Mini Review

Daniela d'Angela, Massimiliano Orso*, Antonio Migliore, Barbara Polistena, Federico Spandonaro and Sergio Bernardini

HTA model for laboratory medicine technologies: overview of approaches adopted in some international agencies

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Abstract: The Health Technology Assessment (HTA) Working Group of the Emerging Technology Division of International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) aims to develop a methodological approach for producing structured HTA information for laboratory medicine technologies. This approach seeks to support decision-making processes at the country, regional, and/or hospital levels regarding the introduction of specific technologies. The focus of this model will primarily be on defining assessment elements within the domains of 'organizational aspects' and 'costs and economic evaluations', potentially differentiated by the type of diagnostic technology (e.g., genetic tests, molecular tests). To achieve this project's goal, a literature review and examination of websites of international HTA agencies have been conducted. The research aims to identify multidisciplinary methodological approaches used to assess laboratory diagnostic technologies and to pinpoint the domains and assessment elements utilized. We found 7 methodological articles describing methodological approaches adopted to assess laboratory diagnostic technologies. Among the HTA organizations considered, 23 reports were found, of which 7 were produced by the European Network of HTA (EUnetHTA), 4 by the National Institute for Health and Care Excellence Diagnostic Assessment Program (NICE DAP), and 12 by other HTA agencies. The EUnetHTA reports were rapid collaborative assessments covering various domains, while the NICE DAP reports focused on diagnostic guidances, including descriptions of technologies, clinical need and practice, diagnostic tests, accuracy, effectiveness, and cost-effectiveness. Finally, a survey targeting laboratory professionals will be conducted to introduce assessment elements, differentiated by the type of diagnostic technology, primarily for organizational and economic domains.

Keywords: Health Technology Assessment (HTA); laboratory medicine; HTA domains; assessment elements

***Corresponding author: Massimiliano Orso**, C.R.E.A. Sanità (Centre for Applied Economic Research in Healthcare), Piazza Mancini, 4,00196 Rome, Italy, E-mail: m.orso@creasanita.it. https://orcid.org/0000-0003-0200-1202
Daniela d'Angela, Barbara Polistena and Federico Spandonaro, C.R.E.A. Sanità (Centre for Applied Economic Research in Healthcare), Rome, Italy; and University of Rome Tor Vergata, Rome, Italy. https://orcid.org/0000-0003-3409-4757 (D. d'Angela). https://orcid.org/0000-0002-0138-0223 (B. Polistena). https://orcid.org/0000-0003-1388-2850 (F. Spandonaro)
Antonio Migliore, C.R.E.A. Sanità (Centre for Applied Economic Research in Healthcare), Rome, Italy. https://orcid.org/0000-0003-1984-0803
Sergio Bernardini, University of Rome Tor Vergata, Rome, Italy. https://orcid.org/0000-0003-1984-6834

Introduction

According to the recent definition of the International Network of Agencies for Health Technology Assessment (INAHTA) and Health Technology Assessment International (HTAi), Health Technology Assessment (HTA) is a multidisciplinary process that uses explicit methods to determine the value of health technology at different points in its lifecycle. The purpose is to inform decision-making to promote an equitable, efficient, and high-quality health system [1]. The HTA Glossary defines health technology as an intervention developed to prevent, diagnose, or treat medical conditions; promote health; provide rehabilitation; or organize healthcare delivery. The intervention can be a test, device, medicine, vaccine, procedure, program, or system. Among the different types of health technologies, this article focuses on diagnostic technologies used in laboratory medicine.

At the international level, in addition to the INAHTA mentioned above and HTAi, a crucial role is played by the European Network of HTA (EUnetHTA). The institutionalization of HTA in Europe has been a lengthy process marked by extensive efforts from both the EU Commission and member state agencies [2]. It is aimed at smart healthcare resource management, reducing duplication among member states, and improving patient access to the best healthcare technologies [3]. Initiatives like EUR-ASSESS (1994) and ECHTA/ECAHI (2000) laid the groundwork, leading to the development of the EUnetHTA project (2006–2008), which produced the HTA Core Model® [4–7]. Three subsequent joint actions funded by the EU Commission furthered this collaboration, culminating in the adoption of the EU HTA Regulation in December 2021 [8–11]. This regulation establishes a coordination group and subgroups to conduct technical HTA work. To support this system, the EU Commission awarded a service contract to the EUnetHTA 21 consortium, comprising HTA agencies from 12 EU member states [12].

