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Policy Perspective

Health Technology Assessment for Molecular Diagnostics: Practices, Challenges, and Recommendations from the Medical Devices and Diagnostics Special Interest Group



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ABSTRACT

Background: Health technology assessments (HTAs) are increasingly used to inform coverage, access, and utilization of medical technologies including molecular diagnostics (MDx). Although MDx are used to screen patients and inform disease management and treatment decisions, there is no uniform approach to their evaluation by HTA organizations. **Objectives:** The International Society for Pharmacoeconomics and Outcomes Research Devices and Diagnostics Special Interest Group reviewed diagnostic-specific HTA programs and identified elements representing common and best practices. **Methods:** MDx-specific HTA programs in Europe, Australia, and North America were characterized by methodology, evaluation framework, and impact. Published MDx HTAs were reviewed, and five representative case studies of test evaluations were developed: United Kingdom (National Institute for Health and Care Excellence's Diagnostics Assessment Programme, epidermal growth factor receptor tyrosine kinase mutation), United States (Palmetto's Molecular Diagnostic Services Program, OncotypeDx prostate cancer test), Germany (Institute for Quality and Efficiency in Health-care, human papillomavirus testing), Australia (Medical Services Advisory Committee, anaplastic lymphoma kinase testing for

non-small cell lung cancer), and Canada (Canadian Agency for Drugs and Technologies in Health, Rapid Response: Non-invasive Prenatal Testing). **Results:** Overall, the few 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. Not all HTAs are directly linked to reimbursement outcomes. **Conclusions:** To improve MDx HTAs, organizations should provide greater transparency, better communication and collaboration between industry and HTA stakeholders, clearer links between HTA and funding decisions, explicit recognition of and rationale for differential approaches to laboratory-developed versus regulatory-approved test, and clear evidence requirements.

Keywords: diagnostics, health technology assessment.

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Introduction

Health technology assessment (HTA) is “the systematic evaluation of the properties and effects of a health technology, addressing the direct and intended effects...as well as its indirect and unintended consequences...aimed mainly at informing decision making regarding health technologies” [1]. Many health care

systems have established HTA programs to inform clinical and coverage decision making for medical technologies. HTA programs are most advanced for pharmaceuticals; however, few systems have established processes specifically delineated for molecular diagnostics (MDx) [2–4]. MDx influence many health care decisions including screening, diagnosis, medical treatment, and prevention [5]. Some HTA programs are taking existing

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systems set up to evaluate pharmaceuticals and applying them to MDx with little modification of process or requirements [3,4,6,7].

An example of this can be seen in Canada's Alberta Health Technologies Decision Process, which considers three main components in its HTA process: Social Systems and Demographics; Technology Effects and Effectiveness; and Economic Considerations. The process includes a systematic literature review, in some cases a meta-analysis of data, and comments on the quality of the evidence supporting the efficacy, safety, and risk of adverse events [8,9]. In contrast, other HTA groups, such as the National Institute for Health and Care Excellence (NICE)'s Diagnostic Assessment Programme (DAP) in the United Kingdom [10], Palmetto's Molecular Diagnostic Services (MolDX®) Program for MDx in the United States [6], have developed specific evaluation frameworks for MDx. As well, the Canadian Agency for Drugs and Technologies in Health (CADTH) uses an evaluation framework applicable to medical devices, diagnostic tests, and medical, dental, or surgical procedures and programs [11].

The objective of this article was to compare several molecular diagnostic HTA programs, describe examples of molecular diagnostic HTAs conducted, and make recommendations to improve and standardize systems moving forward. As part of that process, case studies of four diagnostic HTAs from the United Kingdom, the United States, Germany, and Australia are presented to demonstrate current practices, describe diagnostic attributes being evaluated, and highlight the challenges that need to be overcome for an optimal molecular diagnostic HTA framework to be realized. The recommendations are targeted toward policy decision makers, payers, health technology assessors, and industry members.

Methods

The Medical Devices and Diagnostics (MD&D) Special Interest Group (SIG) of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) was established in 2013. Researchers experienced in this field and working in academia, research organizations, the diagnostics industry, or US or European governments were invited to join the leadership committee of the MD&D SIG. The leadership committee conducted this review across multiple European countries, Australia, and North America. We identified the five health care systems with established MDx evaluation programs and where a detailed description of the program is publicly available. From this process, Australia's Medical Services Advisory Committee (MSAC) [12], Canada's CADTH [11], UK's NICE [10], US's Evaluation of Genomic Applications in Practice and Prevention (EGAPP) [13] and Palmetto's MolDX Program [6], and Germany's Institute for Quality and Efficiency in Healthcare (IQWiG) [14] were identified. First, the programs were assessed on the basis of

1. the program's domain of influence;
2. the purpose of assessment;
3. elements included in the analysis (i.e., product descriptions, clinical effectiveness measures, ethical issues, etc.);
4. inclusion of safety measures;
5. what type of data were included in their analyses;
6. how levels of evidence were evaluated; and
7. whether economics are included in the evaluation.

Then, each program was characterized using the following domains: country, purpose, health problem and current use of technology, description and technical characteristics of technology, population, safety, accuracy and clinical validity, clinical effectiveness, patient preferences, quality of evidence, costs and economic impact, ethical, legal, and social aspects, organizational aspects, environmental factors, and levels of evidence (Table 1).

Together these factors illustrate the programs' relative market impact, complexity, transparency, comprehensiveness, and flexibility of the HTA programs for MDx.

There was no single MDx whose assessment was publicly available across all HTA programs included in the study. Therefore, case studies were developed to illustrate the current evaluation processes and challenges for HTA of MDx. We selected recently completed MDx assessments within the systems included in the study and required that detailed descriptions of the assessments were publicly available. The intent of the case studies was not to comprehensively describe the features of all health care systems with HTA processes for diagnostics, nor summarize MDx that have been evaluated to date. Instead, the case studies demonstrate the process and outcomes from four representative assessments. These include Palmetto's MolDX evaluation of OncotypeDX prostate cancer test, NICE DAP's assessment of epidermal growth factor receptor tyrosine kinase (EGFR-TK) testing, IQWiG's assessment of human papillomavirus (HPV) testing, MSAC's evaluation of anaplastic lymphoma kinase (ALK) gene testing for non-small cell lung cancer (NSCLC), and CADTH's Rapid Response on non-invasive prenatal testing (NIPT).

