



**Ontario  
Health**

HEALTH TECHNOLOGY ASSESSMENTS

# Methods and Process Guide

April 2023

# About This Guide

This guide describes the methods and processes involved in conducting health technology assessments at Ontario Health and the subsequent development of evidence-based funding recommendations by the Ontario Health Technology Advisory Committee. This guide is updated periodically, and we welcome feedback on how we can improve our methods and processes at [OH-HQO\\_HTA@OntarioHealth.ca](mailto:OH-HQO_HTA@OntarioHealth.ca).

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# Introduction

## Health Technology Assessment and Ontario Health

Ontario Health supports better care for all by connecting and coordinating Ontario's health system. To support this, Ontario Health's health technology assessment (HTA) program develops HTA reports that analyze the best available evidence on clinical effectiveness and safety, cost-effectiveness, budget impact, and patient preferences and values related to health technologies. We add analyses of ethical issues, as needed.

The HTA program is a member of the International Network of Agencies for Health Technology Assessment (INAHTA), which defines HTA as<sup>1</sup>:

A multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle. The purpose is to inform decision-making in order to promote an equitable, efficient, and high-quality health system.

We work as a multidisciplinary team of medical librarians; clinical epidemiologists; health economists; senior program advisors; patient, caregiver, and public engagement program specialists; and medical editors, in consultation with health service researchers, patients, families, caregivers, clinical experts, and industry representatives.

Health technology assessments are presented to the Ontario Health Technology Advisory Committee (OHTAC) to inform health care decision-making in Ontario and support funding recommendations to the Ontario Ministry of Health. All our final HTA reports are in the [Ontario Health Technology Assessment Series](#), published online with free access and indexed in the Medline database.

## Ontario Health Technology Advisory Committee (OHTAC)

The Ontario Health Technology Advisory Committee consists of volunteer members from across the province, including health care experts and individuals who can contribute the patient perspective. The committee reviews the findings of HTA reports and then Ontario Health, based on guidance from OHTAC, makes recommendations to the Ontario Ministry of Health about whether the technology should be publicly funded. Recommendations are published online alongside the HTA report and are freely available to the public. The Ontario Genetics Advisory Committee (OGAC) is a standing sub-committee advising OHTAC on the evidence with respect to genetic and genomic health technologies.

# Which Health Technologies Are Evaluated?

The HTA program at Ontario Health assesses a wide variety of innovative (new or disruptive) and existing health technologies and health care services. This may include the assessment of health technologies and health care services in the treatment, prevention, screening, diagnosis, or prognosis of a health condition. The types of health technologies assessed include, but are not limited to:

- Interventions, such as implantable medical devices and genomic therapies
- Medical tests, such as diagnostic, screening, and genetic tests
- Surgical procedures, techniques, and technologies
- Medical imaging for diagnostic, screening, or interventional purposes
- Health care or screening programs
- Complex health system interventions, such as models of health care delivery
- Interventions aiming to improve health equity/outcomes for disadvantaged populations

# How Are Topics Identified?

Topics for HTA review can be suggested by any person or organization from across Ontario through an [open application process](#). Submitted topics are prioritized according to the methods outlined in our [Topic Prioritization Guide](#).

# Phases of a Health Technology Assessment:

Following topic prioritization, there are three phases in the development of an HTA at Ontario Health.

- Defining the Scope
- Evaluating the Evidence
- Making a Recommendation

## Phase 1: Defining the Scope

The first phase of conducting an HTA involves developing the scope, or focus, of the report, specifically in terms of the research questions to be addressed. The scope provides a focused framework for assessing the relevant areas of evidence, including clinical, economic, and patient preferences and values.

The scope is centered upon the request submitted in the HTA application and is further developed by scanning the peer-reviewed published literature, as well as grey literature (defined as "that which is produced on all levels of government, academics, business and industry in print and electronic formats, but which is not controlled by commercial publishers"<sup>2</sup>). We also consult with various external partners, including patients, clinical experts, and representatives from the provincial government, the health system, and industry. We use the PICO(TS) criteria to help develop the research questions for the HTA:

- **P**opulation (the people affected by the condition, circumstance, or health technology)
- **I**ntervention (the health technology under review)
- **C**omparator (alternative[s] to the health technology)
- **O**utcome (patient-important outcomes)
- **T**ime (time frame, if relevant)
- **S**etting (health care setting, if relevant)

The key components of HTA scope development are described below.

### Health Condition and Population

We try to establish the incidence and/or prevalence of the health condition in Ontario, and we specify the intended population for the health technology under review. This may include factors such as the phase of life, severity of the health condition, genotype, and socioeconomic/social determinants of health. We also try to estimate the proportion of the affected population who would be eligible to use the health technology.

### Health Technology

The description of the health technology includes its indications for use, different versions of the technology that might exist, different modes of delivery, and the appropriate

frequency and intensity of use. When the technology is subject to Health Canada regulations, we list all licensed device manufacturers in Canada.

### **Comparator(s)**

A comparator is an alternative intervention used to treat the health condition. The typical comparator used for an HTA is standard care, which is defined as the health technology currently used in Ontario to treat the health condition. Standard care may include drugs, surgical procedures, or one or more alternative health technologies used to treat the health condition of interest. Sometimes standard care consists of no treatment. There may also be more than one comparator. We typically consider comparators that are available in Canada. Reviews of medical tests usually identify a reference standard (an agreed-upon test for classifying patients with and without the health condition) as the primary comparator for that test, as well as any other relevant comparator tests available in Canada.

### **Health Outcomes**

We identify health outcomes that are important and meaningful both to people living with the health condition and to the health system. We try to establish the extent to which the health technology improves these outcomes over the comparator(s).

### **Timing and Setting**

The scope of an HTA may include a specific time (phase of the treatment) for when the health technology is administered to patients (e.g., in reference to the disease trajectory or recovery pathway) and/or the setting in which the health technology is used (e.g., hospital, community, long-term care home). The setting may also define the provider of care (e.g., family physician, specialist).

### **Ontario Context**

The HTA process at Ontario Health is contextualized for Ontario and involves the input of clinical experts, patients, and other stakeholders. Contextualization includes understanding how the health technology is used (or could be used) in Ontario and how the associated health condition or target population is currently managed. This involves identifying alternative treatment options to the health technology, the current standard pathway of care, and any barriers or facilitators to using the health technology, as well as any equity issues (see Health Equity Considerations, below) that impact its use. The scope of the HTA is tailored to Ontario by considering relevant policy issues and controversies. We also explore the use of the health technology in other Canadian provinces and territories and in international health systems to understand its use and provisions for adoption in other jurisdictions.

### **Expert Consultation**

Expert consultation provides clinical practice or Ontario-specific information on the technology, the comparators, and the circumstances under which the technology is or could be used. We may also seek additional information on the potential use of the technology in clinical practice and the training and experience required to use the technology.

To achieve this goal, we aim to contact experts from a variety of groups, relevant clinical disciplines, geographic areas, and health care settings across Ontario to understand potential variations in populations and practice patterns. A concerted effort is made to represent a variety of disciplines, regions, organizations, interests, or experiences to minimize biases and reflect diverse perspectives. Consulted experts may include the HTA applicant, clinicians, researchers, OHTAC or OGAC members, industry representatives, or other people with expertise in the health condition or health technology.

To improve our reports, we obtain feedback from our experts on our draft clinical and economic project plans during the development of the HTA. We also request review of our draft clinical and economic reports, including feedback on any errors or omissions regarding comprehensiveness, accuracy, or interpretation. Experts may help add context to aid interpretation of findings for Ontario; they also help clarify issues that the HTA technical team has identified during conduct of the HTA.

In addition to consulting experts, we also hold an open public comment period, where everyone has the opportunity to provide feedback on both the draft recommendation and the HTA.

### **Minimizing Duplication of Efforts**

To avoid duplication of efforts, we search for existing systematic reviews of clinical literature that align with our clinical research questions to determine whether we could leverage and update an existing review or conduct an overview of reviews. We also search for existing economic evaluations that align with our economic research questions to determine whether we could leverage or adapt a published economic analysis. In addition, we contact Canadian HTA agencies to determine if an equivalent review of the health technology has been or is currently being undertaken elsewhere in Canada. We also determine whether any recent HTAs that would meet our needs have been completed by national or international HTA agencies, specifically in terms of our scope and research questions.

### **Collaboration**

The Ontario Health HTA program is part of the [Pan-Canadian HTA Collaborative](#) (PCC). The PCC aims to share best practices, minimize duplication of effort through the sharing of information, and identify and contribute to joint initiatives in the assessment of health technologies. Depending on the nature of the HTA and the specific research questions, we may collaborate with other Pan-Canadian HTA agencies to develop all or part of an HTA (e.g., a qualitative rapid review or an ethical analysis).

The HTA program also collaborates with clinical programs within Ontario Health, including cancer, cardiac, vascular stroke, mental health and genetic and other clinical areas as they develop within Ontario Health.

### **Health Equity Considerations**

The scope of an HTA may consider issues related to health equity. Unlike the notion of equality, equity is not about sameness of treatment. It denotes fairness and justice in process and in results. Equitable outcomes often require differential treatment and resource

redistribution to achieve a level playing field among all individuals and communities. This requires recognizing and addressing barriers to opportunities for all to thrive in our society.<sup>3</sup> We use the **PROGRESS-Plus** framework to consider whether potential health equity factors may be relevant to the HTA. This framework provides guidance on factors that may lead to health inequities:<sup>4</sup>

- **P**lace of residence
- **R**ace, ethnicity, culture, and language
- **O**ccupation
- **G**ender and sex
- **R**eligion
- **E**ducation
- **S**ocioeconomic status
- **S**ocial capital
- **Plus** other considerations such as age, disability, and sexual orientation

### **PROSPERO Registration**

Each HTA is registered in the [PROSPERO database](#), the international prospective register of systematic reviews.

# Phase 2: Evaluating the Evidence

There are three key evidence components to an HTA:

1. **Clinical:** assesses the available evidence on the clinical effectiveness and safety of the health technology
2. **Economic:** evaluates the cost-effectiveness and affordability of the health technology
3. **Patient preferences and values:** provides insight into patient, family, and caregiver perspectives and contributes to the consideration of the societal, ethical, and equity issues associated with the health condition and health technology

## Clinical Evidence

The objective of the clinical evidence review is to systematically synthesize the best available scientific evidence to answer research questions about the clinical effectiveness and safety of a health technology. This can include diagnostic test accuracy, impacts on clinical decision-making, quality of life, and other patient-important outcomes related to the health technology.

Our clinical evidence review uses systematic review methodology,<sup>5</sup> an approach used to collect, synthesize, and critically appraise all relevant published evidence about a health technology to provide a comprehensive summary of the evidence.

The most appropriate systematic review approach to assess the clinical evidence is guided primarily by the research question(s). We may consider conducting an overview of systematic reviews,<sup>6</sup> an update to or adaptation of an existing review, a diagnostic accuracy review,<sup>7</sup> a network meta-analysis, scoping review, or some type of expedited review,<sup>8</sup> among others.