The EUnetHTA HTA Core Model® [13] is a methodological framework designed for generating and sharing HTA information, that comprises three main components: (1) a standardized set of HTA questions for defining research questions; (2) methodological guidance for answering these questions; (3) a common reporting structure for presenting findings. The Core Model® includes nine domains of assessment: (1) health problem and current use of technology (CUR), (2) description and technical characteristics of technology (TEC), (3) safety (SAF), (4) clinical effectiveness (EFF), (5) costs and economic evaluation (ECO), (6) ethical analysis (ETH), (7) organizational aspects (ORG), (8) patients and social aspects (SOC), (9) legal aspects (LEG). Each domain is subdivided into topics and issues, defining Assessment Elements (AEs). Originally developed for various technology types, it now includes versions tailored for specific assessments, such as diagnostic technologies.

While the Core Model can be applied to evaluate all health technologies, the Health Technology Assessment Working Group of the Emerging Technology Division within the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) is focused on developing a specific methodological approach for structured HTA-tailored to laboratory medicine technologies, by introducing new assessment elements specific by the type of technologies. The proposed approach aims to facilitate decision-making processes at Country, Regional, and Hospital levels for the adoption of a specific technology.

Moreover, HTA should be applied considering various factors that vary depending on the context: local gaps in clinical care (clinical needs), consumer demand, healthcare model, infrastructure (e.g., water quality, electricity stability), healthcare processes, currently available technologies, options for support, ability to implement and sustain a new technology, socioeconomic circumstances, communication channels, time (which influences decision-making and the rate of adoption), and cultural issues.

The global approach to HTA by the IFCC provides an opportunity to recommend the most suitable technology based on the context of different member countries. Indeed, a technology may be deemed emerging in one context, while it is considered established in another. Since different technologies are available, used, and/or reimbursed in different provinces, states, and regions, differences can also exist within the same country.

The standard we aim to establish is intended for laboratory professionals to devise implementation strategies for new technologies in their clinical laboratories (micro level); corporate members seeking to tailor their technology offerings to the sustainability and needs of different countries; and national societies to develop strategies for their health systems regarding the implementation of new technologies in clinical laboratories (macro level). These different levels (macro, meso, micro) require different HTA approaches. Our project aims to identify the optimal HTA approaches, specific to each level. Among the 9 HTA domains described in the EUnetHTA core model, we believe that the first four (TEC, CUR, EFF, and SAF) are often generalizable in different contexts, according also to the Joint Clinical Assessment (JCA) introduced by the Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on health technology assessment, entered into force in January 2022 and applies as of January 2025. However, we acknowledge that differences can also exist in the CUR and EFF domains among different countries or states/regions/provinces. In fact, they can have different capacities, readiness, trained staff, alternative care pathways/technologies available, budgets, etc.

On the other hand, the other five domains (ECO, ETH, ORG, SOC, LEG) are more context-specific and should be used to assess the impact of health technologies in different settings.

The definition of this model will consider all the HTA domains, with a focus on establishing assessment elements (topics and issues) within the domains of ‘organizational aspects’ and ‘costs and economic evaluations’, potentially incorporating distinctions based on the type of diagnostic technology (genetic tests, molecular tests, etc.).

To achieve the final goal of the project, a literature review was conducted, integrated with a search of institutional websites of international HTA agencies. The research aimed to identify specific methodological approaches adopted to assess laboratory diagnostic technologies with a multidisciplinary approach, as well as to identify the domains adopted. An analysis of HTA reports conducted by the most advanced HTA agencies was carried out to understand their structure. In the following steps, an analysis of the assessment elements considered within the individual domains will be carried out. Finally, a survey addressed to laboratory professionals will be conducted to introduce assessment elements mainly focused on organizational and economic domains.

