primary cost-effectiveness analysis	8 (23.3)	[21, 24, 35, 42, 44, 46, 48, 56]
		Primary cost-minimization analysis	2 (5.9)	[27, 29]
		Primary cost-utility analysis	21 (61.8)	[17, 20, 23, 25, 26, 29, 31–34, 36, 40, 41, 45, 47–51, 54, 55]
		Systematic reviews	5 (14.7)	[21, 31, 35, 42, 47]

BIA: Budget Impact Analysis; HTA: Health Technology Assessment; RCT: Randomized Controlled Trial

case reports/series, systematic reviews, and diagnostic test accuracy studies were used less frequently (11.5%, 7.7%, and 7.7%, respectively). Similarly, for the "safety" component observational analytic studies were the most common source (50.0%), followed by systematic reviews (35.7%), RCTs (21.4%), and non-randomized experimental studies (21.4%). When assessing the "post-test clinical pathways" component, clinical practice guidelines were the dominant source (64.7%), followed by observational analytic studies (20.6%) and consensus/position statements/expert opinions (11.8%). Assessments of the "patient-reported outcomes" component showed equal reliance on observational analytic studies and RCTs, each used in 33.3% of reports.

In the personal and societal aspects domain, about 52.2% of the reports conducted primary qualitative interviews, with surveys being the most consulted source at the same percentage.

Finally, in the "organizational aspects" domain, the most frequently utilized sources for the "burden of disease", the professional, material, and financial resources needs, the "budget impact analysis", and the "equity in access" components were disease/death registries and government/regulatory agencies data (70.3%), followed by national health services pricing data (67.6%), data provided by test/drug manufacturers (43.2%), and consensus/position statements/expert opinions (35.1%). For economic evaluations, most reports conducted primary analyses, cost-utility analyses being the most common (68.1%), followed by cost-effectiveness analyses (23.3%) and cost-minimization analyses accounting for 5.9%, while secondary evidence sources included previously conducted cost-utility analyses (44.1%), cost-effectiveness analyses (38.2%), cost-benefit analyses (5.9%), and cost-minimization analyses (5.9%).

Gaps reported in component assessment

The gaps reported in the component assessment across different domains are shown in Fig. 4 and further detailed in Supplementary Table 3. The most frequently recurring gap was a lack of evidence, noted in the assessments of "efficacy" (85.7%), "effectiveness" (62.5%), "safety" (52.2%), "patient-reported outcomes" (50.0%), "clinical accuracy" (44.0%), "analytical accuracy" (31.2%), "economic evaluations" (29.7%), "non-health-related outcomes" (19.0%), "social aspects" (11.1%), and 2post-test clinical pathways" (5.9%). Another common issue was the limited generalizability or applicability of findings, which was particularly prominent in "economic evaluations" (73.0%), and also noted for "effectiveness" (50.0%), "non-health-related outcomes" (42.9%), "efficacy" (40.0%), "clinical accuracy" (36.0%), "safety" (13.0%), "patient-reported outcomes" (7.1%), and "post-test clinical pathways" (2.9%).

For both "current management" (15.0%) and "post-test clinical pathways" (8.8%), the most commonly gaps identified were the need for updated clinical practice guidelines or a lack of standardized clinical pathways. Alongside, lack of data and difficulty in estimating costs were highlighted as primary gaps for "material resources need" (21.9%) and "budget impact analysis" (9.1%). Finally, the need for reference standards or thresholds was frequently reported in the assessment of both "analytical accuracy" (25.0%) and "clinical accuracy" (24.0%) components, and concerns about the quality of evidence were also significantly present in the assessments of "analytical accuracy" (25.0%), "clinical accuracy" (16.0%), and "effectiveness" (15.6%).

