

Health Quality Ontario

Let's make our health system healthier

Health Technology Assessments

Methods and Process Guide

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About This Guide

This guide describes the methods and processes involved in conducting health technology assessments at Health Quality Ontario and the subsequent development of evidence-based funding recommendations by Health Quality Ontario, under the guidance of 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 hta@hqontario.ca.

ABOUT HEALTH QUALITY ONTARIO

Health Quality Ontario is the provincial advisor on the quality of health care. We are motivated by a single-minded purpose: **Better health for all Ontarians.**

Who We Are

We are a scientifically rigorous group with diverse areas of expertise. We strive for complete objectivity, and look at things from a vantage point that allows us to see the forest and the trees. We work in partnership with health care providers and organizations across the system, and engage with patients themselves, to help initiate substantial and sustainable change to the province's complex health system.

What We Do

We define the meaning of quality as it pertains to health care, and provide strategic advice so all the parts of the system can improve. We also analyze virtually all aspects of Ontario's health care. This includes looking at the overall health of Ontarians, how well different areas of the system are working together, and most importantly, patient experience. We then produce comprehensive, objective reports based on data, facts, and the voices of patients, caregivers, and those who work each day in the health system. As well, we make recommendations on how to improve care using the best evidence. Finally, we support large-scale quality improvements—by working with our partners to facilitate ways for health care providers to learn from each other and share innovative approaches.

Why It Matters

We recognize that, as a system, there is much to be proud of, but also that it often falls short of being the best it can be. Plus, certain vulnerable segments of the population are not receiving acceptable levels of attention. Our intent at Health Quality Ontario is to continuously improve the quality of health care in this province regardless of who you are or where you live. We are driven by the desire to make the system better, and by the inarguable fact that better has no limit.

Table of Contents

1	INTRODUCTION	5
1.1	Health Quality Ontario	5
1.2	Health Technology Assessment Program	5
1.3	Which Health Technologies Are Evaluated by Health Quality Ontario?	5
1.4	How Are Topics Identified?	5
1.5	How Are Topics Prioritized?	5
2	PHASES OF A HEALTH TECHNOLOGY ASSESSMENT: CONTENT DEVELOPMENT	7
2.1	Phase 1: Defining the Scope	7
2.1.1	<i>Ontario Context</i>	7
2.1.2	<i>Health Condition and Population</i>	7
2.1.3	<i>Health Technology</i>	8
2.1.4	<i>Comparator(s)</i>	8
2.1.5	<i>Health Outcomes</i>	8
2.1.6	<i>Timing and Setting</i>	8
2.1.7	<i>Health Equity Considerations</i>	8
2.1.8	<i>Ethical, Legal, and Social Issues Considerations</i>	9
2.1.9	<i>Patient Preferences and Values</i>	9
2.1.10	<i>Health Technology Assessment Questions</i>	9
2.2	Phase 2: Evaluating the Evidence	10
2.2.1	<i>Clinical Evidence</i>	10
2.2.2	<i>Economic Evidence</i>	16
2.2.3	<i>Evaluating Patient Preferences and Values</i>	34
2.3	Phase 3: Making a Recommendation	36
2.3.1	<i>Health Quality Ontario Decision Determinants Framework</i>	36
2.3.2	<i>Overall Clinical Benefit</i>	37
2.3.3	<i>Consistency With Expected Societal and Ethical Values</i>	37
2.3.4	<i>Value for Money</i>	38
2.3.5	<i>Feasibility of Adoption Into the Health System</i>	38
2.3.6	<i>Health Quality Ontario Recommendation</i>	38
3	KEY ELEMENTS OF THE HEALTH TECHNOLOGY ASSESSMENT PROCESS	40
3.1	Health Technology Assessment Process Overview	40
3.2	Timelines	40
3.3	Roles and Responsibilities	41
3.4	Health Technology Assessment Process	41
3.4.1	<i>Process Flowchart: All Phases</i>	41