Methods

A literature search was performed in PubMed on October 2nd, 2023 using the following search strategy: ((health technology assessment [Title] OR HTA [Title]) AND (laboratory [Title/Abstract] OR laboratories [Title/Abstract] OR diagnostic [Title] OR diagnosis [Title] OR diagnoses [Title] OR clinical chemistry [Title/Abstract] OR clinical biochemistry [Title/Abstract])). We included articles describing methodological approaches adopted to assess laboratory diagnostic technologies. In addition, we searched the websites of the following HTA agencies using the same keywords: Agency for Healthcare Research and Quality (AHRQ) (United States), Canadian Agency for Drugs and Technology in Health (CADTH) (Canada), Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWIG) (Germany), Medical Services Advisory Committee (MSAC) (Australia), National Institute for Health and Care Excellence Diagnostic Assessment Program (NICE DAP) (United Kingdom), Statens beredning för medicinsk och social utärdering (SBU) (Sweden), and Zorginstituut Nederland (ZIN) (The Netherlands). We aimed to verify whether these organizations had produced HTA reports regarding laboratory medicine and to analyze what type of assessment elements were considered. In addition to the 7 agencies, we also searched the INAHTA database and the EUnetHTA website.

Results

The results of the selection process are depicted in Figure 1. The PubMed search identified 27 records, 7 of which fulfilled our inclusion criteria [14–20]. The characteristics of the included studies are described in Table 1. Studies were published between 2016 and 2023. There were five reviews, one perspective paper, and one analytical framework proposal.

Our aim was to provide an overview of the real use in the HTA sector for specific technologies, in terms of the domains that underlie the use of the HTA tool in specific countries (reimbursement, priority setting, etc.). It should also be considered that within the same domain (e.g., ECO), some assessment elements can be transferred from one country to another, while others are context-dependent due to different resource prices.

Barna et al. [14] performed a scoping review to investigate the HTA methods used for Multi-Analyte Assays with Algorithmic Analyses (MAAAs), aiming to identify the criteria employed for clinical research and reimbursement considerations. They found that the most used criteria were clinical utility and efficiency, followed by economic, ethical, legal, and social aspects.

The recent review by Ferrante di Ruffano et al. [15] which was aimed to describe available guidance documents of international HTA organizations that evaluate diagnostic technologies, identified seven key organizations with test-specific guidance sections. The themes identified encompass: elucidation of claims of test benefits; attitude to direct and indirect evidence of clinical effectiveness (including evidence linkage); searching; quality assessment; and health economic evaluation. Few test-specific methods were identified, with a prevalence of methods focused on diagnostic accuracy. Future challenges include integrating direct and indirect evidence and standardizing approaches to evidence linkage.

Garfield et al. [16] reviewed diagnostic-specific HTA programs focused on molecular diagnostics (MDx) and identified elements representing common and best practices. The included HTA programs failed to identify clear parameters of acceptability related to clinical and analytic performance, clinical utility, and economic impact. Authors suggested that HTA agencies should enhance transparency, improve communication and collaboration between industry and HTA stakeholders, establish clearer connections between HTA findings and funding decisions, explicitly acknowledge and justify differential approaches for laboratory-developed tests compared to regulatory-approved tests, and define clear evidence requirements.

Nurchis et al. [17] aimed to map the available evidence about the use of HTA in the assessment of whole genome sequencing (WGS). The included studies were focused on assessing the clinical utility and cost-effectiveness of genome-wide sequencing, while also addressing policy questions through analyses of organizational and ethical factors. It is crucial to encourage critical reflection during the development of HTA reports for WGS to guide decision-makers in setting research and policy priorities, as well as reimbursement rates.

As the previous study, Payne et al. [18] described current HTA approaches for WGS-based diagnostic tests. HTA stages regarding WGS were analyzed in detail: define the policy question; collate background information; define research objectives; conduct clinical and economic reviews and analysis; produce final HTA report.

Soares et al. [19] provided an analytical framework for establishing the value of diagnostic and prognostic tests for HTA. The value of these tests can be summarized using 3 interlinked components: classification (using test results to define treatment groups), choice (in terms of treatment), and outcomes.