To avoid duplication of efforts, we determine whether any recent systematic reviews of the clinical evidence have been completed by national or international HTA agencies that would meet our needs, specifically in terms of our scope and research questions.

## Clinical Review Plan

The clinical evidence review begins with the development of the clinical review plan, a written record of the context, rationale, and plan for the review. The clinical review plan explicitly defines the scope (including relevant PICO[TS] criteria), research questions, and intended methodological approach for the clinical evidence review, and serves as a communication tool for internal and external stakeholders.

The clinical review plan describes the Ontario-specific policy issues related to the health technology and, where applicable, the regulatory status and Health Canada-approved indication(s). Additional components of the clinical review plan include consideration of equity issues, harms, the eligibility criteria for selecting the studies that will be included in the review, the information sources we intend to use (e.g., electronic databases, grey literature sources), our planned analytical approaches, and the methods we will use to

critically appraise the risk of bias in studies and the quality of the body of evidence. The clinical review plan describes the treatment pathways, potential barriers to access, comparators and standard of care, specific devices, and the regulatory status.

We consult clinical content experts, who review the draft clinical review plan and provide feedback on the PICO(TS) criteria and ensure the scope of the review is relevant to the Ontario context. The health economists, medical librarians, patient, caregiver, and public engagement program specialist who make up the HTA team reviewing the health technology are also consulted to ensure cohesiveness across the components of the HTA.

Amendments to the clinical review plan may be needed as the review progresses. We document any amendments to the systematic review process in the clinical review plan.

### ***Research Questions***

Research questions are central to the clinical evidence review and provide the basis for our literature search, data abstraction, and analytical approaches.

Research questions revolve around the purpose of the health technology; this may include the treatment, prevention, screening, diagnosis, or prognosis of the treatment or health condition. The nature of the research questions highlight the key outcomes being evaluated; for example:

- Effectiveness on clinical outcomes, patient-reported outcomes, population health impact(s), or system outcomes
- Safety and harms
- Diagnostic accuracy and clinical utility
- Prognostic or predictive capability of a test or risk factor
- Impact on access or equity

### ***Health Equity Considerations***

Health equity-focused systematic reviews address the effects of the health technology on disadvantaged populations, specifically in terms of reducing social gradients (i.e., differences in the distribution of prevalence or incidence of risk factors or disease across populations) and/or understanding the effects of the health technology on health equity, either positively or negatively.<sup>9</sup>

The clinical evidence review may not have a primary focus on health equity issues, but may still consider potential health inequities related to the technology or the health condition under evaluation through the use of the PROGRESS-Plus framework.

### ***Literature Search Strategy and Methods***

Typically, we develop the literature search strategy by taking the population and intervention stated in the research question and analyzing relevant published studies on the topic to identify controlled vocabulary (e.g., the Medical Subject Headings [MeSH] terms assigned to studies in the MEDLINE database), related keywords and “natural language” terms for use in the search.

For internal validation, we test the search strategy to confirm that relevant published studies are captured in the MEDLINE database results; once this is confirmed, we translate the search into other databases. At minimum, we search the following databases:

- Cochrane CENTRAL
- Cochrane Database of Systematic Reviews
- Embase
- MEDLINE

We search additional databases, such as the Cumulative Index to Nursing and Allied Health Literature (CINAHL) and Ovid PsycINFO, if appropriate to the topic.

Depending on the review's inclusion and exclusion criteria or the existing body of literature, we may use search filters to target specific study designs and/or apply date limits. We develop our search filters through ongoing surveillance/scanning of peer organizations and published studies concerning information retrieval methodologies, which we test and adapt for our needs. All searches are limited to English-language publications. We also perform a targeted grey literature search of the [International HTA Database](#), HTA organizations and regulatory agency websites, and clinical trial or systematic review registries, following a standard list of sites to check that we have developed internally. In cases where an existing review has been selected for updating, we assess the published search strategies to determine if they meet the needs of our research questions and adapt if necessary.

The search strategy is peer-reviewed using the Peer Review of Electronic Search Strategies (PRESS) Checklist before final execution.<sup>10</sup> We create database auto-alerts to detect any new literature published during the course of HTA development.

We download search results to a reference management software database (EndNote)<sup>3</sup> and remove duplicate records. The full search strategies used for all databases and grey literature sources are included as an appendix to the HTA report and the number of records identified is depicted in a Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram.<sup>11</sup>

### ***Eligibility Criteria***

We specify the criteria by which studies will be included or excluded from the clinical evidence review for each research question. Selection criteria include factors related to the research questions, such as relevant PICO(TS) criteria, appropriate study design (e.g., randomized controlled trial, non-randomized study), sample size, year of publication, and minimum follow-up period.

### ***Types of Evidence***

We consider all types of published English-language evidence in our reviews. This includes evidence from randomized controlled trials and from the analysis of real-world data (i.e., data that are generated outside of clinical trial activities, pertaining to patients' health status and/or the delivery of care).<sup>12-14</sup> The preferred source of evidence depends on the technology and the context of the HTA.

## **Study Screening**

We assess all citations identified through the literature search according to the selection criteria to determine their eligibility for inclusion. The titles and abstracts are reviewed, and, for those studies appearing to meet the eligibility criteria, full-text articles are obtained. Where insufficient information is provided to determine eligibility for inclusion, we attempt to contact study authors. We may also review the reference lists of included studies and contact content experts to identify or validate any additional relevant studies not identified through the search. We use the Covidence systematic review software to manage the evidence review.<sup>15</sup>

Results of the study selection process, including data sources, number of studies screened and included at each stage, and a high-level summary of reasons for exclusion at the full-text stage are reported in a flow diagram, in accordance with the PRISMA Statement.<sup>11</sup>

## **Data Extraction**

Data are extracted from the included studies based on information available in the studies. Relevant information related to study context, methods, PICO(TS) criteria, results, risk-of-bias items, and patient characteristics are extracted. We contact study authors as necessary to obtain clarification regarding the published analysis. All correspondence with study authors is documented in the HTA report.

## **Risk-of-Bias Assessment**

Risk of bias refers to the extent to which the design and conduct of a study may have introduced bias into the study results. Studies with significant risk of bias have been shown to overestimate or underestimate treatment effects.<sup>16,17</sup>

The risk of bias of each eligible study is assessed to determine the potential differences in the internal validity of studies. The broad domains of bias to which a study may be susceptible include the following:

- Confounding
- Selection bias
- Measurement bias
- Performance bias
- Reporting bias
- Bias related to individual study design and circumstances

Numerous tools are available to evaluate the risk of bias in individual studies. We use the tools presented in Appendix 1, which are selected based on study type, methodological comprehensiveness, and pragmatic considerations.

## **Data Synthesis and Meta-Analysis**

Data synthesis involves combining and summarizing the data from the included studies. Synthesis of outcomes depends on the available data and may include quantitative synthesis, including statistical analysis, or a structured narrative synthesis.

Meta-analysis is the statistical method used to combine quantitative results from two or more similar studies. Meta-analysis can provide a summary estimate of the effect of a health technology on a specific outcome. This approach facilitates a quantitative understanding of the benefits and harms of the health technology based on the available evidence. We follow the methodological principles outlined in the *Cochrane Handbook for Systematic Reviews*<sup>5</sup> when performing meta-analyses of patient-important and clinical outcomes for health technologies. A variety of statistical software (e.g., R,<sup>18</sup> Review Manager,<sup>19</sup> Stata<sup>20</sup>) may be used to perform meta-analyses.

Where appropriate, we combine study results using meta-analysis to obtain a summary effect estimate based on the data from all relevant studies. When direct evidence is limited or unavailable, we may use statistical techniques such as network meta-analysis to assess indirect evidence.

Methods of meta-analysis for diagnostic test accuracy reviews differ from those for health treatments. Our methods of evaluating diagnostic test accuracy including evaluations of genetic tests follow those outlined in the *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy*.<sup>7</sup>

We provide a narrative synthesis of results, which involves describing study findings, when meta-analysis is inappropriate owing to clinical or methodological heterogeneity.

### **Quality of Evidence Assessment**

The quality of the body of evidence (i.e., the studies included in the clinical evidence review) for each outcome of interest is assessed according to the *Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Handbook*.<sup>21</sup>

The GRADE criteria provide a transparent, structured process for rating the quality of a body of evidence. The general approach begins with the consideration of study design (randomized controlled trials or observational studies), followed by assessing factors that may influence (i.e., rate down) the quality of evidence:

- Risk of bias
- Inconsistency
- Indirectness
- Imprecision
- Publication bias

Three additional criteria are considered, which may result in rating the quality of evidence higher:

- Large magnitude of effect
- Dose–response relationship
- Accounting for all plausible residual confounding

Based on this appraisal, we determine the overall quality of evidence for each outcome of interest to be High, Moderate, Low, or Very low. The ratings of the quality of evidence reflect the level of confidence, or how certain we are, in the effect estimate (the result) from a meta-analysis or the overall body of evidence of a given outcome.

Specific modifications to the GRADE approach are applied where necessary (for example, to diagnostic accuracy reviews,<sup>22-24</sup> prognostic reviews,<sup>25</sup> and network meta-analyses<sup>26</sup>).

### **Validation**

The clinical evidence review process is designed to uphold the rigour and validity of our evidence syntheses, while delivering timely evidence for decision-making. The scope and clinical evidence review methods are evaluated through an internal peer review of the draft clinical review plan. Internal validation of our screening process is conducted through a calibration exercise between two clinical epidemiologists. The draft clinical evidence review also undergoes an internal peer review process.

### **Considerations in the Clinical Evaluation of Medical Genetic/Genomic Tests**

Most methods for the clinical evaluation of genetic/genomic tests are the same as those for evaluating other types of interventions and tests.<sup>5,7</sup> However, there are some unique considerations for the evaluation of the clinical impact of genetic/genomic tests. These can include challenges relating to the inclusion of multiple health conditions, the assessment of diagnostic accuracy in the absence of a reference standard, and the assessment of true disease prevalence for rare genetic conditions.<sup>27</sup> In developing our clinical evidence review of genetic/genomic technologies, we consider:

- **Population of interest:** our population of interest may include genetically predisposed, high-risk, pregnant, or asymptomatic people (i.e., people who are carriers of a particular gene, but do not express it). In oncology, tests may aim to detect the genetics of the cancer cells among patients with a certain type of cancer to inform treatment decisions or likely prognosis
- **Test accuracy:** the accuracy of a genetic/genomic test may be influenced by the included genes or variants and the laboratory methods by which the test is conducted. Genetic/genomic tests change over time as new knowledge is generated to further understand the genetic underpinnings of risk and disease and technologies available to perform testing. There may be differences in the variants present in the population of interest that affect test performance. Like non-genetic/genomic diagnostic tests, sensitivity and specificity reflect the percentage of positive and negative cases, respectively, correctly identified by a given genetic/genomic test
- **Comparator(s):** a genetic/genomic test may be compared with standard care (which may be no test), or it may be combined with other genetic or non-genetic tests. Further, comparators may include invasive and noninvasive tests
- **Effectiveness and outcome measures:** outcomes may focus on one or more of analytic validity, clinical validity, or clinical utility of the test to weigh the clinical impact of the test.<sup>28</sup> Test results may or may not change the clinical pathway for a patient, and they may have implications for relatives as well as the individual being

tested. Importantly, genetic/genomic tests may not provide a change in treatment, but can provide diagnostic or risk information that is valuable to the patient and their family members.