Overall, there are very few MDx HTAs that are clearly described in process and outcome available in the public domain. Because not all reviews are publicly available, the cases may fall short of true representation and generalizability. However, as case studies they provide context and demonstrate the organization's practices.

Current Practices and Processes for Evaluation of Diagnostics

Table 1 presents the characteristics of the five health care systems for evaluation of MDx included in this review. Although there are some commonalities across programs, there is no one standard HTA process to evaluate MDx [2,3]. We also recognize that the MDx field is relatively new, and professional associations, such as the Association for Molecular Pathology and the American College for Medical Genetics and Genomics, are developing guidance for best practices. As illustrated in Figure 1, the relationship between the HTA organizations, government, and other payers, the level of transparency of the process, and the specific processes and methods (e.g., types of studies considered and level of evidence) differ across the programs. Key differences that create heterogeneity include the following:

1. There is no clear mandate as to which diagnostics need formal HTA (i.e., the vast majority of *in vitro* diagnostics do not undergo a formal national or regional HTA).
2. There is no uniform approach for laboratory-developed tests (LDTs; also called "in-house" or "home-brew" tests): Whether they should be formally evaluated by HTA agencies along with regulatory-approved tests, or whether payers should consider them differently with regard to pricing and reimbursement.
3. Evidence requirements are not clearly delineated with no universal guidance for outcomes to be measured, appropriate study types, performance requirements, comparative effectiveness, and economic thresholds.
4. The impact of HTA recommendations on reimbursement, access, and pricing is often unclear and varies substantially across health care systems [2].
5. It is unclear how criteria assessed in HTA translate into molecular diagnostic pricing and reimbursement decision making.

These and other differences make it not only difficult to know a priori whether a diagnostic will be subject to HTA but also whether the evidence is sufficient to reach reimbursement decisions. Although HTA professionals are working toward establishing evaluation standards that promote quality and access, diagnostic industry members are ultimately trying to understand the pathways to predictably obtain reimbursement.

Although analytical and clinical validity, clinical utility, and cost or cost-effectiveness of the technology for the target population are common parameters considered by all systems, the ways these measures are defined and leveraged within evaluations varies across agencies and across different stakeholder types (e.g., physicians, payers, HTA agencies, and laboratory directors). *Analytical validity* refers to how well the test predicts the presence or absence of a particular biomarker of interest, whereas *clinical validity* refers to how well the genetic variant being analyzed is related to the presence, absence, or risk of a specific disease. Clinical utility assesses whether the test can provide information about diagnosis, treatment, management, or prevention of a disease that will impact clinical decision making and outcomes [15].

Within the programs evaluated, there are no explicit or common methods on how payers evaluate data on analytic and clinical validity and clinical utility. In addition, these are not the only factors considered in making HTA and ultimately reimbursement decisions [16]. The MSAC [12], the EGAPP [13], and the CADTH [11] also incorporate ethical, legal, social, familial, environmental, and/or organizational elements in their evaluation. In the United Kingdom, NICE's DAP focuses on clinical and performance metrics, cost-effectiveness, and the patient care pathway from testing to treatment [10]. The MSAC [12], NICE's DAP [10], the EGAPP [13], and the CADTH [11] produce recommendations to stakeholders primarily on the basis of assessment of the available evidence. Where evidence gaps exist, expert opinions may be solicited; this approach is used by Palmetto's MolDX Program in the United States [17].

Variation exists in submission format as well as the timelines associated with review. For example, the DAP has well-defined requirements for assessment and does not require an extensive submission document, though the timeline is long, taking more than 2 years in some cases (e.g., MammaPrint, Oncotype DX, IHC4, and Mammostrat). It requires manufacturers to address a range of comments from different stakeholders, additional data needs, and/or clarifications throughout the process [18].

Industry members and other agencies have recognized the challenges in current molecular diagnostic HTA approaches, and begun work to address them via multistakeholder working groups. For example, European network for health technology assessment is working to create pan-European Union standards that specifically address some of these issues; however, gaining buy-in from all stakeholders has been challenging [2]. This is similar to dialogue related to evidence standards for diagnostics that has occurred in some systems such as France, the United Kingdom, and the United States.

The significant variations led the MD&D SIG to question how these HTAs are playing out in the real world. The following case studies provide insights into how organizations are structuring diagnostic evaluations and examples of how each process is being applied in the real world. The case studies include Palmetto's assessment of OncotypeDx for prostate cancer in the United States, EGFR-TK assessment in the United Kingdom by NICE's DAP, IQWiG's assessment of HPV testing in Germany, MSAC's assessment of ALK testing for NSCLC in Australia, and CADTH's Rapid Response on NIPT in Canada. For each case study, we present the background about the HTA program and test evaluated, evaluation parameters, and the assessment outcome and its justifications.

The Case of Oncotype DX Prostate Cancer Assay Assessment by Palmetto's MolDX Program in the United States

Background of the HTA program and test evaluated

Medicare, the largest US payer, responded to the rapid growth of MDx, companion diagnostics, and personalized medicines in clinical practice in the recent decades by authorizing Palmetto

GBA to develop a system for HTA, pricing, and reimbursement for diagnostics [17]. Palmetto's MolDX Program was implemented in 2012 and conducts HTAs on both US Food and Drug Administration-approved diagnostics and LDTs. The goals of the program are 1) focusing Medicare coverage to diagnostics that demonstrate clinical validity and utility; 2) tracking utilization for reimbursement through the implementation of unique codes for each diagnostic; 3) creating a consistent and standardized approach for making coverage and pricing decisions for diagnostics; and 4) building a body of evidence demonstrating the effectiveness of diagnostics in the real-world setting by linking specific tests with clinical decision making and patient outcomes [16,17]. Tests are not reimbursed until a favorable decision is reached.