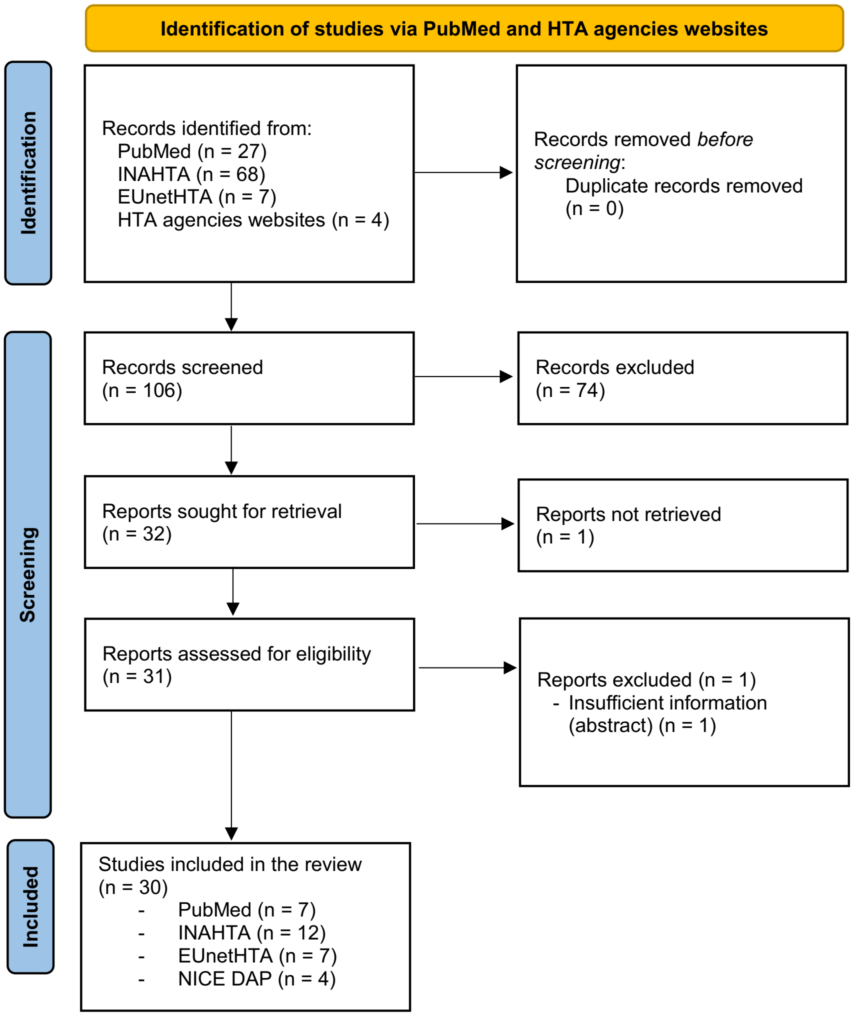

Figure 1: PRISMA 2020 flow diagram. From: Ref. [21]. For more information, visit: http://www.prisma-statement.org/.

Steuten et al. [20] summarized trends and approaches in early-phase HTA on precision biomarkers in oral health and systems medicine. The review highlights the difficulty in demonstrating the health outcomes of biomarkers and next-generation diagnostics, as they may not always directly influence long-term outcomes but rather affect subsequent care processes.

The search in the INAHTA database retrieved 68 reports, 12 of which [22–33] met our inclusion criteria (Table 2). Reports were published between 2009 and 2023. Ten were full HTA reports, while two were rapid HTA reports. The two rapid HTA reports assessed the first 4 domains of the EUnetHTA core model, namely CUR, TEC, SAF, and EFF domains. The full HTA reports also assessed ECO (10/10 reports), ETH (5/10 reports), ORG (4/10 reports), SOC (8/10 reports), and LEG (3/10 reports).