## **Economic Evidence**

The objective of the economic assessment is to determine the relative costs and consequences of the health technology compared with its alternatives and to understand the potential budget implications of funding it in Ontario. Our assessments are conducted from the perspective of the Ontario Ministry of Health and include one or more of the following three components:

1. An economic evidence review to summarize the available economic literature on the health technology
2. A primary economic evaluation to estimate the cost-effectiveness of the health technology
3. A budget impact analysis to estimate how much it would cost to publicly fund the health technology in Ontario

### ***Economic Project Plan***

We begin by developing an economic project plan, which defines the objectives, methods, and data sources of the economic evidence review, primary economic evaluation, and budget impact analysis. Similar to the clinical review plan process, we consult clinical and health economics experts to ensure the economic project plan is relevant to the decision problem and Ontario context.

### ***Economic Evidence Review***

#### ***Research Questions***

The objective of the economic evidence review is to identify and select published economic studies that are relevant for the decision problem. In this section, we summarize and contextualize published evidence on the cost-effectiveness of the health technology compared with the current standard of care for the population of interest. Results of the economic evidence review can inform the need for conducting a primary economic evaluation. We align our research question with the clinical evidence review and patient engagement section, ensuring to specify, at minimum, the population, intervention, and comparator of interest.

#### ***Literature Search Strategy and Methods***

The process of our economic evidence review is similar to that of the clinical evidence review. Typically, the literature search strategy is based on the clinical literature search strategy with an economic and costing filter applied. See Clinical Evidence, above, for more details.

Study selection criteria may include elements such as relevant population, intervention, comparator(s), outcomes (e.g., costs, quality-adjusted life-years [QALYs], incremental cost-effectiveness ratios [ICERs]), study design (e.g., cost-utility, cost-effectiveness, cost-benefit, cost-minimization), setting, and year of publication.

Results of the study selection process, including data sources, number of studies screened and included at each stage, and a high-level summary of reasons for exclusion at the full-text stage are reported in a flow diagram, in accordance with the PRISMA Statement.<sup>11</sup>

We extract data from the included studies, including information on study design, perspective, time horizon, population, intervention, comparator, results (e.g., health outcomes, costs, cost-effectiveness), and sensitivity analyses.

### ***Assessment of Study Applicability and Quality***

We determine the applicability of each identified study to the Ontario context and to our decision problem by applying a modified applicability checklist for economic evaluations originally developed by the National Institute for Health and Care Excellence in the United Kingdom (see Appendix 2).<sup>29</sup> The checklist considers the applicability of the literature to the current decision problem. In this process, we examine several features of published studies, including the target population, interventions, comparators, clinical inputs, cost inputs, and the context (i.e., differences in health care systems, variations in practice and clinical pathways), as well as the date of publication. In addition, we use the second part of the NICE checklist<sup>29</sup> to critically examine the methodological quality of studies deemed applicable to the research question. As part of this assessment, we discuss limitations of the study design, such as modeling techniques, model structure, inputs (clinical effectiveness, natural history, and costs), assumptions, and assessment of uncertainty.

### ***Summary and Contextualization of Published Economic Evidence***

Based on the results of the economic evidence review and preliminary insights from the clinical evidence review, we determine if there is a need to develop a *de-novo* cost-effectiveness model (i.e., conduct a primary economic evaluation) or proceed with a standalone budget impact analysis. A primary economic evaluation may be omitted in the following situations:

- When the clinical evidence is insufficient (i.e., no evidence) or highly uncertain (e.g., very low quality) to support modelling
- When the economic evidence review identifies a recent cost-effectiveness study deemed directly applicable to our research question and is of high methodological quality

When a published cost-effectiveness study conducted in an Ontario or Canadian setting is considered directly applicable to our research question and is of high quality, the study results should provide information about the potential cost-effectiveness of the health technology compared with its alternative(s). In this case, and to avoid duplication of efforts, we would not conduct a primary economic evaluation and would proceed to a budget impact analysis only. If a published study is deemed directly applicable to our research question(s), but is conducted in a non-Ontario or non-Canadian setting, we may use published transferability tools (e.g., the Welte Checklist)<sup>30,31</sup> to determine if the findings of the published economic study are transferrable to our decision problem within the Ontario context.

In some circumstances, validated economic models developed for other contexts may be applicable to our review. In these cases, and to reduce duplication of effort, we may request a copy of the model(s) or rebuild them, adapting them to the Ontario context. If this is done, models will first be assessed for usefulness and adaptability (see Minimizing Duplication Efforts, above).

## **Primary Economic Evaluation**

### **Objective and General Principles**

The objective of the primary economic evaluation is to assess the cost-effectiveness (costs and health outcomes) of the health technology compared with the current standard of care in Ontario. When developing a model, we follow the CADTH guidelines for economic evaluations<sup>32</sup> and methodology reports by the International Society for Pharmacoeconomics and Outcomes Research–Society for Medical Decision Making (ISPOR-SMDM) Modelling Good Research Practices Task Force.<sup>33-37</sup> To ensure transparency in reporting, we follow the Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) statement.<sup>38</sup>

### **Types of Analysis**

We select the type of analysis for the primary economic evaluation based on the nature of the research question, the health condition, and the availability of relevant data. We typically employ cost-utility or cost-effectiveness analyses, which compare the costs and health outcomes associated with the health technology against its comparator(s). For health outcomes, cost-effectiveness analyses use natural units of clinical effect (e.g., lives saved, heart attacks prevented), whereas cost-utility analyses use a generic measure of health gain (e.g., QALYs). Cost-utility analysis is preferred when utility data are available, as it is the reference case approach recommended by the CADTH guidelines for economic evaluations.<sup>39</sup> Cost-utility analyses would allow decision makers to compare results across different conditions and interventions.

### **Population**

The population used in our primary economic evaluation is all patients eligible for the health technology. We identify this population based on the intended use of the health technology, Health Canada recommendations, and expert opinion. We specify the relevant characteristics of a patient cohort representing the target population (e.g., demographic features, disease severity, risk factors, expected application of the health technology). We may further stratify the target population into smaller, more homogeneous subgroups to reflect variations in clinical effectiveness, natural histories, and/or treatment pathways.

### **Study Perspective**

We primarily adopt the perspective of the publicly funded health system (i.e., the Ontario Ministry of Health). Other perspectives may also be undertaken; for example, that of an institution (e.g., hospital) or society, such as when there are likely to be large impacts on costs and health outcomes beyond those associated with the health system (e.g., improvement in patient or caregiver productivity, reduction of out-of-pocket costs).

### **Model Structure**

We determine the appropriate model type and structure based on the stated decision problems, the nature of the health technology, the natural history of the health condition, and choices made concerning the relevant outcomes within the model. We strive to ensure the model structure is consistent with the reality of the health condition by selecting treatment pathways (disease states or branches) that reflect the underlying biological processes of the health condition and the impact of the health technology. Clinical and economic experts verify the treatment pathways and model structure. Common model types are decision-tree and state-transition (Markov) models (which can be simulated at a cohort or an individual level [i.e., microsimulation]). The software programs we use to build models and run analyses include TreeAge Pro,<sup>40</sup> Excel,<sup>41</sup> SAS,<sup>42</sup> and R.<sup>18</sup>

### **Comparator(s)**

Our choice of comparator(s) is based on factors related to the target population and the indication of the intervention (i.e., the purpose of the health technology) and aligns with the clinical evidence review. All approved, available, and technically feasible alternatives indicated for the health condition could be considered potential comparators. Typically, the comparator is standard of care, which we define as the current or most common treatment used in Ontario for the health condition. We consult with clinical experts to understand all likely alternatives. We try to anticipate the entry of future comparators into the market.

### **Time Horizon**

We select the model's time horizon, the time period over which we compare the costs and clinical consequences (health outcomes) of health interventions, based on the nature of the health condition (e.g., acute, chronic, palliative). We choose a time horizon that is sufficiently long to capture the main health effects and costs relevant to the decision problem.<sup>39</sup> We typically use a lifetime horizon (a time period consisting of a person's life span) for chronic diseases (e.g., depression, Parkinson's disease) and when the alternative treatments have differential effects on mortality. In these instances, it may be necessary to extrapolate primary data beyond the duration of the study (e.g., from short-term to long term effectiveness); thus, consideration of the strength of evidence for this forecasting could be important.<sup>43</sup> We use shorter time horizons when there are no differential mortality effects between treatment options or when differences in costs and clinical outcomes are likely limited to a short period of time (e.g., for acute conditions, such as a nondisplaced fracture). We may also explore the impact of different time horizons on the results in scenario analyses.

### **Discount Rate**

Various costs and health outcomes may occur at different points in time. To account for this, we typically discount costs and quality-adjusted life years to present values (i.e., by calculating the current value of a future sum of money given a specified rate of return, also known as the discount rate).<sup>32</sup> We use an annual discount rate of 1.5% as per the most recent CADTH guidelines for economic evaluations.<sup>44</sup> In our sensitivity analyses, we also assess different discount rates (e.g., 0%, 3%).

## ***Assumptions***

It is impossible to capture all the complexities and variations associated with a disease, its management, and the population(s) of interest. To simplify our economic model and account for data unavailability, we often make assumptions regarding parameters and aspects of the disease or its management. Clinical assumptions are usually validated by clinical experts, and policy-related assumptions are usually informed by the Ontario Ministry of Health, or other health system partners where relevant. Economic assumptions are often vital to understand the model structure and dynamics. Our analysis includes a description of and justification for the assumptions we used to build and run a model, as well as a discussion of the limitations introduced by the assumptions. We assess the impact of assumptions on our results in a sensitivity analysis (see Uncertainty, below).

## ***Identifying Model Inputs and Valuing Outcomes***

Once we finalize the structure of the model, we identify and obtain the required model inputs (e.g., clinical effectiveness, costs, utilities) from relevant sources, including the clinical evidence review, additional published clinical and economic literature, publicly available information (e.g., government websites), and expert opinion. Most model inputs have a point estimate, representing the most likely value, and a distribution around the point estimate to quantify uncertainty or variability in the value. To ensure transparency, we provide the sources of our data along with our methods for identifying data.

## ***Clinical Inputs***

### *Natural History*

The natural history of a disease is the occurrence (i.e., the probability or rate) of clinical outcomes at baseline, with no intervention. The baseline occurrence of clinical outcomes may be modelled based on a population receiving standard care. When possible, we model the natural history using inputs that represent the Canadian context.

### *Clinical Effectiveness*

Clinical effectiveness is typically modelled using relative treatment effects (e.g., relative risks, odds ratios, hazard ratios), obtained for the new intervention relative to the comparator(s) included in the model.