3.5	Process Detail: Topic Identification and Prioritization Phase.....	43
3.5.1	<i>Application Pre-assessment</i>	43
3.5.2	<i>Vignette Development</i>	43
3.5.3	<i>Final Prioritization</i>	43
3.6	Process Detail: Scope Development Phase	44
3.6.1	<i>Expert Consultation</i>	44
3.6.2	<i>Clinical and Patient Engagement Review Plan Development</i>	44
3.7	Process Detail: Literature Search Phase	44
3.8	Process Detail: Evidence Development and Draft Report Preparation Phase	45
3.8.1	<i>Review of Clinical Evidence, Screening, and Analysis</i>	45
3.8.2	<i>Present HTA Findings and Draft Recommendation Options for Consideration to Advisory Committees</i>	46
3.9	Process Detail: Editing and Ministry Notification Phase	46
3.9.1	<i>Editing</i>	46
3.9.2	<i>Ministry Notification</i>	46
3.10	Process Detail: Open-for-Feedback Phase	46
3.10.1	<i>Open-for-Feedback Posting</i>	47
3.10.2	<i>Notifying Stakeholders</i>	47
3.10.3	<i>Summarizing and Addressing Public Comments</i>	47
3.11	Process Detail: Health Quality Ontario Board of Directors Approval and Final Web-Posting Phase 47	
3.11.1	<i>Briefing Note</i>	47
3.11.2	<i>Letter to the Minister of Health and Long-Term Care</i>	48
3.11.3	<i>Final Posting to Health Quality Ontario Website</i>	48
	APPENDICES	49
	Appendix 1: Health Quality Ontario Health Technology Assessment Topic Prioritization Guide ^a	49
	Appendix 2: Risk-of-Bias Assessment Tools	50
	Appendix 3: Modified Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Checklist.....	51
	Appendix 4: Health Quality Ontario Budget Impact Analysis Reporting Checklist	53
	Appendix 5: Health Quality Ontario HTA Direct Patient Engagement Needs Assessment.....	54
	ABBREVIATIONS	58
	GLOSSARY	59
	REFERENCES	61

1 INTRODUCTION

1.1 Health Quality Ontario

Health Quality Ontario is the province's advisor on health care quality. The mandate of Health Quality Ontario is guided by the 2010 *Excellent Care for All Act*. A key part of this mandate is “to mak[e] recommendations, based on evidence, concerning the Government of Ontario's provision of funding for health care services and medical devices.”¹ We fulfill this mandate through our health technology assessment (HTA) program.

1.2 Health Technology Assessment Program

Health Quality Ontario's HTA program develops HTA reports that analyze available evidence on clinical benefit, value for money, and patient preferences and values. HTA reports are prepared by a team of medical librarians; clinical epidemiologists; health economists; patient, caregiver, and public engagement program analysts; and medical editors, in consultation with health service researchers, patients, families, caregivers, clinical experts, and industry representatives.

1.3 Which Health Technologies Are Evaluated by Health Quality Ontario?

The focus of Health Quality Ontario's HTA program is medical devices and health care services. This includes, but is not limited to, medical devices, medical tests (including genetic tests), surgical procedures, health care programs, and complex health system interventions, including models of health care delivery.

1.4 How Are Topics Identified?

Any person or organization may submit an HTA topic request online through Health Quality Ontario's [open application process](#). Medical devices are often licensed by Health Canada before they are evaluated through an HTA.

1.5 How Are Topics Prioritized?

To help determine which topics are reviewed first, topics are prioritized using 10 explicit criteria ([Appendix 1](#)) that reflect the general domains of proposed clinical benefit and harm, burden of illness, and need, as well as equity and economic considerations.

We collect information based on these criteria for each HTA topic considered for prioritization. Each criterion is given a rating, which is reviewed by a small working group composed of Health Quality Ontario staff, members of the Ontario Health Technology Advisory Committee (OHTAC; a committee of the Health Quality Ontario board of directors), and representatives of the Ministry of Health and Long-Term Care. We rank topics in order of priority to create a draft list, which is then reviewed and finalized by OHTAC. Prioritization occurs at least twice a year, subject to the number of applications received. In each round of prioritization, OHTAC considers both new topics and deferred topics from previous rounds of prioritization.