Through the search on the EUnetHTA website, we found seven HTA reports of interest:

- POCT/point of care tests: d-dimer and troponin.
- C-reactive protein point-of-care testing (CRP POCT) to guide antibiotic prescribing in primary care settings for acute respiratory tract infections (RTIS).
- Stool DNA testing for early detection of colorectal cancer.
- Added value of using the gene expression signature test mammaprint® for adjuvant chemotherapy decision-making in early breast cancer.
- Screening of fetal trisomies 21, 18 and 13 by noninvasive prenatal testing.
- Rapid collaborative review on the current role of antibody tests for novel coronavirus sars-cov-2 in the management of the pandemic.
- Rapid collaborative review on the diagnostic accuracy of molecular methods that detect the presence of the sarscov-2 virus in people with suspected covid-19.

These seven reports were rapid collaborative assessments that included the CUR, TEC, SAF, and EFF domains; in

Table 1: Characteristics of included studies identified via PubMed.

First author, year	Design	Technology	HTA organizations	Model	HTA domains assessed
Barna 2018	Scoping review	Multi-analyte assays with algorithmic analyses (MAAAs)	– EUnetHTA – USA OHPG – EGAPP	– EUnetHTA core model® – Evaluation of genomic applications in practice and prevention ACCE framework	– Clinical validity and utility criteria – Economic, ethical, legal, and social aspects
Ferrante di Ruffano 2023	Methodological review	Diagnostic tests	– AHRQ – CADTH – IQWiG – MSAC – NICE DAP – SBU – ZIN	The approaches of 7 key HTA organizations and 34 other organizations are described	Main themes found: – Elucidation of claims of test benefits; – Attitude to direct and indirect evidence of clinical effectiveness (including evidence linkage); – Searching; – Quality assessment; – Health economic evaluation Except for dealing with test accuracy data, approaches were largely based on general approaches to HTA with few test-specific modifications The differences between the approaches concern the elucidation of test claims and attitude to direct and indirect evidence
Garfield 2016	Review of HTA programs on diagnostics and case studies	Molecular diagnostics (MDx)	– MSAC – NICE DAP – EGAPP – CADTH HTERP – Palmetto GBA MolDX – IQWiG	Six diagnostic technologies assessment evaluation frameworks were identified	The included HTA programs that have MDx-specific methods do not provide clear parameters of acceptability related to clinical and analytic performance, clinical utility, and economic impact The case studies highlight similarities and differences in evaluation approaches across HTAs in the performance metrics used (analytic and clinical validity, clinical utility), evidence requirements, and how value is measured
Nurchis 2022	Scoping review	Whole genome sequencing (WGS)	– HQO – CADTH – NIHR – KCE – SBU	Five HTA organizations elaborated: one full HTA, four rapid reviews, and two other documents	Clinical utility, cost-effectiveness, organizational and ethical considerations
Payne 2017	Perspective paper	Whole genome sequencing (WGS)	None	HTA stages with reference to WGS: – Define the policy question; – Collate background information; – Define research objectives; – Conduct clinical and economic reviews and analysis; – Produce final HTA report	As reported by the paper: "*Evidence requirements for HTAs of genomic-based diagnostic tests:* – *Evidential requirements and particular challenges of HTAs of WGS are described using the PICO framework* – *Defining the population of interest in an HTA of WGS is problematic for a number of reasons such as the need, at times, to consider the wider family unit as the service user rather than the individual* – *WGS can be considered a complex intervention, and consideration must be given to the precise nature of the test and how it fits into broader care pathways*

Table 1: (continued)