We obtain information on the relevant treatment effect estimates from the clinical evidence review. As mentioned in the clinical evidence review section (above), we can use effectiveness estimates from randomized clinical trial data or from observational studies, using real-world effectiveness data. When identifying model inputs, we simultaneously consider the quality (lack of bias and GRADE<sup>21</sup> assessment), comprehensiveness, and relevance of the literature. With respect to comprehensiveness, we favour estimates that are representative of the published literature as a whole, as opposed to estimates obtained from a single study. When available, meta-analyses of high-quality studies directly comparing the health technology with its relevant comparator(s) are typically preferred for the reference-case estimates.<sup>45</sup> A single study may be used in cases where there is sparse clinical literature, where only one high-quality study is available, or where there is a large degree of heterogeneity among studies, making a meta-analysis unfeasible. When direct

clinical evidence is limited or unavailable, we may use network meta-analyses or indirect comparisons to estimate effectiveness.

Proxy measures or intermediate endpoints may also be used, but only when there is an established link with patient-important outcomes.<sup>46</sup> For example, when evaluating a cardiovascular disease, modelling may be used to link intermediate outcomes (e.g., blood pressure) to patient-important outcomes (e.g., cardiovascular-related mortality).

We perform sensitivity analyses to assess the impact of treatment effects obtained from different sources (e.g., effectiveness or efficacy estimates, adherence, whether an intention-to-treat analysis was applied, time horizon over which patients were followed and examined). We also discuss limitations of the clinical evidence when present.

#### *Clinical Harms*

We include clinical harms that have a large impact on health effects and/or costs and resources. We describe how these harms are identified and the methods we used to incorporate them into the model. When harms are not included, we provide a clear justification.

#### **Cost Inputs**

Costing analysis depends on the perspective used in the model. We perform costing according to standard guidelines for economic evaluation and costing of health care resources.<sup>39,47</sup> Our perspective is usually the health care payer, in which we systematically identify, measure, and value all costs relevant to the Ontario Ministry of Health. Costs that are identical (both unit cost and resource quantities) between the intervention and comparator may be excluded as they have no effect on the result. Examples of typical costs included in the model are those associated with use of the health technology, physician, and/or health care staff services, prescription drugs (covered under provincially funded plans), diagnostic and/or laboratory tests, medical procedures, hospitalization, etc.

We typically consider variable (i.e., operational) costs in the reference case analysis. Capital and overhead costs may be considered in the sensitivity analysis, depending on the decision problem and potential funding mechanism.

Several approaches for costing may be used, depending on the treatment pathway and available costing data. We may obtain costs from previously published Ontario costing studies or administrative data to inform cost inputs (e.g., costing using a case-mix grouping methodology for hospital stays). Alternatively, where appropriate, we may use a micro-costing approach in which we measure and value the individual items. Costing comprises two steps: (1) estimating the resource quantities in natural units (e.g., number of visits); and (2) applying a price (unit cost) to each item (e.g., cost per visit). We specify the data sources used for estimating resource quantities and prices, along with the dates and methods by which they were collected. Resource use may be derived from a single clinical study, an existing database (e.g., Canadian Institute for Health Information or IntelliHealth Ontario databases such as the Discharge Abstract Database, the National Ambulatory Care Reporting System, and the Ontario Health Insurance Plan claims database), expert

consultation or the broader literature. Unit costs may also be derived from public websites, administrative databases, published literature, the device manufacturer, or clinical experts.

#### *Currency, Price Date, and Conversion*

Because prices change over time, it is necessary to report dates with prices. As per CADTH guidelines,<sup>47</sup> when Canadian prices of health care goods or services are unavailable for the current year, we inflate them using the general Consumer Price Index for all good and services.<sup>47</sup> We typically estimate the price of technology in Canadian dollars and in collaboration with industry or experts. When the price of a resource item is not available in Ontario or Canada, we rely on foreign prices from health care jurisdictions similar to Canada, other publicly available sources, or expert opinion.

#### **Valuing Health Outcomes**

Health outcomes are the measures of benefit in the economic evaluation and may be expressed in natural units specific to the health condition (e.g., myocardial infarctions avoided, life years gained) or generic measures such as quality-adjusted life-years (QALYs).<sup>46</sup> Generally, we use QALYs when utility values (values that an individual or society gives a particular health state or outcome) are available and natural units when there are certain data limitations (e.g., when no utility values are available).

Our economic evaluations follow the CADTH guidelines for economic evaluation,<sup>39</sup> which recommend the use of QALY for the reference case analyses when data are available. QALY is usually preferred because it considers both length of life and health-related quality of life; it can be applied across different patient populations and disease areas, although it has certain limitations.

We typically obtain utility values associated with each health state or event from the published literature. If required, we may conduct a targeted search in MEDLINE. The search strategy is based on the population and/or intervention, depending on the topic, with a health state utility-value filter applied.<sup>48</sup> Preference is given to studies with representative, generalizable patient populations and preference-based elicitation techniques. When possible, we use utility values that reflect the Canadian population.

#### **Analysis**

A reference case analysis refers to the results obtained from running an economic model with the most likely or preferred set of assumptions and input values.<sup>49</sup> In the reference case, when possible, the model is analyzed probabilistically. We perform multiple Monte Carlo simulations, with values for the input parameters drawn from distributions reflecting the underlying parameter uncertainty (see below for details), and we calculate the costs and health outcomes for each simulation. The mean costs and health outcomes (e.g., QALYs) from all simulations for the intervention and comparator(s) are used as the reference case results. In addition, the 95% credible intervals (estimated from the 2.5 and 97.5 percentiles) are presented for costs and outcomes. Typically, we calculate the ICER of the intervention versus each comparator. An ICER is equal to the difference in mean costs between interventions (incremental cost) divided by the difference in mean outcomes or

effects between interventions (incremental effectiveness). It reflects how much extra one would have to pay to obtain one additional unit of health benefit.

The calculated ICER may be compared to different commonly used willingness-to-pay values worldwide in economic studies. If the ICER is below a particular willingness-to-pay value, the health technology may be considered cost-effective at that particular value. For transparency, we typically present results over a range of willingness-to-pay values.

Several approaches for considering willingness-to-pay thresholds have been proposed internationally, including selecting thresholds based on per capita gross domestic product (GDP),<sup>50</sup> league tables,<sup>50,51</sup> and benchmark interventions.<sup>50,52</sup> However, given limitations to the proposed methods for determining cost-effectiveness (willingness-to-pay) threshold methods,<sup>50</sup> OHTAC and OGAC has not adopted a defined threshold at which a health technology would be deemed to provide either poor or good value.

### **Uncertainty**

To support decision making, we assess uncertainty and limitations of the economic model, using several methods, for example:

- **Probabilistic analysis:** we examine the joint effects of uncertainty in all input parameters simultaneously. In each simulation, input values are randomly drawn from the assigned distributions. Typical distributions for costs, probabilities, utilities, and relative risk measures are gamma (for costs), beta (for probabilities or utilities), and lognormal (for relative risks).<sup>46</sup> We present these results in the form of a cost-effectiveness acceptability curve (CEAC, see Appendix 3), where the proportion of simulations in which each treatment alternative was preferred is shown at a range of willingness-to-pay values. This curve represents the probability that the health technology is cost-effective at a particular willingness-to-pay value compared with the existing alternative(s). The curve reflects the robustness of the model and our confidence in its conclusions
- **One-way sensitivity analyses:** we vary point estimates or distributions for key input parameters (e.g., probabilities, costs, utilities, treatment effects) one at a time, to assess the imprecision and individual impact of each parameter on cost and effectiveness outcomes<sup>32</sup>
- **Scenario analyses:** we explore the implications of potential changes to the model and/or estimates. These can be used to explore structural uncertainty or subsets of parameter uncertainty. For instance, in addition to the reference case analysis (the "best guess"), the scenarios could include ideal ("best case") and pessimistic ("worst case") cases, or other relevant cases. In addition to structural uncertainty, there may be variability in the target population (owing either to differences in clinical practice or to patient heterogeneity), which we address by conducting specific scenario analyses
- **Subgroup analyses:** we assess variability due to patient heterogeneity. Important patient subgroups are identified in the clinical review or at the beginning of the economic evaluation, as appropriate

### **Validation**

Our models are subjected to rigorous internal validation. We validate our evaluation by verifying the model, its equations, and results (by a secondary health economist), consulting with clinical experts to ensure the model has face validity, and cross-validating our results with previously published economic evaluations addressing similar decision problems.

### **Transparency**

We ensure transparency by providing detailed information on model structure and input parameters in our reports. We include schematic model diagrams to facilitate the understanding of the model structure and we list the most important model assumptions. We also state and justify our choice of data sources and methods used to analyze data.

### **Equity**

Assessments of equity in health care economic evaluations are focused primarily on health care inequalities or uneven distributions of health outcomes or health care resources.<sup>39</sup> As recommended by the 2017 CADTH guidelines,<sup>39</sup> our economic analyses acknowledge the implications of two types of health equity: horizontal and vertical. Horizontal equity considers that people with similar characteristics are treated the same (“equal treatment of equals”), while vertical equity justifies the differential treatment of people with different characteristics (“unequal treatment of unequals”).<sup>53</sup>

Some research has suggested the use of equity weights to address disparities in health outcomes observed in disadvantaged populations. However, this methodological approach may result in more favourable cost-effectiveness estimates for disadvantaged populations. In addition, the potential opportunity costs to other populations when such weights are used are unclear.<sup>54</sup> Therefore, the 2017 CADTH guidelines suggest the use of equal weights for all outcomes in the reference case, regardless of the characteristics of people receiving, or affected by, the intervention in question.<sup>39</sup>

To address potential health inequities in our economic evaluation, we may define possible vertical inequities prior to or after the adoption of a new health technology. We do this by conducting subgroup analyses in specified subpopulations or for a specific type of device (within the examined device class). This allows us to assess the robustness of our cost-effectiveness estimates in defined subgroups within our primary economic evaluations.

### **Summarizing Economic Evaluation Results**

We report the results of our primary economic evaluation following standard guidelines for economic evaluations.<sup>32</sup> To provide a clear understanding of both the cost-effectiveness of the health technology and the certainty of our conclusions, we present our reference case results as an ICER. We provide a cost-effectiveness acceptability curve (see Figure A1, Appendix 3), as described above (*Analysis*), or a scatter plot of ICER simulations on the cost-effectiveness plane (see Figure A2, Appendix 3). We also present cost breakdowns (e.g., device, service, or genetic test costs; treatment costs; adverse event costs), additional clinical outcomes (e.g., life-years, meaningful clinical event rates), and results of different scenario analyses, as appropriate.

We summarize the key findings of our evaluation and describe how they support our conclusions. In addition, we clarify the strengths and limitations of our input parameters and analysis. We indicate the key areas of uncertainty, the main variables affecting our cost-effectiveness conclusions, and the potential subgroup impacts, which may provide areas for future research.