The criteria for coverage decision making are publicly available; however, the specific evidence reviewed and how coverage decisions are made is not fully transparent (e.g., information considered confidential and/or proprietary may be omitted) and can vary substantially from test to test. In the case of the Oncotype DX® Prostate Cancer Assay, Palmetto conducted a formal review that established positive coverage via a local coverage determination in late 2015.

The test is a prostate biopsy-based 17-gene reverse-transcriptase polymerase chain reaction assay, representing four molecular pathways (androgen signaling, cellular organization, stromal response, and proliferation), that provides a biologic measure of cancer aggressiveness. It is indicated for men who are considered candidates for active surveillance and is designed to inform decisions between AS and immediate treatment.

Evaluation parameters

The clinical performance of the assay was assessed leveraging data from a prospective-retrospective study of 395 patients with National Comprehensive Cancer Network (NCCN) very low-, low-, and intermediate-risk disease with the objective to determine whether the test results added independent predictive information beyond standard clinical and pathologic data as to whether the patient was likely to progress. In multivariable analysis, the Oncotype DX(R) Genomic Prostate Score (GPS) was found to predict adverse pathology at radical prostatectomy and allow more patients for active surveillance when used with NCCN criteria. The second study, a multicenter longitudinal assessment of 402 men, looked at tumor aggressiveness. It demonstrated that the test predicted biochemical recurrence, adverse pathology, and metastatic recurrence (though rare).

Assessment outcome

As a result of these study findings, Palmetto (via the MolDX Assessment Program) found that the "potential usefulness of this test is that it allows physicians to determine which patients with early prostate cancer are candidates for active surveillance and are more likely to have a good outcome without needing to receive definitive treatment" [19]. The assessment directly informed the development of a Local Coverage Determination for Medicare, leading to test reimbursement. However, criteria for coverage included use within a defined patient subset and that ordering clinicians must have completed a training/certification program in order to use/bill for/and get reimbursed for the test. This last requirement is perhaps an interesting foreshadowing of HTA agencies understanding that the value of many MDx is influenced by how and for whom they are used.

In the case of this test, evidence of clinical utility was supplemented by recommendation within an evidence-based clinical practice guideline (e.g., NCCN), which frequently weighs heavily into evaluation outcomes. Table 2 provides additional examples of MDx that Palmetto recently reviewed and resulting coverage decisions.

Table 1 – Diagnostic technologies assessment evaluation frameworks.

Domain	MSAC [12]	NICE DAP [10]	EGAPP [13]	CADTH HTERP [11]	Palmetto GBA MolDX [6]	IQWiG [14]
Country Purpose	Australia <ul style="list-style-type: none"> To advise the Australian Minister for Health and Ageing on evidence relating to the safety, effectiveness, and cost-effectiveness of new medical technologies and procedures 	United Kingdom <ul style="list-style-type: none"> To evaluate diagnostic technologies that have the potential to improve health outcomes but whose introduction is likely to be associated with an overall increase in cost to the NHS 	United States <ul style="list-style-type: none"> To formulate recommendations for genetic tests and other genomic applications for health care providers, public health practitioners, policymakers, and consumers using an evidence-based approach 	Canada <ul style="list-style-type: none"> To develop guidance and/or recommendations on nondrug health technologies for a range of stakeholders within the Canadian health care system using evidence-based and a multicriteria framework 	United States <ul style="list-style-type: none"> To identify and establish coverage and reimbursement for molecular diagnostic tests 	Germany <ul style="list-style-type: none"> To evaluate benefits, harms, and economic implications of interventions: To support the Federal Joint Committee (G-BA) and the National Association of Statutory Health Insurance Funds in fulfilling their legal duties
Health problem and current use of technology	<ul style="list-style-type: none"> Intended role of index test and intended use of test 	<ul style="list-style-type: none"> Care pathway, including sequence of tests and treatments, outcomes and costs, and other considerations 	<ul style="list-style-type: none"> Potential public health impact based on prevalence/incidence of the disorder, prevalence of the gene variants, or number of individuals likely to be tested, test availability in clinical practice, and other practical considerations 	<ul style="list-style-type: none"> Background on health condition Issue and policy question(s) 	<ul style="list-style-type: none"> Intended purpose 	<ul style="list-style-type: none"> Potential benefits of medical interventions Patient-centered health information
<ul style="list-style-type: none"> Description and technical characteristics of technology 	<ul style="list-style-type: none"> Proposed function and technical aspects of tests 	<ul style="list-style-type: none"> Details about technology and comparators provided 		<ul style="list-style-type: none"> Current options for diagnosis/screening regulatory status in Canada, etc. Alternative diagnostic technologies that address the same issue 	<ul style="list-style-type: none"> Description of assay 	<ul style="list-style-type: none"> Description of the intervention
Population	<ul style="list-style-type: none"> Incidence, prevalence, and natural history of target condition Description of potential impact of test on patient mobility and mortality, activities of daily living, and quality of life 	<ul style="list-style-type: none"> Patient characteristics, conditions to be diagnosed, and etiologies of the conditions 	<ul style="list-style-type: none"> Prevalence/ incidence of the disorder, prevalence of gene variation, number of individuals likely to be tested The availability of interventions for individuals with a positive test result or their family members 	<ul style="list-style-type: none"> Size of affected population 	<ul style="list-style-type: none"> Intended patient population(s) 	<ul style="list-style-type: none"> Intended patient population(s)
Safety	<ul style="list-style-type: none"> Safety of index test vs. comparator 	<ul style="list-style-type: none"> Significant adverse effects and test preparation effects 		<ul style="list-style-type: none"> Safety in absolute terms, and in comparison to comparators 		<ul style="list-style-type: none"> Optional
Accuracy and clinical validity	<ul style="list-style-type: none"> Assessment of clinical validity 	<ul style="list-style-type: none"> Assessment of clinical validity 	<ul style="list-style-type: none"> Assessment of analytic and clinical validity 	<ul style="list-style-type: none"> Assessment of analytic and clinical validity 	<ul style="list-style-type: none"> Assessment of analytic and clinical validity 	<ul style="list-style-type: none"> Assessment of analytic and clinical validity
Clinical effectiveness	<ul style="list-style-type: none"> Assessment of clinical utility 	<ul style="list-style-type: none"> Assessment of clinical utility 	<ul style="list-style-type: none"> Assessment of clinical utility 	<ul style="list-style-type: none"> Assessment of clinical utility 	<ul style="list-style-type: none"> Assessment of clinical utility 	<ul style="list-style-type: none"> Assessment of clinical utility
Patient preferences				<ul style="list-style-type: none"> Acceptability of test by the patient 		
Quality of evidence	<ul style="list-style-type: none"> QUADAS tool 	<ul style="list-style-type: none"> QUADAS tool 	<ul style="list-style-type: none"> Involves the adequacy of each evaluation component (analytical validity, clinical validity, and clinical utility): low, medium, high 			<ul style="list-style-type: none"> QUADAS tool