First author, year	Design	Technology	HTA organizations	Model	HTA domains assessed
					– *Reliable estimates of the value for money offered by a new test are reliant on comparisons with relevant existing technologies: usually current practice. In the case of diagnosing rare inherited conditions, multiple comparators to genomic-based tests may be available including traditional genetic testing and pedigree analysis by a genetic counselor* – *Significant challenges in relation to the measurement of costs and outcomes of WGS exist* – *A reliance on health-related outcomes in currently applied quality-adjusted life-year-based approaches to economic evaluation in healthcare means that certain diagnostics for untreatable conditions are unlikely to be deemed cost-effective despite being valued by stakeholders* – *There is a lack of clarity regarding the true cost of WGS-based diagnostic tests which may lead to erroneous estimates of cost–effectiveness informing HTAs.*"
Soares 2018	Analytical framework proposal	Diagnostic and prognostic tests	None	Analytical framework for establishing the value of diagnostic and prognostic tests for HTA	As reported by the paper: "*This paper outlines a coherent framework for the assessment of diagnostic and prognostic tests for HTA using a linked-evidence, or decision modeling, approach. It is solidly grounded on the indirect mechanism of value accrual for these health technologies that can be summarized using 3 interlinked components: classification (using test results to define treatment groups), choice (in terms of treatment) and outcomes*"
Steuten 2016	Review	Precision biomarkers in oral health and systems medicine	None	Trends and approaches in early phase HTA	As reported by the paper: (1) *"The potential value of precision biomarkers in oral health and systems medicine is tremendous as they facilitate noninvasive, low-cost, and widely accessible detection and monitoring of a wide array of local, infectious, and systemic disease*" (2) *Rapid developments in biomarker and next-generation diagnostics in oral health require a pro-active strategy to managing development and uptake of these techniques, in order to maximize health benefit for expenditure* (3) *Health Technology Assessment (HTA) is a multidisciplinary scientific process that informs the evidence-based transition of new discoveries from laboratory to clinic, considering medical, economical and sometimes social and ethical arguments*

Table 1: (continued)

First author, year	Design	Technology	HTA organizations	Model	HTA domains assessed
					(4) *Early stage HTA is a proactive approach to health economic evaluation of diagnostic technologies, which identifies key drivers of diagnostic value as early as possible and herewith guides the efficiency of the diagnostics innovation process* (5) *HTAs are increasingly undertaken in dentistry, but the quality of the evaluations remains relatively low compared to pharmaco-economic studies* (6) *The potential cost-effectiveness of biomarkers for oral health or systems medicine is as yet largely unexplored* (7) *Demonstrating health outcomes of biomarkers and next-generation diagnostics are particularly challenging because they do not influence long-term outcomes directly, but rather impact subsequent care processes* (8) *Biomarker testing costs are typically less of a barrier to uptake in practice than the biomarker's impact on longer term health outcomes* (9) *As a single biomarker or next-generation diagnostic in oral health can inform decisions about numerous diagnosis-treatment combinations, early stage HTA is crucial in prioritizing the most valuable diagnostic applications to pursue (first)* (10) "*For the vast array of oral health biomarkers currently developed, early HTA is necessary to timely and iteratively assess their comparative effectiveness and herewith anticipate inevitable questions about value for money from regulators and payers*"

AHRQ, Agency for Healthcare Research and Quality; CADTH, Canadian Agency for Drugs and Technologies in Health; EGAPP, Evaluation of Genomic Applications in Practice and Prevention; HQO, Health Quality Ontario; HTERP, Health Technology Review Panel; IQWiG, Institute for Quality and Efficiency in HealthCare; KCE, Belgian Health Care Knowledge Centre; MSAC, Medical Services Advisory Committee; MolDX, Molecular Diagnostic Services Program; NICE DAP, National Institute for Health and Care Excellence Diagnostics Advisory Programme; NIHR, British National Institute for Health Research; OHPG, Office of Public Health Genomics; PICO, Population, Intervention, Comparator and Outcomes; SBU, Swedish Agency for Health Technology Assessment and Assessment of Social Services; ZIN, Zorginstituut Nederland. The texts in italics are quotes from the cited articles.

some cases, also ETH, ORG, SOC, and LEG domains were considered, while the ECO domain was not analyzed. Only in two reports the ETH, ORG, SOC, and LEG domains were considered in the main text, while in other reports they were included in appendices, providing only short answers in the case of a "yes" evaluation of the assessment elements. In the first report, the two assessment elements addressed in the main text were: (1) how does the test affect the current work processes? (2) How does the test modify the need for other technologies and the use of resources? In the second report, 27 assessment elements were addressed.

Table 2: Characteristics of included studies identified via INAHTA database.