Health Quality Ontario, under the advisement of the Ontario Genetics Advisory Committee (OGAC; a subcommittee of OHTAC), is currently developing a framework for the prioritization of genetic topics.

2 PHASES OF A HEALTH TECHNOLOGY ASSESSMENT: CONTENT DEVELOPMENT

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

2.1 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 questions to be addressed. A defined scope provides a focused framework for assessing the relevant areas of evidence, including clinical, economic, and patient preferences and values.

The scope is 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”²). We also consult with various external individuals, including patients, clinical experts, provincial government partners, health system partners, and industry representatives. We explore relevant information about the population, intervention, comparator(s), outcome, timing, and setting of the intervention (collectively referred to as the PICO[TS] criteria) to help inform the research questions:

- **Population** (the people affected by the health technology)
- **Intervention** (the health technology)
- **Comparator** (alternative[s] to the health technology available in Ontario)
- **Outcome** (patient-important outcomes)
- **Time** (time frame, if relevant)
- **Setting** (health care setting, if relevant)

The key components of HTA scope development are described below.

2.1.1 Ontario Context

The HTA process at Health Quality Ontario is contextualized for Ontario and involves the input of clinical experts, patients, and other stakeholders. Contextualization includes understanding how the health technology is currently being used or might be used in Ontario and how the health condition it treats is currently managed. This involves looking at what comparators are available for the health technology, what barriers or facilitators to using the health technology exist, as well as any equity issues (e.g., geographical barriers to receiving treatment) that impact on its use. The scope of the HTA is developed from the perspective of 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.

2.1.2 Health Condition and Population

We try to establish the incidence and/or prevalence of the health condition in Ontario, and we specify the population affected by the health condition; this may include such factors as the

phase or stage of the health condition (e.g., acute, chronic, palliative), genotype, and sociodemographic factors such as sex, gender, and age range. We also try to estimate the proportion of the affected population who would be eligible to use the health technology.

2.1.3 Health Technology

The description of the health technology (sometimes referred to as the intervention) 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 a medical device or a medical test available in a kit format, we contact Health Canada to determine if it is licensed by Health Canada and, if it is, to obtain the current approved indication(s) for use and a list of all licensed device manufacturers in Canada.

2.1.4 Comparator(s)

A comparator is another health technology used to treat the health condition. In an HTA, the health technology being reviewed is compared with its comparator(s). The typical comparator used for an HTA is standard care, which is 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 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 identify a reference standard for the test (an agreed-upon test for classifying patients with and without the health condition) as the primary comparator, as well as any other relevant comparator tests available in Canada.

2.1.5 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 whether the health technology improves these outcomes to a greater extent than do the comparator(s).

2.1.6 Timing and Setting

The scope of an HTA may include a specific timing 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).

2.1.7 Health Equity Considerations

The scope of an HTA may be further defined by issues of health equity. Health Quality Ontario has arrived at a working definition of health equity based on feedback received from people working in the health system and people who have experienced barriers to receiving high-quality care: “Health equity allows people to reach their full health potential and receive high-quality care that is fair and appropriate to them and their needs, no matter where they live, what

they have, or who they are.”³ (To learn more about Health Quality Ontario’s approach to health equity, please visit our [website](#).)

Health inequities are differences in health status or health distribution among populations that are avoidable, unjust, and unfair.⁴ These inequities may result in differences in disease status, health outcomes, and access to care across different population groups.⁵ Health inequities may be linked to factors such as socioeconomic status, sex, gender, place of residence, and occupation, among others.⁵

By using the **PROGRESS-Plus** framework⁵ in the design and execution of an HTA, we consider whether health equity may be relevant to the research questions. This framework provides guidance on factors that may lead to health inequities:

- **Place of residence**
- **Race, ethnicity, culture, and language**
- **Occupation**
- **Gender and sex**
- **Religion**
- **Education**
- **Socioeconomic status**
- **Social capital**
- **Plus** other considerations such as age, disability, and sexual orientation

In the HTA analysis, the population of interest may be defined or categorized (subgrouped) by sociodemographic groups (according to the PROGRESS-Plus framework) that may be adversely affected by health inequities.