### ***Considerations in the Economic Evaluation of Medical Genetic/Genomic Technologies***

Most methods for the economic evaluation of genetic/genomic technologies are the same as those for all health technologies. However, genetic/genomic economic evaluations do have some unique features, as suggested in the CADTH Guidelines for Treatments with Companion Diagnostics,<sup>55</sup> including the following:

- **Population of interest:** our research question guides the definition of the population, which may include genetically predisposed, high-risk, or asymptomatic people (i.e., people who are carriers of a particular gene but do not express it). Modelling may consider population subgroups to examine heterogeneity among individuals based on certain characteristics or risk groups
- **Test accuracy:** the accuracy of a genetic/genomic test may be influenced by the quality of the technology and the laboratory setting in which the test is conducted. Sensitivity and specificity reflect the percentage of positive and negative cases, respectively, that are correctly identified by a given genetic/genomic test.<sup>56</sup> Modelling typically captures these measurement properties of the diagnostic tests and may also include sequential testing strategies and consequences related to the screening and/or diagnostic testing conducted
- **Comparator(s):** our choice of appropriate comparator(s) is guided by the scope of the HTA. A genetic/genomic test may be compared with standard care (which may be no test), or it may be combined with other genetic/genomic or non-genetic/genomic tests. Further, comparators may include invasive and noninvasive tests<sup>57,58</sup>
- **Effectiveness and outcome measures:** the results of a genetic/genomic test may change the clinical pathway of a patient. In this case, we model the new pathway to ensure that the results of a genetic test are linked with its impact on the patient management strategy and clinical effectiveness measures. We assess the cost-effectiveness of genetic/genomic testing depending on the research question and on the availability and quality of existing data. We use the best available evidence for the effectiveness data.

### ***Budget Impact Analysis***

#### ***Objective***

The objective of the budget impact analysis is to estimate how much it will cost to adopt the health technology into the Ontario health system (i.e., we conduct the analysis from the perspective of the Ontario Ministry of Health). To ensure transparency, our analyses follow a checklist developed by Ontario Health, adapted from the report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force.<sup>59</sup>

### ***Analytic Considerations***

Our budget impact methods are adapted from principles of good practice by the International Society for Pharmacoeconomics and Outcomes Research.<sup>59</sup> Our general approach is to identify the current mix of interventions in a specific disease area and predict how the introduction of the health technology may affect the budget (i.e., the budget impact of the health technology).<sup>59</sup> As shown in Figure A3 (Appendix 4), we estimate the budget impact of introducing the new intervention by calculating the cost difference between two scenarios: the “current scenario” (current clinical practice without the new intervention) and the “new scenario” (anticipated clinical practice altered by the new intervention). The budget impact analysis may stand alone or be accompanied by a cost-effectiveness analysis as described above. Our budget impact analyses, typically have a 5-year time horizon.

### ***Capturing the Size of the Population of Interest***

Our population for any budget impact analysis consists of all people in Ontario eligible to receive the health technology. The current size of the population of interest can be estimated based on either population data or claims data.<sup>60</sup> When using population data, the size of the population of interest can be estimated using epidemiological inputs, such as the prevalence and incidence of the disease being evaluated. When applicable, we include predicted changes in the population of interest and disease severity mix over the model time horizon. When available, the size of the population of interest can be forecasted using volumes reported through administrative databases (e.g., IntelliHealth Ontario). The size of population of interest may also be informed by expert opinion or the Ontario Ministry of Health.

### ***Determining the Intervention Mix***

Multiple interventions are typically available in the health system at the same time, but are used at different rates (referred to as the intervention mix). We often start by estimating the current mix, which could be no intervention or one or more standard of care interventions, likely to be replaced by the new health technology. The interventions included in the current mix are usually the comparators included in the primary economic evaluation (if one is conducted). We then estimate the new intervention mix after the new health technology is introduced into the health system. The new intervention mix depends on how quickly we expect the new health technology to be adopted (i.e., the uptake rate) and the extent to which it will replace the current interventions. The intervention mix and the uptake rate of a new health technology may be extrapolated from currently available real-world data (e.g., Ontario administrative data, observational studies and patient registries), informed by external stakeholders (e.g., clinical experts, manufacturers, the Ontario Ministry of Health), or modelled after other jurisdictions (Canadian jurisdictions where possible). The uptake rate may also depend on the current capacity of the system.

### ***Resource Use and Costs***

We estimate resource use and costs associated with adopting the new health technology. Depending on the health technology and conditions, we may include costs of the health technology, related health services and procedures, treatment-related adverse events, and condition-related costs (e.g., long-term costs related to disease progression). If we only conducted a budget impact analysis (no primary economic evaluation), we typically focus

on short-term costs associated with the health technology. If a primary economic evaluation has been developed, we would obtain undiscounted costs from the primary economic evaluation results (usually include both short-term and long-term costs).

### ***Reference Case and Sensitivity Analyses***

The budget impact represents the difference in the mean total costs of the new intervention compared with the current scenario. Similar to our primary economic evaluation, we conduct sensitivity analyses to test key parameter input values and their impact on the total and annual budget (e.g., the price of new technology, uptake or size of population of interest), and we evaluate assumptions made in the analysis.

### ***Summarizing Budget Impact Results***

We present costs for both the current scenario and the new scenario for each year of the budget impact analysis for the given population of interest at an assumed uptake rate. For costs, we typically present total costs and costs disaggregated by costing components (e.g., costs associated specifically with the device, health service, genetic test, treatment, administration, changes in health outcome over the time horizon, etc.).

We discuss the results of our budget impact analysis, describing our main findings and their relevance to the current practice and, where available, we provide a comparison to the findings of other reports and reviews. We describe strengths and limitations related to issues such as study design, methods used, evidence available, generalizability of results, and quality of data inputs and sources.

## **Patient Preferences and Values Evidence**

Exploring patient preferences and values provides a unique source of information about people's experiences of a health condition and the health technologies or interventions used to manage or treat that health condition. It includes the impact of the condition and its treatment on the person with the health condition, their family and other caregivers, and the person's personal environment. Engagement also provides insights into how a health condition is managed by the province's health system.

Information shared from lived experience can also identify gaps or limitations in published research (e.g., outcomes important to those with lived experience that are not reflected in the literature).<sup>61-63</sup> Additionally, lived experience can provide information and perspectives on the ethical, social values, and equity implications of health technologies or interventions.

Because the needs, preferences, priorities, and values of those with lived experience in Ontario are important to consider to understand the impact of the technology in people's lives, we may speak directly with people who live with a given health condition, including those with experience of the technology or intervention we are exploring.

Information about preferences, values, and lived experience related to a health technology, condition, or context can be explored through a qualitative or quantitative literature review or direct patient engagement activities. The decision to undertake a systematic review and/or direct patient engagement depends on our information needs and is made on a case-by-case basis. Our methodologies for patient engagement are guided in part by a report of the OHTAC Public Engagement Subcommittee.<sup>63,64</sup>

## ***Quantitative Preferences Evidence***

We undertake a literature review to gain an overview of the available evidence on quantitative preferences, when appropriate. The purpose is to answer broad, exploratory research questions related to patient (and sometimes provider) preferences. The definition of preference varies within the literature. Within the context of clinical decision-making, preference has been defined as, "the processes that individuals use in considering the potential benefits, harms, costs, limitations, and inconvenience of the management options in relation to one another."<sup>65</sup> We document our plan for review in the Quantitative Preferences Evidence (QPE) Review Plan (similar to the Clinical Review Plan).

## ***Research Question***

A review of the quantitative evidence of preferences and values can address a variety of research questions. The preferences evaluated may include those of the population of interest, but may also be those of health care providers or informal caregivers or family members, depending on the technology. The outcomes of interest may be health or nonhealth outcomes relevant to the alternative treatment under consideration, and broadly include those directly or indirectly related to a health condition, intervention, or nonhealth consequence.

### ***Literature Search Strategy and Methods***

The QPE literature search is based on the clinical review search strategy. We use the Ovid interface to search MEDLINE and the EBSCO interface to search the Cumulative Index to Nursing & Allied Health Literature (CINAHL) to capture quantitative evidence of preferences and values. There is indirect evidence from qualitative informational retrieval research, demonstrating CINAHL's additional value.<sup>66</sup> Typically, the population and intervention of the clinical literature search strategy are adapted by adding a filter for preferences and values developed by Selva et al.<sup>65</sup> In some instances, only the population or intervention may be used, depending on the circumstances. Additional health care provider terms are also added to the search filter to reflect the topic in question.

### ***Eligibility Criteria***

We specify the criteria by which studies will be included or excluded from the review of quantitative evidence for each research question. Eligibility criteria may include factors such as relevant PICO(TS) criteria, study design (e.g., surveys, discrete choice experiment), sample size, year of publication, and minimum follow-up period.

### ***Study Screening***

We assess all studies identified through the literature search according to the selection criteria to determine their eligibility for inclusion. The titles and abstracts are reviewed, and, for those studies appearing to meet the specified eligibility criteria, full-text articles are obtained. We may also review the reference lists of included studies and contact content experts for any additional relevant studies not identified through the search. We use the Covidence systematic review software to manage the evidence review.<sup>15</sup>

Results of the study selection process, including data sources, number of studies screened and included at each stage, and a high-level summary of reasons for exclusion at the full-text stage are reported in accordance with the PRISMA Statement, including citation flow diagram.<sup>11</sup>

### ***Data Extraction and Synthesis***

We extract data from the included studies based on information available in the publications. Relevant information related to study design and characteristics, results, and PICO are extracted and summarized in both narrative and tabular format in the HTA report. We contact study authors as necessary for clarification regarding the published analysis. All correspondence with study authors is documented in the HTA report.

### ***Direct Patient Engagement***

Patient engagement seeks to understand the lived experience by eliciting perspectives from patient populations in Ontario, with particular patient representation guided by the nature of the health technology being reviewed. We use a planned approach to direct our patient engagement activities, which includes a needs assessment to determine if direct patient engagement is needed and the development of an engagement plan to determine which methodology to employ.

## ***Needs Assessment***

We conduct a needs assessment (Appendix 5) to assess whether direct engagement with patients would contribute important additional context to the HTA.

A needs assessment considers five explicit criteria:

- The burden of illness
- The purpose and impact of the health technology
- Equity considerations (e.g., variability in access to treatment)
- The degree of public controversy associated with the health technology (noting any particular attention paid by the media, policy leaders, advocacy groups, or the general public)
- Any gaps in the clinical or economic literature that might be addressed through direct patient engagement activities (i.e., evidence regarding patient-important outcomes)

We evaluate the findings of the needs assessment qualitatively and in discussion with the HTA team and subject matter experts specific to each project.

## ***Engagement Plan***

If the needs assessment concludes that direct patient engagement would add valued context and information to the HTA, we develop an engagement plan. The design of the engagement plan depends on a variety of factors, including whether there is any relevant existing literature on patient needs, values, and preferences; resources; the timeline of the HTA, and whether focused outreach is needed to engage remote or hard-to-reach communities.

For HTAs that include direct patient engagement, activities may include in-person or telephone interviews, focus groups, and/or online surveys. Engagement is purposeful; we make an effort to reach out to key informants and partners who can help us connect with people with direct lived experience.<sup>62</sup> Key informants may be clinical experts, representatives of advocacy organizations, care delivery or clinic staff, or patient advisory network staff. In addition, we approach key informants and partners who support underserved populations to broaden access to our engagement. To that end, we may distribute a call for participation through online forums, social media, and via clinicians where appropriate.