Costs and economic impact	<ul style="list-style-type: none"> • Cost-effectiveness 	<ul style="list-style-type: none"> • Cost-effectiveness considered • Costs of tests, follow-up testing, treatment, treatment of adverse effects from test or treatment, and monitoring needed before or after the treatment • Modeling to measure and value health effects for diagnostic assessments can be conducted 	<ul style="list-style-type: none"> • Cost-effectiveness 	<ul style="list-style-type: none"> • Cost-effectiveness • Cost of tests, equipment, personnel, consumables, and maintenance • Availability of evidence of value for money • Expected lifespan and total budget impact of the test 	<ul style="list-style-type: none"> • Price determination occurs for diagnostic tests that meet the Medicare criteria for coverage • Cost of special equipment, labor, and supplies, such as reagents 	<ul style="list-style-type: none"> • Cost-effectiveness and budget impact analysis • Direct costs and resource use • Indirect costs (loss of productivity) potentially considered on cost side
Ethical, legal, and social aspects	<ul style="list-style-type: none"> • Ethical and legal aspects related to test, and ethical, legal, and social stakes related to genetic tests • Potential psychological and social impacts of this test on patient or family 		<ul style="list-style-type: none"> • Familial, ethical, societal, or intermediate outcomes considered sometimes • Societal perspectives on whether use of the test in proposed clinical scenario is ethical and reviewed before evidence review 	<ul style="list-style-type: none"> • Ethical, legal, and social issues such as patient access to the test in Canada, patient access to proper interpretation of the results, support, and follow-up 		<ul style="list-style-type: none"> • Optional
Organizational aspects	<ul style="list-style-type: none"> • Accessibility limits for test, information on molecular test accessible to health care professionals and public, and availability and accessibility of professional services 		<ul style="list-style-type: none"> • Integration of test into routine practice 	<ul style="list-style-type: none"> • Integration of test into existing workflow • Training/competency requirements • Repair and maintenance 		
Environmental factors				<ul style="list-style-type: none"> • Environmental impact of test 		
Levels of evidence	<ul style="list-style-type: none"> • The ranking of studies by “levels” of evidence on the basis of type of study design • A systematic review of Level 2 studies • These include RCTs, non-randomized experimental trial, cohort study, case-control, time series, case series with either post-test or pretest/post-test outcomes 	<ul style="list-style-type: none"> • Evidence is searched for studies that follow patients from testing, through treatment, to final outcomes (e.g., systematic reviews, RCTs, cohort studies, and observational studies) • Data test accuracy studies reviewed • Models of the management or treatment of the condition after diagnosis explored. Expert opinion or expert elicitation may be used to provide a parameter value for model(s), or model(s) can be redesigned to use other parameters 	<ul style="list-style-type: none"> • The hierarchies of data sources for analytic validity, and of study designs for clinical validity and utility, designated for all as Level 1 (highest) to Level 4 • Data sources include meta-analyses of RCTs, controlled trials, longitudinal cohort, cohort, case-control, and cross-sectional studies, unpublished and/or non-peer-reviewed research, clinical laboratory or manufacturer data, consensus guidelines, and expert opinion 			<ul style="list-style-type: none"> • The hierarchy of evidence for diagnostic test studies • Data sources include bibliographic databases, guideline databases, hand searching in selected scientific journals, contacts with experts/industry/patient organizations, publicly accessible documents from regulatory authorities

CADTH, Canadian Agency for Drugs and Technologies in Health; EGAPP, Evaluation of Genomic Applications in Practice and Prevention; HTA, health technology assessment; HTERP, Health Technology Review Panel; IQWiG, Institute for Quality and Efficiency in Health Care; MSAC, Medical Services Advisory Committee; MolDX, Molecular Diagnostic Services Program; NHS, National Health Service; NICE DAC, National Institute for Health and Care Excellence Diagnostics Advisory Programme; QUADAS, Quality Assessment of Diagnostic Accuracy Studies; RCTs, randomized controlled trials.

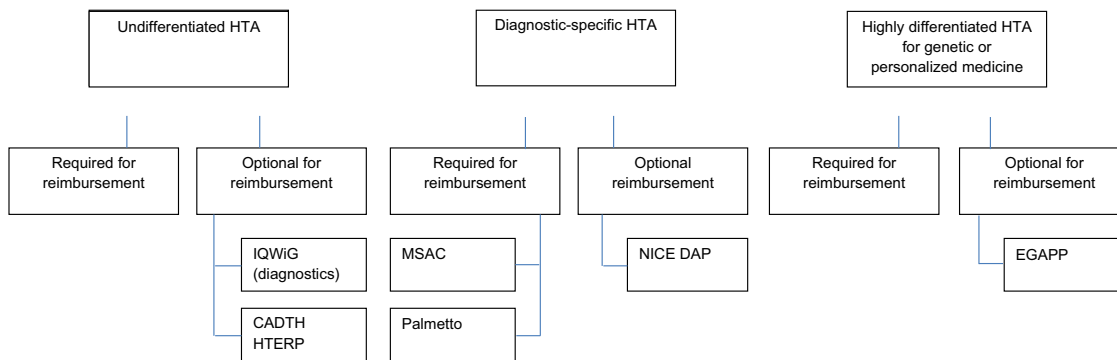


Fig. 1 – Current HTA Programs for Molecular Diagnostics. CADTH, Canadian Agency for Drugs and Technologies in Health; EGAPP, Evaluation of Genomic Applications in Practice and Prevention; HTA, Health technology assessment; HTERP, Health Technology Review Panel; MSAC, Medical Services Advisory Committee; NICE DAP, National Institute for Health and Care Excellence Diagnostics Advisory Programme.