Discussion

This systematic review showed that numerous evaluations of genetic and genomic applications have indeed been conducted since 2009, reflecting their increasing availability and revealing several interesting characteristics of the reports. Indeed, most reports were produced in Canada, the United Kingdom, and Australia, and they primarily aimed to inform general policy making for single-gene or panel genetic tests. Cancer patients were the most commonly assessed population and staging or treatment was the most frequently considered clinical setting. In contrast, genomic tests accounted for only a small proportion of assessed technologies, suggesting that

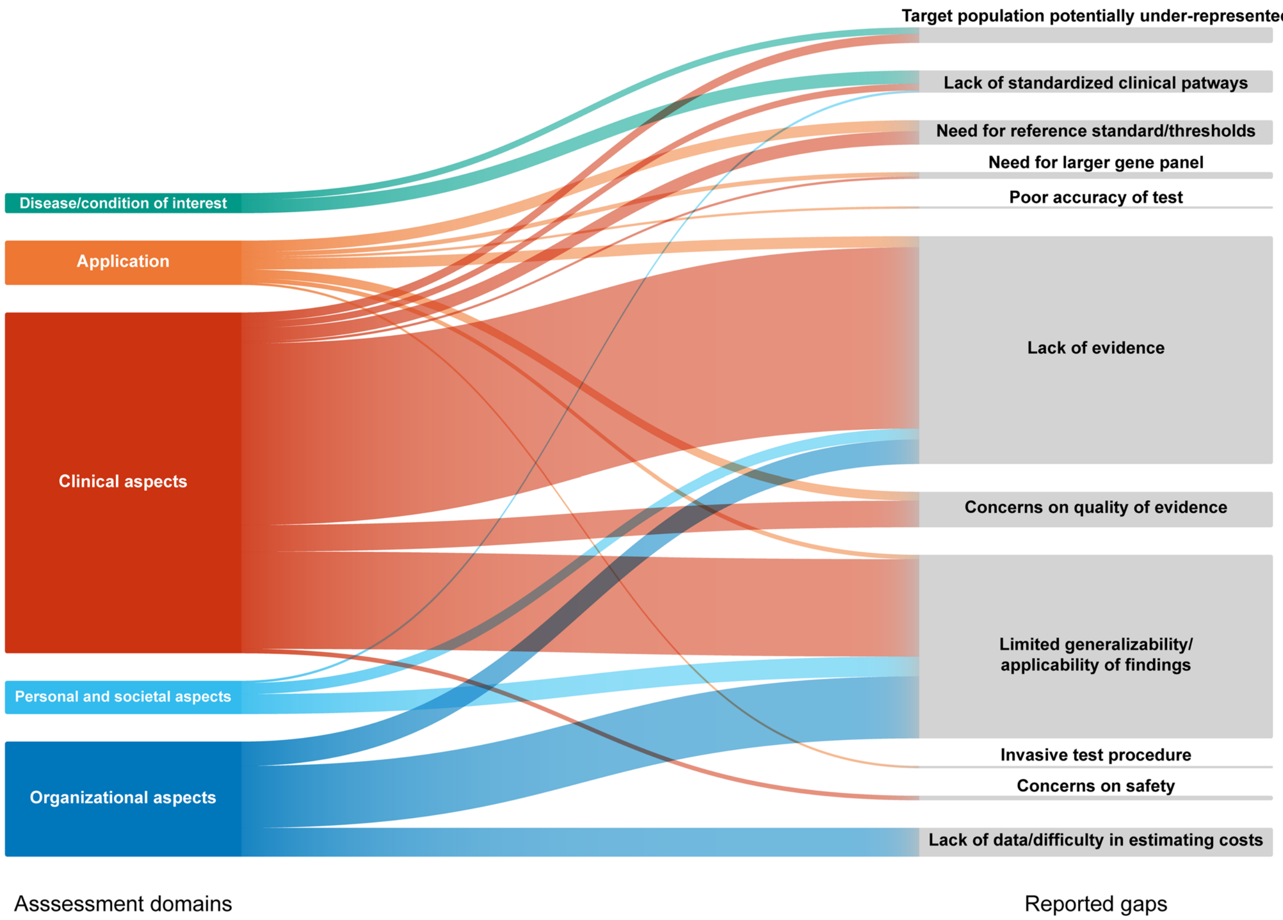

Fig. 4 Alluvial diagram for gaps reported in component assessment, by domain. Left nodes correspond to the assessment domains, right nodes correspond to reported gaps, and edges' thickness is weighted according to number of gaps. See Supplementary Table 3 for further detail