## ***Outreach***

Our outreach methodology follows Ontario Health's data collection and privacy standards. We inform peer support groups and health care providers about our projects and ask them to share information about our engagement activities. After learning about a particular project, people interested in participating may contact Ontario Health staff directly to express their interest in participating in an engagement activity.

### ***Interviewing Participants***

Interview questions relate to the lived experience of the health condition, people's experiences of different treatments, and, when possible, the health technology being evaluated.<sup>63</sup> We coordinate our engagement and directed questions with the clinical and economic research questions to see if there are any gaps in the clinical or economic literature that could be explored during direct patient engagement activities.

We conduct our engagement activities in a variety of settings, including in the community, at Ontario Health's offices, over the phone, and online. We provide participants with a letter of information and a consent form (if requested) for participation in the engagement activity, which includes information regarding privacy protection. We also inform participants that the information they share will be kept confidential and stored securely. Further, we inform participants that their participation is voluntary and will in no way affect the care they receive. Our data collection is anonymous; we do not identify patients in the HTA report, nor do we keep patients' personal health information. Ontario Health's direct patient engagement activities are designed for quality improvement purposes (i.e., to improve health care in Ontario) and not as research studies. As such, our patient engagement work is exempt from research ethics review.<sup>64</sup>

### ***Summarizing the Findings***

Participant interviews are transcribed, which enables us to code and explore themes in the resulting transcripts using a modified version of grounded theory.<sup>67-69</sup> Survey responses are also coded. We use the qualitative data analysis software NVivo<sup>70</sup> to identify and compare themes using a constant comparative analysis approach. We also select quotes from participants to include in our written reports to illustrate the impact of the health technology on patients' quality of life. Lived experience evidence provides insight into patient needs, priorities, preferences, values, and quality of life with respect to the health condition and health technology and explores the impact the health technology could have on participants' quality of life, or those of family members and caregivers.

### ***Qualitative Evidence***

When appropriate and practicable, we may collaborate with other pan-Canadian HTA agencies (e.g., CADTH, Canadian Agency for Drugs and Technologies in Health) to conduct a review of qualitative literature on patient and/or provider preferences.

### ***Ethics Considerations***

Depending on the nature of the HTA and the specific research questions, we may include ethics considerations into the report. We use a trigger tool described by Krahn et al.,<sup>71</sup> which was adapted from the European Network for Health Technology Assessment (EUnetHTA) model, to determine when a full ethics and social values analysis is warranted. Selected trigger components include: (a) technology decision is identified as being value (or preference) sensitive; (b) use by vulnerable or marginalized populations; and (c) screening interventions; (d) autonomy, privacy, or confidentiality issues especially salient. We may collaborate with other Pan-Canadian HTA agencies to conduct an ethics analysis.

# Phase 3: Making a Recommendation

The [Ontario Health Technology Advisory Committee](#) reviews the findings of HTA reports on health technologies and health care services, and, through a deliberative process, makes recommendations regarding public funding for the technology. The findings of HTAs of genetic/genomic tests are first reviewed by the [Ontario Genetics Advisory Committee](#), a subcommittee of OHTAC.

Subsequently, Ontario Health, based on guidance from OHTAC, makes recommendations to the Ontario Ministry of Health regarding public funding.

## Decision Determinants Framework

OHTAC bases its recommendations on a careful review and deliberation of the information gathered in the HTA. In making recommendations, OHTAC is guided by a decision determinants framework. This framework provides considerations for developing a recommendation within five domains. These determinants do not have a hierarchy, and the relative weight of each domain is specific to the individual health technology being assessed. Each of these domains are evaluated according to the following considerations<sup>71,72</sup>:

- **Overall clinical benefit**
  - *Effectiveness*: how effective is the health technology/intervention likely to be (taking into account any variability)?
  - *Safety*: how safe is the health technology/intervention likely to be?
  - *Burden of illness*: what is the likely size of the burden of illness pertaining to this health technology/ intervention?
  - *Need*: how large is the need for this health technology/intervention?
- **Patient preferences and privacy**
  - *Patient preferences and values*: do patients have specific preferences, values, or needs related to the health condition, health technology/intervention, or life impact that are relevant to this assessment?
  - *Autonomy, privacy, confidentiality, and/or other relevant ethical principles as applicable*: are there concerns regarding accepted ethical or legal standards related to patient autonomy, privacy, confidentiality, or other ethical principles that are relevant to this assessment?
- **Equity and patient care**
  - *Equity of access or outcomes*: are there disadvantaged populations or populations in need whose access to care or health outcomes might be improved or worsened that are relevant to this assessment?
  - *Patient care*: are there challenges in the coordination of care for patients or other system-level aspects of patient care (e.g., timeliness of care, care setting) that might be improved or worsened that are relevant to this assessment?
- **Cost-effectiveness**

- *Economic evaluation*: how efficient is the health technology/intervention likely to be?
- **Feasibility of adoption into health system**
  - *Economic feasibility*: how economically feasible is the health technology/intervention?
  - *Organizational feasibility*: how organizationally feasible is it to implement the health technology/intervention?

## **Recommendation**

Following deliberations on the findings of an HTA, a draft recommendation is prepared regarding public funding for the health technology with rationale supporting the recommendation decision. The completed HTA report and draft funding recommendation are posted for public feedback on our website for 3 weeks. OHTAC considers all feedback before issuing a final recommendation. Ontario Health shares the final funding recommendation with the Ontario Ministry of Health. The HTA report is published in the journal *Ontario Health Technology Assessment Series*, which is indexed in MEDLINE and Embase. Both the HTA report and the final recommendation are published on our website.

# Key Process Elements Of The Health Technology Assessment Timelines

The time to complete an HTA report varies depending on topic complexity and resources, but in general projects adhere to the timeline shown in Table 1.

**Table 1: Health Technology Assessment Timeline**

Phase	Description	Approximate Duration
Scope development and literature searches	Develop clinical, economic, and patient preferences and values review plans; complete literature searches	2.5 months
Evidence development and draft report preparation; draft report presentation	Complete analyses; prepare draft HTA report; present draft HTA findings to OHTAC; OHTAC develops draft recommendation  Genetic topics: complete analyses; prepare draft HTA report; present draft HTA findings to OGAC; OGAC develops draft recommendation; draft recommendation then presented to OHTAC for approval	4 months
Production	Edit HTA report and draft recommendation document; notify the Ontario Ministry of Health of draft recommendation; post HTA report and recommendation for public feedback; OHTAC finalizes recommendation (if genetic report, OGAC finalizes genetic test recommendation, which is then reviewed by OHTAC)	6–6.5 months
Final ministry notification and web posting	Share approved HTA report and funding recommendation with the Ontario Ministry of Health and post finalized HTA report and recommendation on Ontario Health's website	1 month
<b>Total project duration</b>		<b>~13–14 months</b>

Abbreviations: HTA, health technology assessment; OGAC, Ontario Genetics Advisory Committee; OHTAC, Ontario Health Technology Advisory Committee.

## Roles and Responsibilities

Table 2 presents the roles and responsibilities of those involved in the development of an HTA report and Ontario Health recommendation.

**Table 2: Roles and Responsibilities of Those Involved in the Development of an HTA Report and Ontario Health Recommendation**

Role	Responsibilities
HTA team	Receives HTA topic suggestion applications; supports OHTAC and OGAC in topic prioritization process; completes clinical, economic, and patient

Role	Responsibilities
	preferences and values evidence reviews; prepares draft HTA reports; manages HTA report production and approval process
OHTAC	OHTAC prioritizes HTA topics; reviews draft HTA reports; reviews public feedback received; makes draft and final recommendations; reviews and approves OGAC recommendations
OGAC	OGAC is the sub-committee of OHTAC for genetic/genomic HTA topics. OGAC prioritizes genetic/genomic HTA topics; reviews draft genetic/genomic HTA reports; reviews public feedback received; makes draft recommendations; provides draft recommendations to OHTAC for approval
Expert consultants (e.g., patients, clinicians, industry representatives)	Provide contextualization for the HTA
External stakeholders (e.g., clinicians, researchers, industry representatives, patients, caregivers)	Provide feedback on completed health technology assessments and draft recommendations through the open-for-feedback process
Ontario Ministry of Health	Participates in the prioritization of HTA topics, reviews draft HTA reports and provides feedback on clinical and economic plans; receives draft and final recommendations; uses recommendations to inform decision-making regarding public funding of health technologies

Abbreviations: HTA, health technology assessment; OGAC, Ontario Genetics Advisory Committee; OHTAC, Ontario Health Technology Advisory Committee.

## Health Technology Assessment Process

The following section describes the typical process phases for an HTA at Ontario Health.

### Process Detail: Scope Development Phase

#### **Expert Consultation**

Expert consultation occurs throughout the HTA process and is conducted by the HTA team members assigned to the HTA.

#### **Plan Development**

The HTA team works collaboratively to ensure the alignment of scope, research questions, and literature search strategies. The clinical epidemiologist develops the clinical review plan to guide the work of the clinical epidemiology team. The health economist develops an economic project plan to guide the work of the health economics team and ensure methodological alignment with the clinical review and patient preferences and values plans. The patient and public partnering analyst develops a patient engagement plan to guide the work of the patient engagement team. The clinical review plan is approved by the manager of Clinical Reviews, the patient engagement plan is approved by the Team Lead, Patient and Public Partnering, and the economic project plan is approved by the manager, Health Economic Evaluations.

#### **Quantitative Preferences Evidence Review Plan Development**

When appropriate, the clinical epidemiologist also develops the Quantitative Preferences Evidence Review Plan, similar to the clinical review.

### **Process Detail: Literature Search Phase**

During this phase, the HTA team develops literature search strategies for the clinical, economic, and quantitative preferences sections of the HTA. Once the search strategies are finalized, the literature searches are conducted by the medical librarian, and the search results and related documents are shared among HTA team members and filed for future reference.

### **Process Detail: Evidence Development and Draft Report Preparation Phase** ***Review of Evidence, Screening, and Analysis***

During this phase, we conduct a clinical evidence review to screen the literature search results to determine which studies are relevant to the clinical research question(s). Findings are summarized in the draft clinical report. We conduct an economic evidence review to summarize and critically appraise the available economic literature relevant to the health technology. A primary economic evaluation may be conducted, which typically includes building a model to perform cost-utility or cost-effectiveness analyses. Finally, we conduct a budget impact analysis. Findings are summarized in the draft economic report.

If appropriate, we conduct a quantitative preference evidence review to answer broad, exploratory research questions related to patient (and sometimes provider) preferences. Findings are summarized in the draft quantitative preferences report.

The patient and public partnering analyst conducts a needs assessment regarding direct patient engagement activities to obtain information about patient experiences, preferences, and values. Taking this assessment into consideration, the HTA program director, in conjunction with the Team Lead, Patient and Public Partnering, then decides whether to proceed with direct patient engagement activities. The decision to undertake direct patient engagement depends on the needs of the HTA and is made on a case-by-case basis.

If it is decided to undertake direct patient engagement, the Patient Preferences and Values team decides on the most appropriate engagement activity to pursue. For direct patient engagement, the HTA team prepares and then executes an engagement strategy defining the types of patients to be consulted, the nature of the data collection (i.e., interview, focus group, and/or survey), and questions to be asked.