Table 2 – Diagnostics illustrative MDx Palmetto local coverage determinations.

Test reviewed (LCD)	Coverage decision	Select coverage guidance excerpt
Circulating Tumor Cell (CTC) Marker Assays (L34631) [32]	Noncoverage	Although detection of elevated CTCs during therapy is a definitive indication of subsequent rapid disease progression and mortality in [different cancers], no data have been forthcoming to demonstrate improved patient outcomes, or that the assay changes physician management to demonstrate improved patient outcomes.
NRAS Genetic Testing (L34627) [33]	Limited coverage	<p>Palmetto GBA will cover NRAS testing for metastatic colorectal cancer, per NCCN guidelines (Version 3.2014). All other NRAS testing is noncovered.</p> <ul style="list-style-type: none"> Colorectal cancer: The 2013 NCCN Colorectal Practice Guidelines for Colon Cancer describe a recent study which reported that 17% of 641 patients from the PRIME trial without KRAS exon 2 mutations were found to have mutations in exons 3 and 4 of KRAS or mutations in exons 2, 3, and 4 of NRAS. A predefined retrospective analysis of a subset of these patients showed that progression-free survival and overall survival were decreased in those who received panitumumab plus FOLFOX compared to those who received FOLFOX alone. NCCN Colorectal Guidelines (Version 3.2014) recommend “All patients with metastatic colorectal cancer should have tumor tissue genotyped for RAS mutations (KRAS and NRAS). Patients with any known KRAS mutation or NRAS mutation should not be treated with either cetuximab or panitumumab.” Consequently, Palmetto GBA is expanding coverage of NRAS to patients with metastatic colorectal cancer. Melanoma: The prognostic significance is still not well understood and further investigation of the histologic types with specific NRAS mutations in a larger series is necessary to validate these apparent impacts on patient outcomes.
Infectious Disease Molecular Diagnostic Testing (L31747) [30]	“Full” coverage	<p>Molecular diagnostic testing, which includes deoxyribonucleic acid (DNA)- or ribonucleic acid (RNA)-based analysis, with or without amplification/quantification, provides sensitive, specific, and timely (i.e., relative to that of traditional culture-based methods) identification of diverse biological entities, including microorganisms and tumors.</p> <p>A standardized nucleic acid probe reacts directly with nucleic acids in the test sample. This format is termed a Nucleic Acid Test (NAT). If the test sample contains the organism of interest, the reaction (e.g., hybridization) of these elements will create a detectable end point.</p>
ConfirmMDx Epigenetic Molecular Assay (L35368) [34]	Coverage with evidence development	<p>Limited coverage is provided for the ConfirmMDx epigenetic assay for prostate cancer to reduce unnecessary repeat prostate biopsies. While prospective evidence is currently being generated, retrospective evidence of clinical utility supports the potential value of this diagnostic test and serves as adequate evidence of likely clinical utility to support limited coverage. Palmetto GBA is aware that MDxHealth has initiated the PASCUAL Clinical Trial to prospectively address outcomes to establish clinical utility. While patient participation in the PASCUAL trial is not a prerequisite to the limited coverage, coverage is limited to providers enrolled in the ConfirmMDx Certification and Training Registry program.</p> <p>The performance of this assay in a large, blinded clinical validation study demonstrated an NPV of 90%, which is considerably higher than that afforded by standard histopathology review. A mathematically based budget impact model using the assay in urologic practices to decide upon the need for repeat biopsies reported significant cost and medical resource savings by avoiding unnecessary, invasive biopsies over current standard of care methods.</p>

LCD, local coverage determination; MDx, medical diagnostics.

The Case of NICE’s DAP Appraisal of EGFR-TK Mutation Testing for Predicting Response to First-Line Tyrosine Kinase Inhibitor Drugs in Advanced NSCLC

Background of the HTA program and test evaluated

The DAP is part of NICE’s program to evaluate medical technologies, and is leveraged for evaluating complex diagnostic tests on the “basis of clinical utility and cost-effectiveness analysis or where meaningful assessment requires the consideration of multiple technologies or indications” [10]. MDx that have the potential to improve health outcomes at an increased cost to the system are within the domain of evaluation. In 2012, the DAP conducted its first assessment of MDx, EGFR-TK mutation testing for predicting erlotinib and gefitinib response in advanced NSCLC

[20]. In 2009, NICE had recommended erlotinib and gefitinib for first-line use in NSCLC and EGFR-TK mutation testing was included in the assessment [21,22], but a review of different testing approaches was not conducted.

Evaluation parameters

The assessment of EGFR-TK testing included both regulatory-approved (i.e., CE marked) and nonregulatory-approved LDTs, and alternative testing strategies using two or more test types. In contrast to NICE drug appraisals that evaluate whether specific drugs should be used, the EGFR-TK was assessed on the premise that testing should be and is already being done with the central question being which test should be used. Testing approaches included in the assessment are presented in Table 3.

Table 3 – Tests/methods appraised and in use in the UK NHS.