comprehensive genomic technologies are still emerging within HTA evaluations, likely due to their complexity and novelty [58]. On the same line, populations groups other than patients, such as family members, pregnant women, and the general population, as well as healthcare settings focused on prevention or screening, were underrepresented. On the one hand, this may be driven by the ever-growing interest in discovering new personalized treatments for increasingly common cancers [59]. On the other hand, it is often easier to conduct studies on patients with pressing clinical needs than on healthy individuals, somehow limiting the exploration of preventive population-based interventions since such studies pose unique challenges in terms of duration of the follow-up and sample size [60]. Nevertheless, early detection of cancer through screening can significantly reduce cancer-specific mortality [61–63], and limited assessment of these new technologies may hinder the implementation of innovative preventive strategies and delay the availability of potentially effective preventive interventions for the population.

Our analysis of the evaluation process revealed significant heterogeneity in the components assessed across the included reports and highlighted notable evidence gaps that may indicate shortcomings in key areas. Broadly speaking, the evaluation of any diagnostic test should first establish its diagnostic accuracy and the clinical utility [64], and genetic and genomic applications are no exception. Our findings suggest that the "clinical accuracy" and, to a greater extent, the "analytical accuracy" components were generally inadequately assessed, either entirely neglected or based on poor-quality evidence or of limited generalizability. Moreover, report authors frequently noted a lack of reference standards and thresholds for the tests in study, likely because diagnostic accuracy studies, their main source of evidence, are often conducted in contexts other than clinical practice with different reference standards [65, 66]. Nevertheless, analytical and clinical accuracy form the basis for any discussion on a test's clinical utility, and therefore, their thorough evaluation should be a priority. This is particularly important as the growing prevalence of genomic tests will make it increasingly challenging to establish valid gold standards.

Clinical utility refers to a test ability to enhance health outcomes [67]. Although there is no universally accepted definition, clinical utility generally encompasses the broad concepts of efficacy and safety [68]. In our review, the "efficacy", "effectiveness" and "post-test clinical pathways" components were generally widely investigated, as they are deemed essential aspects of clinical utility and so some form of assessing is expected. However, some authors reported a complete absence of evidence on such pivotal aspects, especially, and most concerning, for the "efficacy" component. This gap may be explained by the challenges of conducting proper randomized clinical trials for genetic and genomic technologies and ultimately of providing the building blocks for evidence. Ideally, such trials should evaluate the whole test-treatment pathway to obtain direct evidence on both the predictive nature of the test and the efficacy of the treatment chosen based on its results [69]. As a result, more than 30% of the report investigating efficacy had to rely on non-randomized experimental studies, and overall, insufficient evidence was the most frequent gap reported. To address these challenges, alternative study designs may be required for genetic and genomic technologies and extensions to conventional randomized controlled trials have been proposed, such as randomized test-treatment studies with an adaptive design, especially for low-prevalence conditions [70], as well as basket and umbrella trials that test several treatments targeted for a specific genetic marker common to multiple diseases, or multiple interventions for different patient profiles of the same condition [71, 72]. Although some reports may have attempted to compensate for the lack of experimental evidence on the full test-treatment pathway by using non-randomized or analytical observational studies, these approaches are prone to known biases and must rely on linked evidence approaches [73]. The type and frequency of outcomes used to assess the "efficacy" and "effectiveness" components reflect the dominant population and healthcare field, i.e., patients diagnosed with cancer, with disease recurrence/progression and all-cause mortality emerging as the most common outcomes. "Patient-reported outcomes" was the most frequently overlooked component in the "clinical aspects" domain, and when they were assessed, they were limited to perceived quality of life and estimates of anxiety and depression. Yet, patient reported outcomes (PROs) are increasingly recognized as a viable means to achieve a more holistic understanding of the impact of an intervention, and their evaluation is recommended by regulatory bodies [74], so their inclusion may support the successful implementation of genetic and genomic technologies, particularly given the challenges in generating robust efficacy evidence. The high proportion of reports not investigating safety is also concerning. Moreover, when safety was investigated, it was often assessed solely through false negative (FN) and false positive (FP) rates, along with procedure- or treatment-related adverse events. In contrast, the rate of secondary or uncertain findings was rarely considered. Although FN and FP rates are reliable indicators of a test's safety, revealing the likelihood of a patient entering an incorrect clinical pathway, and thereby that the test may potentially causing harm [75] or instill a false sense of security, the potential harmful effects of secondary or uncertain findings should be given greater consideration. Such results may lead to unexpected clinical pathways, increased anxiety, and unnecessary diagnostic procedures or treatments [76, 77].