If deemed appropriate, both a quantitative preferences evidence review and direct engagement may be conducted. Findings are summarized in the draft patient preferences and values report.

### ***Qualitative Rapid Reviews and Ethical Analyses***

When appropriate and suitable organizations have been identified, Ontario Health collaborates with partners to produce qualitative rapid reviews and ethical analyses in support of its HTA projects. Care is taken to ensure alignment of project scope and research questions.

### ***Present HTA Findings and Draft Recommendation Options for Consideration to Advisory Committees***

When the HTA team has finalized a draft report summarizing the evidence, the team presents its findings to OHTAC and OHTAC prepares a draft recommendation. Draft reports

on genetic topics are presented first to OGAC and then to OHTAC. For genetic topics, OGAC prepares a draft recommendation, which is then presented to OHTAC. Draft recommendations are guided by a decision determinants framework (see Decision Determinants Framework, above). The draft recommendation and draft HTA report are then submitted for editing.

### **Process Detail: Editing and Ministry Notification Phase**

In this phase, the draft HTA report is edited by a medical editor following a procedure and timeline agreed upon by and communicated to the full HTA team. The draft recommendation is also edited at this time.

The draft recommendation and HTA report are submitted to the communications branch of the Ontario Ministry of Health for a 15-calendar-day notification period. Any comments from the Ontario Ministry of Health are addressed prior to proceeding to the open-for-feedback phase.

### **Process Detail: Open-for-Feedback Phase**

#### ***Open-for-Feedback Posting***

All draft recommendations and HTA reports are made available for public feedback on the Ontario Health website for 21 calendar days. A plain-language summary is provided with each HTA report. Draft recommendation documents are provided in English and French.

#### ***Notifying Stakeholders***

Once the draft recommendation and HTA report are posted on the website, the HTA team prepares and sends a communication to a list of key stakeholders, inviting them to comment on the draft recommendation and/or HTA report. Relevant stakeholders may include clinical experts, patient groups, professional associations, and manufacturers.

#### ***Summarizing and Addressing Public Comments***

Following the open-for-feedback period, the HTA team assesses, summarizes, and then presents all feedback to OHTAC or OGAC (for genetic topics). The relevant committee considers the feedback to determine whether any amendments need to be made to the draft recommendation. Amendments are made prior to finalizing the recommendation.

### **Process Detail: Final Notification and Posting to Ontario Health Website**

The approved HTA report and final funding recommendation are shared with the Ontario Ministry of Health for a 20-day notification period. At the close of this period, the documents are posted to the Ontario Health website. Final recommendation documents are provided in English and French.

# Abbreviations

**CINAHL:** Cumulative Index to Nursing and Allied Health Literature

**GDP:** gross domestic product

**HTA:** health technology assessment

**ICER:** incremental cost-effectiveness ratio

**ISPOR:** International Society for Pharmacoeconomics and Outcomes Research

**MeSH:** Medical Subject Headings

**NHS EED:** National Health Service Economic Evaluation Database

**OGAC:** Ontario Genetics Advisory Committee

**OHTAC:** Ontario Health Technology Advisory Committee

**PRESS:** Peer Review of Electronic Search Strategies

**PRISMA:** Preferred Reporting Items for Systematic Reviews and Meta-analyses

**QALY:** quality-adjusted life-year

**QPE:** quantitative preferences evidence

# Glossary

**Adverse event:** Any unexpected problem that happens during treatment, regardless of the cause or severity.

**Clinical epidemiology:** The application of the principles of epidemiology to study the causes and effects of decision making in the practice of clinical medicine.

**Cost-effectiveness analysis:** An analysis to determine the value of a process or procedure relative to another approach by comparing the cost to the benefit. The benefit is usually expressed by a measure such as number of symptom-free days or life-years added. The resulting value (the cost of achieving the benefit) is usually compared to the value of a different process or procedure to determine which one offers the greatest benefit to cost ratio.

**Cost-minimization analysis:** In an economic analysis, where two interventions provide the same benefit, a review of costs is undertaken to determine the most cost-effective choice.

**Cost-utility analysis:** A type of analysis that estimates the value for money of an intervention by weighing the cost of the intervention against the improvements in length of life and quality of life. The result is expressed as a dollar amount per "quality-adjusted life-year" or QALY.

**Epidemiology:** The study of the occurrence and distribution of health-related events in a specified population to aid understanding of the causes of the events.

**Health economics:** The study or analysis of the cost of using and distributing health care resources.

**Health technology assessment:** A multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle. The purpose is to inform decision-making in order to promote an equitable, efficient, and high-quality health system.

**Incremental cost-effectiveness ratio:** The incremental cost-effectiveness ratio (ICER) is a summary measure that indicates, for a given health care intervention, how much more a health care consumer must pay to get an additional unit of benefit relative to an alternative intervention. It is obtained by dividing the incremental cost by the incremental effectiveness. Incremental cost-effectiveness ratios are typically presented as the cost per life-year gained or the cost per quality-adjusted life-year gained.

**Meta-analysis:** A technique to determine the current state of research into a specific defined topic of study by combining the results of all studies on that topic.

**Point estimate:** A specific number that is taken to be the best estimate of some aspect of a sampled population.

**Probabilistic analysis:** A type of analysis where the value of one or more unknown factors is estimated through the use of a technique that determines the most likely value or range of values for that factor. For instance, the Monte Carlo simulation will run a scenario many times using randomly assigned numbers where the value of a particular factor is unknown. The simulation indicates which outcomes are most common, and therefore most probable.

**Quality-adjusted life-year (QALY):** A measurement that takes into account both the number of years gained by a patient from a procedure and the quality of those extra years (ability to function, freedom from pain, etc.). The QALY is commonly used as an outcome measure in cost–utility analyses.

**Randomized controlled trial:** A type of study in which subjects are assigned randomly into different groups, with one group receiving the treatment under study and the other group(s) receiving a different treatment or a placebo (no treatment) in order to determine the effectiveness of one approach compared with the other.

**Reference case:** An analysis with the most likely or preferred set of assumptions and input values.

**Reference standard:** A population or value used as a basis of comparison for the population under study. Where the population under study is said to deviate from a standard, this is the standard it deviates from.

**Scope:** The broadness or narrowness of a review. Generally described in the Methods section through the defining of inclusion and exclusion criteria, the scope limits the range of an investigation to a defined set of issues or data.

**Sensitivity analysis:** Every evaluation contains some degree of uncertainty. Study results can vary depending on the values taken by key parameters. Sensitivity analysis is a method that allows estimates for each parameter to be varied to show the impact on study results. There are various types of sensitivity analyses. Examples include deterministic, probabilistic, and scenario.

**Systematic review:** A process to answer a research question by methodically identifying and assessing all available studies that evaluate the specified research question. The systematic review process is designed to be transparent and objective and is aimed at reducing bias in determining the answers to research questions.

**Willingness-to-pay value:** A willingness-to-pay value is the monetary value a health care consumer is willing to pay for added health benefits. When conducting a cost–utility analysis, the willingness-to-pay value represents the cost a consumer is willing to pay for an additional quality-adjusted life-year. If the incremental cost-effectiveness ratio is less than the willingness-to-pay value, the health care intervention of interest is considered cost-

effective. If the incremental cost-effectiveness ratio is more than the willingness-to-pay value, the intervention is considered not to be cost-effective.

# Appendices

## Appendix 1: Risk-of-Bias Assessment Tools

The following are the preferred tools for assessing the risk of bias by study type:

### Randomized controlled trial

- Cochrane Risk of Bias Tool 1<sup>73</sup>
- Cochrane Risk of Bias Tool 2<sup>17</sup>

### Observational study

- Scottish Intercollegiate Guidelines Network (SIGN) Checklist 3: Cohort Studies<sup>74</sup>
- SIGN Checklist 4: Case-Control Studies<sup>75</sup> (Note: typically case-control studies are not relevant to intervention studies)
- Downs and Black Checklist<sup>76</sup>
- Risk of Bias Assessment Tool for Nonrandomized Studies (RoBANS)<sup>77</sup>
- Cochrane Risk of Bias in Non-Randomized Studies—of Interventions (ROBINS-I)<sup>78</sup>
- Task Force on Community Preventive Services (TFPCS) tool<sup>79</sup>
- Effective Public Health Practice Project Quality Assessment Tool (EPHPP)<sup>80</sup>

### Diagnostic accuracy study

- Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2)<sup>81</sup>
- Quality Assessment of Diagnostic Accuracy Studies-Comparative (QUADAS-C)<sup>82</sup>

### Systematic review

- Risk of Bias in Systematic Reviews (ROBIS)<sup>83</sup>

### Prognostic study

- QUality In Prognosis Studies (QUIPS) for prognostic factor studies<sup>84</sup>
- Prediction model Risk Of Bias ASsessment Tool (PROBAST) for prognostic prediction model studies<sup>85</sup>

### Prevalence study

- Hoy et al, 2012 tool<sup>86</sup>

# Appendix 2: Applicability Assessment of Economic Studies

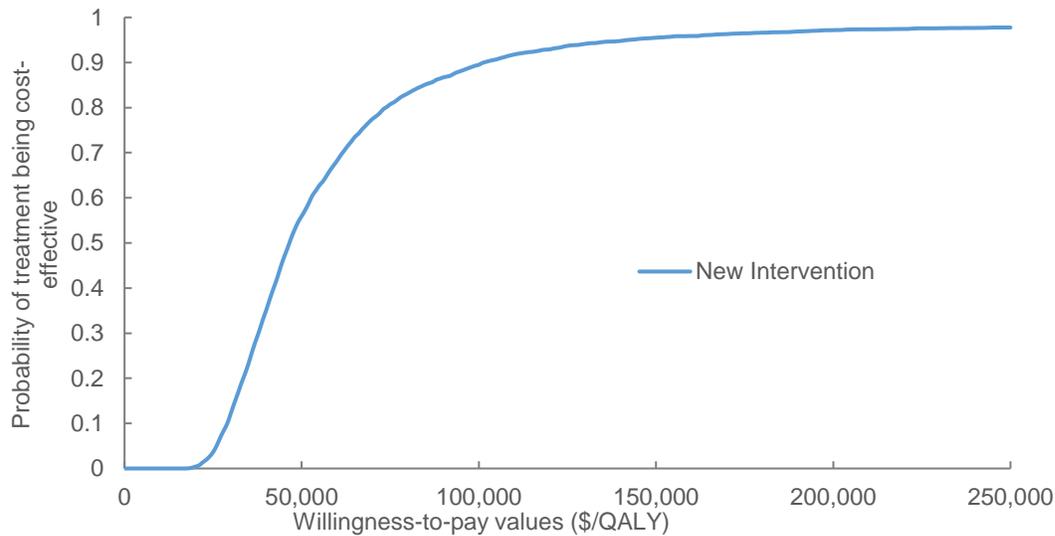
**Table A1: Study Applicability Appraisal Checklist**

Question	Possible Responses
Is the study population similar to the research question?	Yes/Partially/No/Unclear/NA
Are the interventions similar to the research question?	Yes/Partially/No/Unclear/NA
Is the health care system studied sufficiently similar to Ontario?	Yes/Partially/No/Unclear/NA
Were the perspective(s) clearly stated? If yes, what were they?	Yes/Partially/No/Unclear/NA
Are all direct effects included? Are all other effects included where they are material?	Yes/Partially/No/Unclear/NA
Are all future costs and outcomes discounted? If yes, at what rate?	Yes/Partially/No/Unclear/NA
Is the value of health effects expressed in terms of quality-adjusted life-years?	Yes/Partially/No/Unclear/NA
Are costs and outcomes from other sectors fully and appropriately measured and valued?	Yes/Partially/No/Unclear/NA
Overall judgment	Directly applicable/Partially applicable/Not applicable

Abbreviation: NA, not applicable.