Tests/methods	Data considered	Decision analytic model approach(es)	Outcome
Therascreen EGFR RGQ PCR Kit (CE-marked* real-time PCR)	<ul style="list-style-type: none"> • RCT utility data • Published UK technical performance study • Laboratory survey • Expert opinion 	<ul style="list-style-type: none"> • Comparative effectiveness • Linked evidence • Assumption of equal prognostic value 	Recommended
Therascreen EGFR Pyro Kit (CE-marked* pyrosequencing)	<ul style="list-style-type: none"> • Laboratory survey • Expert opinion 	<ul style="list-style-type: none"> • Assumption of equal prognostic value 	Insufficient evidence for recommendation
Cobas EGFR Mutation PCR Test (CE-marked* real-time PCR)	<ul style="list-style-type: none"> • RCT utility data • Laboratory survey • Expert opinion 	<ul style="list-style-type: none"> • Assumption of equal prognostic value 	Recommended
Pyrosequencing AND fragment length analysis (FLA)	<ul style="list-style-type: none"> • Laboratory survey • Expert opinion 	<ul style="list-style-type: none"> • Assumption of equal prognostic value 	Insufficient evidence for recommendation
Single-strand conformation polymorphism analysis	<ul style="list-style-type: none"> • Laboratory survey • Expert opinion 	<ul style="list-style-type: none"> • Assumption of equal prognostic value 	Insufficient evidence for recommendation
High-resolution melt analysis	<ul style="list-style-type: none"> • Laboratory survey • Expert opinion 	<ul style="list-style-type: none"> • Assumption of equal prognostic value 	Insufficient evidence for recommendation
Next-generation sequencing	<ul style="list-style-type: none"> • Laboratory survey • Expert opinion 	<ul style="list-style-type: none"> • Assumption of equal prognostic value 	Insufficient evidence for recommendation
Direct (Sanger) sequencing of exons 19–21 only	<ul style="list-style-type: none"> • RCT utility data • Expert opinion 	<ul style="list-style-type: none"> • Comparative effectiveness • Linked evidence • Assumption of equal prognostic value 	Not in scope
Direct (Sanger) sequencing of exons 18–21 only	<ul style="list-style-type: none"> • RCTs • Expert opinion 	<ul style="list-style-type: none"> • Linked evidence • Assumption of equal prognostic value 	Recommended only in combination with other tests (see table rows below)
Sanger sequencing of samples for NSCLC samples with > 30% tumor cells OR Cobas EGFR Mutation PCR Test for samples with <30% content	<ul style="list-style-type: none"> • RCTs (Sanger only) • Laboratory survey • Expert opinion 	<ul style="list-style-type: none"> • Assumption of equal prognostic value 	Recommended
Sanger sequencing of samples for NSCLC samples with > 30% tumor cells OR Therascreen EGFR Mutation PCR Test for samples with <30% content	<ul style="list-style-type: none"> • RCTs (Sanger) • Expert opinion 	<ul style="list-style-type: none"> • Assumption of equal prognostic value 	Recommended
Sanger sequencing followed by FLA AND real-time PCR (RT-PCR) of negative samples	<ul style="list-style-type: none"> • RCTs (Sanger) • Laboratory Survey • Expert opinion 	<ul style="list-style-type: none"> • Assumption of equal prognostic value (FLA/RT-PCR) 	Recommended

CE, XX; PCR, polymerase chain reaction; NHS, National Health Scheme; NSCLC, non-small cell lung cancer; RCT, randomized controlled trial.
* CE-marked, regulatory approved.

The assessment of EGFR-TK mutation testing involved several noteworthy approaches for collection of the evidence to support usefulness of diagnostics, including the following:

1. Acceptance of “real-world” observational evidence (e.g., patient registry studies) rather than experimental data exclusively. In addition to reviewing available data identified in a systematic review, the DAP
 - performed a Web-based survey on test performance and use in 13 laboratories in the United Kingdom and
 - supported retrospective evidence collection using archived tissue samples to link test performance to patient outcomes.
2. Cost-effectiveness was assessed using different decision analytic approaches depending on data available for each test type/testing strategy (see Table 3 for details) [20].
 - “Comparative effectiveness” approach for tests with progression-free survival or overall survival data, which reflects clinical utility;
 - “Linked evidence” approach (i.e., indirect correlation of test use with overall outcomes that include treatment efficacy) for tests with data on accuracy for predicting drug response, which reflects clinical validity; and
 - For tests that are not amenable to the other two approaches, “assumption of equal prognostic value” approach is used; this involves collecting test performance data via a provider survey.
3. Clinical and cost-effectiveness evidence evaluated in the 2009 assessment of gefitinib (in combination with EGFR-TK mutation testing) [22].

In contrast to HTA programs for diagnostics in other countries (e.g., Australia [MSAC], Canada [CADTH, Ontario Health Technology Advisory Committee], United States [Palmetto]) [23–25], the DAP demonstrated some flexibility in considering a range of evidence including indirect comparisons and linked-evidence analyses to compare tests on the basis of modeled patient outcomes and costs [20]. The DAP, however, concluded that assumptions made on comparative effectiveness used in these models were unlikely to hold true due to potential differences in the populations of the compared trials. Furthermore, the DAP concluded that results of the cost-effectiveness analyses were not sufficiently robust because of uncertainty in input costs and overall survival estimates.

The appraisal of EGFR-TK mutation tests highlights the difficulty in robust comparative cost-effectiveness analysis for diagnostics due to evidence requirements that are largely divergent and unclear on a global scale. This led to limited availability of direct comparisons, and uncertainties surrounding clinical utility, which is largely determined by the pharmacological treatment effect rather than testing strategies [24,26].

Assessment outcome

The outcome of the assessment was that EGFR mutation testing is worthwhile and both commercially available tests (Roche’s cobas and QIAGEN’s therascreen) and the reference test (Sanger Sequencing) can be used.

The Case of HPV Testing for Cervical Cancer Screening in Germany, Assessed by IQWiG

Background of the HTA program and test evaluated

In Germany, HTA submissions for diagnostics are usually not required for reimbursement. Only screening tests are required to be formally assessed before receiving reimbursement in the outpatient setting, which is determined by the Einheitlicher Bewertungsmaßstab [14]. In February 2010, the relevant HTA

agency, IQWiG, evaluated HPV DNA testing as a possible addition or replacement to cytology for primary screening of women for cervical cancer.