On the same line, the "non-health-related outcomes" component was investigated by only about half of the reports. This may be because these outcomes, deeply linked to contextual factors, were often evaluated through primary qualitative studies conducted by the HTA bodies. These types of studies are used to assess outcomes like the preferences and values of both patients and healthcare professionals, as well as the psychological impact on patients and families, and they heavily rely on qualitative methods that require specialized expertise. Accordingly, the most commonly reported gap for non-health-related outcomes was the limited generalizability or applicability of findings, a major challenge in a qualitative research [78]. Nonetheless, non-health outcomes are considered key components of the personal utility [79], a concept that refers to the subjective benefits individuals derive from testing. These benefits may not necessarily directly translate into clinical outcomes but can significantly impact patients' lives by enhancing self-awareness and enabling informed decision-making [79]. The concept of personal utility complements and partially overlaps with the more established notion of clinical utility [80], with some authors rejecting any distinction between the two [64], and it may help to more precisely define the values of these applications, especially genomic ones [81, 82], and efforts have been made to develop standardize measures for it [83].

Ethical, legal and social aspects were all under-investigated in the reports included. In general, ethical analyses are rarely integrated into the HTA process, primarily due to the lack of a formal definition and clear requirements for ethical evaluation [84]. Nonetheless, ethical considerations for genetic and genomic tests should always be taken into account, given their unique implications, such as issues of autonomy and confidentiality [85]. Similarly, an international legal framework for regulating genetic technologies is lacking [86] and methodologies for assessing social and legal aspects are highly heterogeneous. These factors, along with the frequent overlap of social and legal issues with ethical concerns [87], likely contribute to their underreporting. Recently, the concept of Genomic Utility has arisen as a way to summarize health, economic, personal, societal, and family utilities, and a tool is being developed in order to standardize its measurement and to facilitate its inclusion in HTA process and policy decisions [82].

Finally, the most underreported components in the "organizational aspects" domain were the "equity in access", "budget impact analysis" and "professional resources need". In contrast, "economic evaluations", "burden of disease" and "material" and "financial resources need" components were more frequently investigated. Economic evaluations are a cornerstone in assessing health interventions, as they allow for the identification of the most cost-effectives options. In our reports, the "economic evaluations" component mainly relied on primary cost-utility analyses, although they were often regarded as not very informative by the authors. Despite cost-utility analyses being the more appropriate type of economic evaluation in modern economic evaluations [88], they may struggle, in the context of genetic and genomic applications, to capture the full range of health and non-health effects of testing when estimating the utilities to be incorporated into QALYs [89]. Regarding the resources need components (professional, material and financial), the only gap reported was the difficulty in estimating costs. Since genetic and genomic applications should be evaluated not in isolation, but within the context of a delivery model integrated into a clinical or preventive pathway or policy [90], cost considerations and budget impact analysis are essential to complement economic evaluations for assessing a technology's sustainability and affordability, and, thus, these analyses should be integrated more into the HTA process [91]. However, few budget impact analysis guidelines are available [92], especially for non-pharmacological interventions [93].

Based on our findings, the generic HTA framework dominates the methodological landscape, overshadowing the ACCE framework, which is the oldest and specifically designed for assessing genetic tests [94], and reflecting a trend toward modernization and standardization in the assessment process. However, in line with a recent scoping review on indicators of clinical utility [95], we observed that certain evaluation dimensions specific to genetic and genomic applications– particularly those emphasized by the ACCE and EGAPP frameworks, such as analytical accuracy and ethical, legal, and social aspects– tend to be overlooked by the HTA framework. Moreover, despite employing a similar approach, the diversity and heterogeneity in reporting, and the gaps identified in key evaluation domain and components, underscore the need for broader standardization in the assessment of genetic and genomic technologies. In this context, HTA Core Model® was developed by the European Network for Health Technology Assessment (EUnetHTA) with the aim to provide a consistent HTA framework across the European Union (EU) [96, 97] and informed the methodological principles of the recently-enforced EU regulation on HTA [98]. Despite being underrepresented in the reports analyzed, since most were conducted outside the EU, the HTA Core Model®, with its modular and hierarchical structure, could serve as a solid basis for developing a standardized framework for evaluating genetic and genomic technologies [11]. Such a foundation may integrate, as needed, the strengths of the ACCE and EGAPP frameworks, especially in the areas of technological characteristics and clinical aspects. However, further analyses are needed to define an optimal framework.