Source: adapted from the National Institute for Health and Care Excellence.<sup>29</sup>

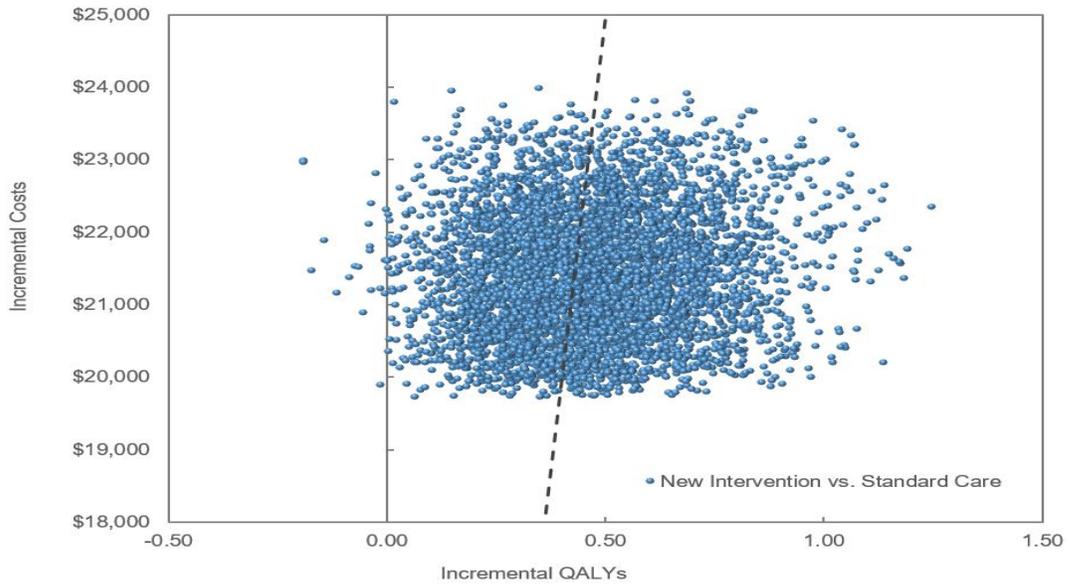
## Appendix 3: Results of Probabilistic Analysis: Cost-Effectiveness Acceptability Curve and Cost-Effectiveness Plane



**Figure A1: Cost-Effectiveness Acceptability Curve Showing the Probability of a New Intervention Being Cost-Effective at Different Willingness-to-Pay Values**

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Note: results of the probabilistic analysis can be summarized by considering how many of the Monte Carlo simulations have an ICER below a certain willingness-to-pay value. For example, the line in the graph indicates that 56% of the simulations have an ICER below \$50,000/QALY; in other words, the probability of the new intervention being cost-effective is 56% at a willingness-to-pay of \$50,000/QALY.

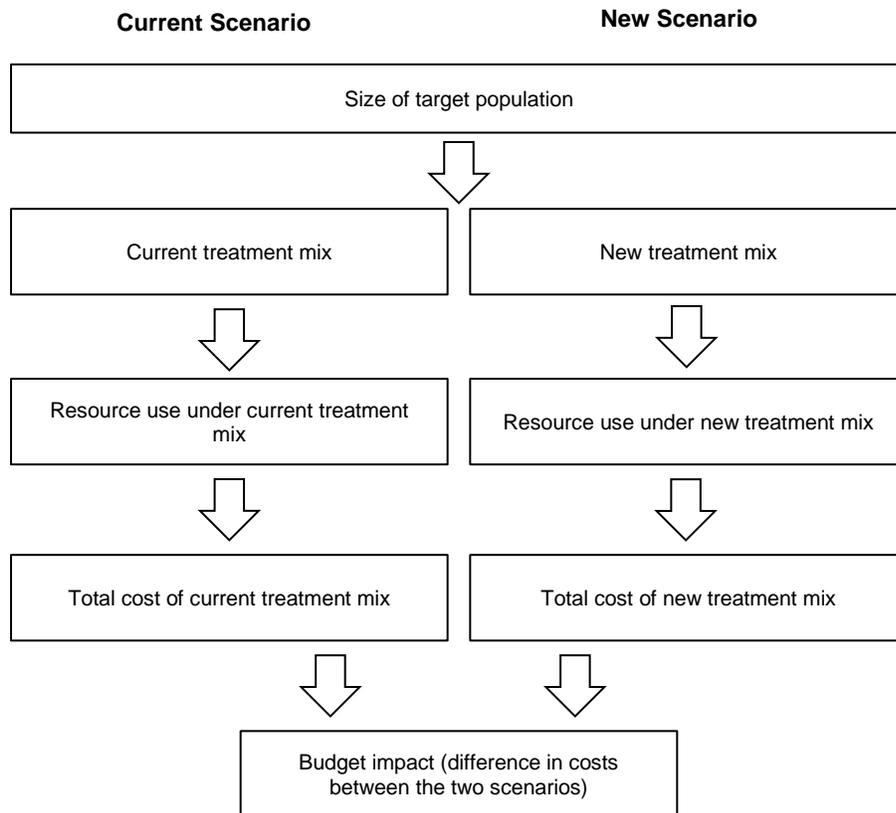


### Figure A2: Monte Carlo Simulation Results on the Cost-Effectiveness Plane

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Note: this graph shows 5,000 Monte Carlo simulations of the output of a cost-effectiveness model. Each dot in the graph represents the result of one Monte Carlo simulation of the probabilistic analysis. Values on the x-axis indicate the difference in effectiveness (in terms of incremental QALYs) between the new intervention and standard care. Values on the y-axis indicate the differences in cost between the new intervention and standard care. The dotted line represents a slope equal to an ICER of \$50,000/QALY.

# Appendix 4: Budget Impact Model Schematic



**Figure A3: Budget Impact Model Schematic**

# Appendix 5: HTA Direct Patient Engagement Needs Assessment

## **Purpose of the Needs Assessment**

- To determine if direct patient engagement activities are needed to obtain relevant information about the lived experience of the health condition and/or health technology
- To define the goals and objectives of proposed direct patient engagement activities
- To scope the optimal type of engagement activity for the project

## **HTA Needs Assessment Background**

The needs assessment includes the following:

- Description of the health condition and its prevalence in the Ontario population
- Description of the health technology and the prevalence of its use in Ontario
- Description of the population(s) impacted by the health condition and health technology (e.g., types of patients, caregivers, and members of the public)

**Table A2: Criteria for Assessing the Need for Direct Patient Engagement**

	Low Need	Moderate Need	High Need
Impact of illness or disability (on patient, caregiver, and family)	Low burden of illness or disability with minimal impact on daily activities and quality of life	Moderate burden of illness or disability with some impact on daily activities and quality of life	High burden of illness or disability with significant impact on daily activities and quality of life
Nature of technology	Monitoring or screening technology  Noninvasive technology  Convenient to receive treatment with technology  Temporary impact: technology will be used for a limited amount of time by the patient population	Diagnostic technology, including personalized medicine test  Moderately convenient/inconvenient to receive treatment with technology	Treatment technology  Highly invasive technology  Inconvenient to receive treatment with technology  Permanent impact: technology will be used permanently by the patient population
Degree of public controversy (in media, politically, clinically, publicly)	Low degree of public controversy	Some degree of public controversy	High degree of public controversy
Equity	Few equity issues  Condition impacts the population equally  Easy access to technology	Some equity issues  Moderate access to technology	Many equity issues  Condition impacts a specific patient population  Difficult to access technology
Gaps in clinical or economic research that can be supplemented by lived experience	Few gaps	Some gaps	Many gaps

**Direct Patient Engagement Criteria**

***Impact of the Health Condition***

What is the perceived impact of the health condition on people with the condition and/or their caregivers?

***Nature of the Health Technology***

Does the health technology monitor, diagnose, or treat a particular health condition? Is it temporary or permanent?

### ***Degree of Public Controversy***

How politically sensitive is the health technology or health condition? For example, has this HTA project been requested by the Ontario Ministry of Health? Do advocacy organizations have an established position on the health technology? Is there media exposure related to the technology and/or health condition?

### ***Equity***

Does the health condition impact a particular patient population, or is the condition common across the general population of Ontario? Are there any equity issues associated with access to existing health technologies? Are there any perceived or potential equity issues associated with accessing the health technology? With regard to accessing the health technology, are there particular patient populations at risk, marginalized, or hard-to-reach?

### ***Gaps in Clinical or Economic Research***

Are there any gaps in the clinical or economic literature that could be supplemented by engaging directly with people with the health condition and/or who have undergone treatment with the health technology being reviewed?

### ***Goals for Engagement***

What are the goals for patient and public engagement for the HTA?

- To elicit lived-experience values that will help contextualize the HTA findings:
  - Understand the impact of lived experience on patient quality of life
  - Understand the caregiver experience
  - Understand the impact of the side effects of the health technology
  - Understand the perceived effectiveness of existing health technologies and/or the health technology
- To address information gaps in the literature:
  - Understand the impact of the use of the health technology and its relevant comparator(s) on the lived experience of patients
  - Understand the impact of the health outcomes associated with the use of the health technology and its relevant comparator(s) on the lived experience of patients
  - Understand the impact of the costs associated with existing health technologies and/or the health technology under review on the lived experience of patients

### ***Parameters and Constraints Involved in Considering Direct Patient Engagement Activities***

- What are the timelines for the HTA? When will it be presented to OHTAC or OGAC?
- Are there any facilitators or barriers to connecting with people with the health condition and/or with experience of the health technology? Does the health condition or health technology impact specific subpopulations, including any marginalized populations?

- Is there an existing body of qualitative or quantitative literature that has already examined patient preferences and values, the quality of life of those with the health condition, or the impact of the health technology?

**Summary of the Needs Assessment**

Responses to the above questions and key assessment questions are evaluated to assess whether direct patient engagement is appropriate for and would add value to the HTA.

**Approach and Activities**

If direct patient engagement is considered appropriate for and necessary to add value to the HTA, the nature of the responses to the needs assessment inform the engagement strategy. More than one engagement approach or activity may be appropriate.

**Table A3: Engagement Approach and Methodologies for Evidence-based Analysis**

Engagement approach	Engagement methodologies
Gather information/listen	Survey, storytelling, presentation, qualitative research
Discuss/involve	Interview, focus group

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