Evaluation parameters

In its evaluation, the IQWiG reviewed randomized controlled multicenter studies with parallel groups; its decision was made in November 2011 [27]. The factors considered included the following:

1. overall survival;
2. disease-specific (tumor-specific) survival;
3. invasive cervical cancer;
4. high-grade cervical intraepithelial dysplasia or in situ cervical cancer (CIN3/CIS);
5. composite outcome of CIN3/CIS and invasive cervical cancer;
6. direct and indirect harms from screening; and
7. health-related quality of life, including psychosocial aspects.

Supplementary information considered included the following:

1. moderate-grade cervical intraepithelial dysplasia;
2. composite clinical outcome of CIN3/CIS and invasive cervical cancer;
3. sensitivity and specificity of the test; and
4. clinical ramifications and resource use after an initial positive test result.

Assessment Outcome

The assessment concluded that although there was an “indication of a benefit” of a screening strategy including HPV testing alone or in combination with cytology-based testing versus a screening strategy including cytology-based testing alone, the potential harm from HPV testing alone or in combination with cytology-based testing could not be assessed because of a lack of data. As a result, HPV testing was not reimbursed for primary screening in Germany.

Since the original assessment, several large studies have been published addressing some of the concerns discussed above [28,29]. In addition, the US Food and Drug Administration approved one HPV test for primary screening in April 2014. In October 2013, the IQWiG initiated another assessment of HPV testing; a so-called Rapid Report was issued in June 2014 [35]. No studies were identified or included that had not already been included in the first assessment. Nonreimbursement was again the decision because “There are still no data or no evaluable data available on mortality, quality of life and potential harm.”

Case of the Australian MSAC’s Review of ALK Gene Arrangement Testing in Patients with NSCLC to Determine Eligibility for Treatment with Crizotinib

Background of the HTA program and test evaluated

The MSAC is an independent expert committee that evaluates new technologies on the basis of clinical and cost-effectiveness, and considers “the circumstances under which public funding should be supported” [12]. Abbott Molecular and Pfizer Australia (the applicant) submitted to the Australian Department of Health in June 2013 a joint proposal requesting public funding for fluorescence in situ hybridization (FISH) testing for ALK gene rearrangement status in patients with NSCLC. Crizotinib, a novel, targeted anticancer agent developed by Pfizer, is indicated for the treatment of patients with a confirmed ALK gene expression as a second- or third-line treatment option.

Evaluation parameters

The committee reviewed the proposed clinical protocol, the clinical data to support it, and the population eligible for testing [36]. The applicant proposed both expanding the test-eligible population to include patients with squamous cell tumor pathology and not restricting to patients with wild-type EGFR status: both are proposed descriptors that the MSAC felt could allow “leakage of testing” to patients where the proposed benefits of crizotinib are not well supported.

The applicant proposed a two-step process wherein patients would first be triaged with an ALK immune-histochemical (IHC) staining of tumor tissue before proceeding to the ALK-FISH diagnostic. Although the MSAC acknowledged that IHC staining is justified as a triage test (there was seen to be low likelihood of patients missing out on crizotinib because of an inaccurate IHC result), the MSAC expressed concern about the appropriate level of “signal” to proceed to ALK-FISH testing. The MSAC, in its review document, wrote that “the numbers and costs of ALK gene arrangement testing would increase if the extent of overexpression moves.”

The MSAC reviewed evidence that crizotinib confers an incremental benefit in survival to patients testing positive for ALK. The MSAC questioned the “biological plausibility” and generalizability of the purported benefits of crizotinib. In a review of seven studies reporting on the overall survival rates in NSCLC (including studies in patients with and without ALK rearrangement), only one demonstrated a better prognosis. Given the lack of demonstrative evidence suggesting a clear benefit, the MSAC delayed action until a review of Australian patient data was available.

Assessment outcome

The MSAC, the independent expert panel charged with reviewing medical services and technology, concluded that although ALK-FISH is an appropriate diagnostic tool the applicant did not provide sufficient evidence to support practical implementation of its proposal.

The acceptance of Abbott’s ALK-FISH test as the evidentiary standard for determining ALK status was not disputed by the MSAC. And when providing its recommendation to the Department of Health, the MSAC did not refute any claims of diagnostic value; rather it questioned (including but not limited to) 1) the comparative health outcomes of ALK status, 2) the appropriate position of ALK testing in the diagnostic sequence, and 3) optimal patient population to be included for ALK testing.

MSAC’s review of ALK-FISH testing demonstrates that despite real-world evidence (Abbott’s ALK-FISH diagnostic was used to determine inclusion in crizotinib’s global registration studies), the potential cost-impact to public health care budgets appears to have had an impact on the committee’s recommendation.

Case of the CADTH Rapid Response on NIPT in Canada

HTA program and test evaluated

CADTH is a federal HTA agency in Canada responsible for assessing novel technologies from a clinical and cost standpoint. It helps decision makers keep pace with newly available technologies by making recommendations on the basis of comprehensive reviews, but is not directly linked to reimbursement outcomes. The case of the Rapid Assessment of NIPT demonstrates how a structured review, focused on cost, of NIPT was conducted and the outcomes that resulted [31]. The NIPT uses cell-free DNA to determine the presence of aneuploidy associated with Down syndrome (trisomy 21), Edwards syndrome (trisomy 18), and Patau syndrome (trisomy 13). The NIPT has a false-positive rate of about 0.2% and a detection rate of about 98% for trisomy 21.

Evaluation parameters

CADTH looked at the cost-effectiveness of the NIPT and the evidence-based guidelines regarding its use. Four studies and one evidence-based guideline were evaluated, after 260 citations were reduced to 28 potential relevant articles. Of the economic studies, three demonstrated increased costs and one decreased costs. Two of the studies were from Canada, one from the United States, and one from Australia and all were from the payer perspective. The comparator used was screening strategies without the NIPT (i.e., amniocentesis). All cost-effectiveness studies included in the review included clinical data as presented in previously published articles. The assessment did not separately review the clinical data. The rapid review urged interpreting the results with caution given the discrepancy in results among reviewed studies.