This work has several strengths. To the best of our knowledge, it is the first systematic review investigating assessment reports on genetic and genomics applications. Moreover, to address the fragmentation in reporting key aspects of assessment and to facilitate comparability, we extracted and categorized the reports characteristics using a harmonized approach, agnostically of the specific framework used in individual reports. This unified approach also allowed us to identify recurrent gaps and barriers in assessment domains, notably the concerning lack of evidence in key areas such as clinical aspects, as well as a general absence of evaluation in others, such as personal and societal aspects. On the other hand, some limitations must be acknowledged. First, the observed geographical distribution of reports may have been influenced by the choice to include only reports written in English and Italian. Reports written in local languages and published in national agencies repositories only may have been missed. However, since no reports were excluded by language, these findings may reflect the presence of centralized health systems, robust, long-established HTA agencies [99] and nationally funded genetic/genomic programs [100] in countries such as Canada, the United Kingdom, and Australia. By contrast, reports from other countries with highly decentralized health systems and less established HTA agencies, were less represented, such as United States, where approaches to HTA are less systematic and no national agency is dedicated to HTA [101]. In line with this, we may have also excluded reports that focused on single domains, as we aimed to analyze only comprehensive HTA reports– i.e., those considering at least three assessment domains, as per our inclusion criteria. Moreover, no assessment reports from low- and middle-income countries were found, possibly reflecting unique challenges faced in accessing and evaluating these technologies [102]– as a result, caution is needed when generalizing the review's findings to these regions. Second, most of the reports retrieved focused on oncologic applications, which may limit the generalizability of our findings. Nevertheless, we found no meaningful differences across reports addressing other disease areas. Finally, as we used a unified approach to classify reports characteristics, some nuances related to the complexity of individual aspects may have been simplified in the synthesis process. Nevertheless, we believe that a relevant degree of detail has been maintained.

Conclusions

In conclusion, this review highlights the immaturity of genetic and genomic technologies, as showed by the limited body of evidence sustaining their implementation. Moreover, challenges exist in both evidence generation and consistency of evaluation frameworks. To ensure that decisions regarding the adoption of these technologies are evidence-based, equitable, and aligned with public health priorities it appears imperative, on the one hand, to strengthen methodological research and standardize study designs and measures of clinical, personal, and economic utility, and on the other hand to standardize the evaluation process itself, which currently appears extremely varied and inconsistent.

Abbreviations

ACCE	Analytic validity, Clinical validity, Clinical utility, Ethical, legal, and social implications
AHRQ	Agency for Healthcare Research and Quality;
BIA	Budget Impact Analysis;
EGAPP	Evaluation of Genomic Applications in Practice and Prevention;
EU	European Union;
EUnetHTA	European Network for Health Technology Assessment;
FN	False Negative;
FP	False Positive;
HIQA	Health Information and Quality Authority;
HTA	Health Technology Assessment;
MSAC	Medical Services Advisory Committee;
NIHR	National Institute for Health Research;
NIPH	Norwegian Institute of Public Health;
NPV	Negative Predictive Value;
PHG	Public Health Genomics;
PM	Personalized Medicine;
PPV	Positive Predictive Value;
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses;
PROSPERO	International Prospective Register of Systematic Reviews;
RCT	Randomized Controlled Trial;
SickKids	The Hospital for Sick Children Technology Assessment Task Force

Supplementary Information

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Supplementary Material 1

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Data availability
All relevant data is included in the article.

Declarations

Ethics approval and consent to participate
As this study did not involve the collection of primary data, the protocol did not require institutional review board approval, and obtaining consent was not necessary.

Consent for publication
Not applicable.

Competing interests
The authors have no competing interests to declare.

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