2.1.8 Ethical, Legal, and Social Issues Considerations

When defining the scope of an HTA, we consider any ethical, legal, or social issues associated with the use or adoption of the health technology, as well as any policies or legislation that may influence the context for the technology’s implementation in Ontario.

2.1.9 Patient Preferences and Values

The scope of the HTA includes a consideration of the preferences and values of the patients, families, and caregivers affected by the health condition and health technology. We develop a needs assessment and patient engagement plan to obtain information about these issues.

2.1.10 Health Technology Assessment Questions

After defining the scope, we establish clearly defined clinical, economic, and patient preferences and values research questions, relevant to the Ontario context, for evidence development and appraisal.

2.2 Phase 2: Evaluating the Evidence

There are three key evidence components to an HTA:

1. **Clinical:** assesses the available evidence on the clinical benefits and harms of the health technology
2. **Economic:** evaluates value for money and affordability
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

In the clinical evidence review, we identify the possible clinical benefits and harms associated with using the health technology. The clinical evidence review systematically identifies, synthesizes, and analyzes relevant clinical evidence to provide an assessment of the clinical benefits and harms associated with the health technology. Patient-important outcomes (e.g., quality of life, reduced mortality) are of primary importance to evaluating the benefits and harms of the technology.

For the economic assessment, we first conduct a systematic literature review to summarize the evidence from all relevant economic studies that have been published on the health technology. When appropriate, we then conduct a primary economic evaluation to determine the cost-effectiveness (value for money) of the health technology compared with its alternatives. Finally, we estimate the potential budget impact (affordability) of publicly funding the health technology in Ontario.

We conduct a needs assessment to assess the value of obtaining information about the preferences and values of people with lived experience of the health condition and health technology through direct patient engagement activities. This needs assessment considers the existing evidence on patient preferences and values with regard to the health condition and health technology and what new information we might be able to obtain through direct patient engagement activities. Topics for which direct patient engagement will provide additional information about lived experience and patient preferences and values are prioritized for direct patient engagement activities.

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

2.2.1 Clinical Evidence

The objective of the clinical evidence review is to synthesize the relevant scientific evidence on the clinical benefits and harms of the health technology.

Our clinical evidence review is based on systematic review methodology, 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 by the research questions and the existing body of literature on the technology. We review existing

systematic reviews and HTA reports during the scoping phase to determine the nature of the existing evidence. When we identify recently conducted, rigorous systematic reviews that meet our selection criteria, we may consider conducting an overview of systematic reviews or an update to or adaptation of an existing review.

To avoid duplication of efforts, we contact Canadian HTA agencies to determine if an equivalent review of the health technology has been or is currently being performed elsewhere. We also determine whether any recent HTAs of the health technology have been completed by national or international HTA agencies that would meet our needs, specifically in terms of our research questions and PICO(TS) criteria.

2.2.1.1 Clinical Review Plan

The clinical evidence review begins with the development of a clinical review plan, which is a written record of the rationale and plan for the review. The clinical review plan also 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, for medical devices and genetic tests where applicable, the Health Canada–approved indication(s). Additional components of the clinical review plan include 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 anticipated data synthesis and analytical approaches, and the methods we will use to assess risk of bias in studies and the quality of the body of evidence.

We engage clinical content experts to consult on the clinical review plan and ensure the review is relevant to the Ontario context. Clinical content experts review the draft clinical review plan and provide feedback on the PICO(TS) criteria and scope of the review. The health economists; medical librarians; and patient, caregiver, and public engagement program analysts 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 systematic review progresses. We document any amendments to the systematic review process in the clinical review plan.