Assessment outcome

Universal screening with the NIPT was found not to be feasible from a cost standpoint. However, use with high-risk women in lieu of invasive testing (i.e., amniocentesis) was considered feasible. The rapid assessment recognized that in addition to their assessment, social and ethical issues may need to be considered when incorporating the NIPT into screening and diagnostic practice in Canada. The results of this report are not binding to specific reimbursement outcomes.

Discussion and Policy Recommendations

The case studies discussed provide illustrative examples of the current evaluation processes and challenges for MDx. The three examples have in common that evidence expectations varied (clinical utility, patient outcomes, mortality, and quality of life) and the selection and acceptance of evidence reviewed and coverage decision making were not fully transparent. All described HTA processes are lengthy from the perspective of the respective manufacturers. Missions of HTA agencies vary as well: Palmetto, for example, serves as a reimbursement gatekeeper similar to Australia’s MSAC for diagnostics, whereas NICE’s DAP assesses diagnostics in all phases of a product life cycle that could already have reimbursement.

HTA organizations today do not provide consistent parameters of acceptability in terms of clinical and analytic performance, clinical utility, and economic impact. Current approaches have also yet to consider, with the exception of screening tests in some systems, whether different evidence expectations should be applied to different test applications (i.e., risk assessment, screening, diagnosis, treatment selection, and monitoring) or test types (i.e., IVD vs. LDT). DAP’s review of EGFR-TK mutation tests highlighted that there can be considerable uncertainty surrounding the actual performance of LDTs. For example, a local laboratory that uses the same method may achieve similar performance as the laboratory participating in the trial, but there is no assurance that accuracy and reproducibility will be maintained in other laboratories performing the same test. In contrast, regulatory-approved tests are uniformly validated and designed to deliver consistent results across different laboratories. This highlights the need for clear evidence guidelines that are sensitive to the unique challenges in generating clinical evidence for diagnostic tests.

Without such standards, HTA is left to subjective judgment rather than objective assessment as to which tests meet, exceed, or fail to meet standards. Clear and commonly accepted standards are needed across two dimensions: 1) study types that are appropriate to demonstrate the value of MDx in the context of the respective care pathway and 2) transparency of HTA processes, including test selection for formal HTA and review criteria [4].

Furthermore, differences in the HTA processes and requirements between health systems represent major challenges for manufacturers in how best to generate appropriate evidence base that can demonstrate molecular diagnostic value. Critics of the current systems believe that the heterogeneity in HTA processes, practices, and requirements for MDx results in fewer life-saving or life-improving tests being broadly available to patients in need [3,16,24,25]. Well-defined evidence requirements will inform evidence development strategies for manufacturers and may help attract investment into the diagnostics sector. Finally, clear definition of the criteria used to assess the value of MDx and clear links between meeting the criteria and reimbursement and pricing outcomes are needed.

We recommend that HTA agencies incorporate several elements into molecular diagnostic HTAs to address the identified challenges. See Table 4 for recommendations.

1. Clear guidance as to the characteristics of MDx that will be assessed, study design preferences and prioritization criteria for HTA at a regional and/or national level;
2. Early and ongoing opportunities for dialogue between health care decision makers, health technology assessors, payers, clinicians, patients, and industry;
3. Early guidance to manufacturers on evidence development, comparator, or likelihood of an HTA for MDx;
4. Opportunities for stakeholders to comment on evaluation methods and evidence used to analyze the test;
5. A checklist summarizing all required documents and communication streams associated with the submission;
6. An overview of the timing for HTA, and re-evaluation details (the timing, requirements) if a negative assessment is reached;
7. Where possible, harmonized HTA requirements across national/regional HTA groups to enhance timely access to

Table 4 – Recommended changes to molecular diagnostic HTA processes.

1. Clear guidance as to the characteristics of molecular diagnostics that will be assessed, study design preferences and prioritization criteria for HTA at a regional and/or national level
2. Early and ongoing opportunities for dialogue between health care decision makers, health technology assessors, payers, clinicians, patients, and industry
3. Early guidance to manufacturers on evidence development, comparator, or likelihood of an HTA for molecular diagnostics
4. Opportunities for stakeholders to comment on evaluation methods and evidence used to analyze the test
5. A checklist summarizing all required documents and communication streams associated with the submission
6. An overview of the timing for HTA, and re-evaluation details (the timing, requirements) if a negative assessment is reached
7. Where possible, harmonized HTA requirements across national/regional HTA groups to enhance timely access to molecular diagnostics and streamline the process and reduce workload for manufacturers and HTA bodies
8. Clear definition of how criteria assessed in HTA translate into molecular diagnostic pricing and reimbursement decision making
9. Explicit recognition of and rationale for differential approaches to LDTs vs. IVDs, and whether HTA-related reimbursement outcomes are consistently applied to both

HTA, health technology assessment; IVD, in vitro diagnostic; LDT, laboratory-developed test.

MDx and streamline the process and reduce workload for manufacturers and HTA bodies;

8. Clear definition of how criteria assessed in HTA translate into molecular diagnostic pricing and reimbursement decision making; and
9. Explicit recognition of and rationale for differential approaches to LDTs versus IVDs, and whether HTA-related reimbursement outcomes are consistently applied to both.

These proposed improvements would enhance the collaborative nature and transparency of the process, which would be well received by manufacturers and clinical stakeholders.

Ultimately, the HTA process for MDx is still evolving. There is significant opportunity at regional, national, and international levels to inform this development. Our proposed recommendations may help address major challenges that many systems currently face by enhancing collaboration and transparency. Establishing a true and open dialogue will mark a productive next phase of HTA for diagnostics in which patients, clinicians, payers, and health systems will benefit from timely access to innovative and beneficial diagnostics.

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