Report	Methods	Type of HTA	CUR	TEC	SAF	EFF	ECO	ETH	ORG	SOC	LEG
CADTH 2016 [22]	Systematic review	Full	X	X	X	X	X				
HIQA 2020 [23]	Review	Rapid	X	X	X	X					
HIQA 2021 [24]	Systematic review; GRADE	Full	X	X	X	X	X	X	X	X	X
HIQA 2023 [25]	Systematic review	Full	X	X	X	X	X	X	X	X	X
HIQA 2023 [26]	Systematic review; GRADE	Rapid	X	X	X	X					
HQO 2019 [27]	Systematic review; GRADE	Full	X	X	X	X	X	X	X	X	
KCE 2009 [28]	Systematic review	Full	X	X	X	X	X			X	
NIPH 2020 [29]	Systematic review; GRADE	Full	X	X	X	X	X				
NIPH 2022 [30]	EGAPP; extended framework described by Pitini et al.	Full	X	X	X	X	X	X	X	X	X
Ontario Health 2020 [31]	Systematic review; GRADE	Full	X	X	X	X	X			X	
Ontario Health 2020 [32]	Systematic review; GRADE	Full	X	X	X	X	X			X	
Ontario Health 2020 [33]	Systematic review; GRADE	Full	X	X	X	X	X	X		X	

HTA, Health Technology Assessment; CUR, health problem and current use of technology; TEC, description and technical characteristics of technology; SAF, safety; EFF, clinical effectiveness; ECO, costs and economic evaluation; ETH, ethical analysis; ORG, organizational aspects; SOC, patients and social aspects; LEG, legal aspects; CADTH, Canadian Agency for Drugs and Technologies in Health; HIQA, Health Information and Quality Authority; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; HQO, Health Quality Ontario; KCE, Belgian Health Care Knowledge Centre; NIPH, Norwegian Institute of Public Health; EGAPP, Evaluation of Genomic Applications in Practice and Prevention.

Lastly, the search on the websites of the seven HTA agencies identified four reports produced by NICE DAP. No other reports were identified in the other agencies.

NICE DAP

– DG9. EGFR-TK mutation testing in adults with locally advanced or metastatic non-small-cell lung cancer.
– DG11. Faecal calprotectin diagnostic tests for inflammatory diseases of the bowel.
– DG12. Measuring fractional exhaled nitric oxide concentration in asthma: NIOX MINO, NIOX VERO and NObreath.
– DG20. SepsiTest assay for rapidly identifying bloodstream bacteria and fungi.

The 4 reports by NICE DAP are diagnostic guidances and include the description of the technologies, clinical need and practice, diagnostic tests (intervention and comparator), and outcomes in terms of accuracy, clinical effectiveness, and cost-effectiveness.

Discussion

The analysis of reports from the included studies showed how reports regarding diagnostic technologies vary between different agencies, in terms of domains and assessment elements considered. This difference can be partly explained by the different roles played by the agencies analyzed in the first phase of the project. The rapid relative effectiveness assessments by EUnetHTA usually include the four main domains, namely CUR, TEC, EFF, and SAF, and, in some cases, they also consider ETH, ORG, SOC, and LEG domains. The ECO domain is generally not included in these reports. Instead, NICE DAP reports consider the clinical and economic comparative effectiveness of two or more diagnostic technologies, but ethical, organizational, social, and legal aspects are not formally analyzed. Due to the variability of domains and assessment elements investigated, and due to the different roles of the agencies in different countries, our research project intends to identify a set of assessment elements for each domain specific to different types of diagnostic technologies (genetic, molecular, etc.). According to Regulation (EU) 2021/2282 on Health Technology Assessment for assessments in European countries, the clinical aspects will be assessed mainly at the European level (JCA), while the non-clinical ones, like organizational and costs and economic evaluation, need adaptation at the country, regional and hospital level. As a priority for those two domains and specifically for local/hospital level, in the subsequent phases of the project, we will identify the assessment elements considered in the reports produced. A survey aimed at clinical experts in the sector and expert HTA methodologists will allow us to confirm or revise those already considered by the various agencies and propose new ones, with a distinction by type of laboratory diagnostic technology.

The ultimate aim of the project, which will end by 2025, is to define, in collaboration with IFCC, a model for the evaluation of laboratory diagnostic technologies to support decision-making processes at country, regional, and/or hospital levels regarding the introduction of specific technologies.

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