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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 Healthcare, 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.

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.