2.2.1.2 Research Questions

Research questions are critical in defining and focusing the purpose of the clinical evidence review and provide the basis for our literature search, data abstraction, and analytical approaches. A clinical evidence review typically addresses one well-defined research question but may comprise multiple related research questions.

Research questions evaluating a health technology are defined explicitly and include the population, intervention, and comparator(s) of interest. Where relevant, research questions also address whether a specific setting or time frame is of interest.

Research questions state the purpose of the health technology; this may include the treatment, prevention, screening, diagnosis, or prognosis of the health condition.

Research questions also highlight the key outcomes being evaluated; for example, effectiveness, harms, diagnostic accuracy, or prognostic or predictive capability.

Research questions for specific categories of health technology have certain characteristics. For example, research questions regarding diagnostic or screening test accuracy will include a definition of the index test(s) (i.e., the test[s] being evaluated) and the reference standard (an agreed-upon test for classifying patients with and without the health condition), whereas research questions regarding prognostic tests will state the specific prognostic factors under review.

2.2.1.3 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.⁶

A systematic review may not have a primary focus on health equity issues but may still address potential health inequities related to the effect of the intervention on the health condition under evaluation.

In the HTA report, we may report on the effects of the intervention across different population subgroups (based on the PROGRESS-Plus framework categories⁵) if such information is provided in the studies identified.

2.2.1.4 Literature Search Strategy and Methods

Typically, the population and intervention formulate the basis of the literature search strategy. We use relevant published studies on the HTA topic to analyze controlled vocabulary (e.g., the Medical Subject Headings [MeSH] terms assigned to studies in the MEDLINE database) and identify keywords and “natural language” terms to use in the search strategy.

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, the following databases are searched in the Ovid database platform interface:

- Cochrane CENTRAL (not searched if conducting a review of systematic reviews)
- Cochrane Database of Systematic Reviews
- Embase
- HTA Database
- MEDLINE
- National Health Service Economic Evaluation Database (NHS EED)

Additional databases, such as the Cumulative Index to Nursing and Allied Health Literature (CINAHL) and Ovid PsycINFO, are searched if appropriate to the topic.

We may use search filters to target specific study designs and/or date limits, depending on the project's inclusion and exclusion criteria or the existing body of literature. We always use an English-language limit. We also perform a targeted grey literature search of HTA agency websites and clinical trial or systematic review registries, following a standard list of sites to check that we have developed internally.

The final search strategy is peer-reviewed using the Peer Review of Electronic Search Strategies (PRESS) Checklist before final execution.⁷ We create database auto-alerts to alert the team of any new literature published during the course of HTA development.

We download search results to a reference management software database (EndNote).⁸ We then scan published study titles and remove duplicates. The full search strategies used for all databases and grey literature sources are included as an appendix to the HTA report and captured diagrammatically within the HTA report in a Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram.⁹

2.2.1.5 Study Selection Criteria

We specify the criteria by which studies will be included or excluded from the clinical evidence review for each research question. Selection criteria may include factors such as relevant PICO(TS) criteria, study design (e.g., randomized controlled trial, cohort study), sample size, year of publication, and minimum follow-up period. English language and full-text publication are standard inclusion criteria for Health Quality Ontario evidence reviews. The study designs included in the clinical evidence review are those appropriate to the research questions.

2.2.1.6 Study Screening

We assess all studies identified through the literature search according to the selection criteria to determine their eligibility for inclusion. A single reviewer independently reviews the titles and abstracts, and, for those studies appearing to meet the specified 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 for any additional relevant studies not identified through the search. We use the DistillerSR systematic review software to manage study screening.¹⁰

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 within the HTA report in a PRISMA flow diagram.⁹

2.2.1.7 Data Extraction

A single reviewer extracts data 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 and summarized in both narrative and tabular format in the HTA report.

We contact study authors as necessary to obtain relevant data not reported in the publication or for clarification regarding the published analysis. All correspondence with study authors is documented in the HTA report.

2.2.1.8 Risk-of-Bias Assessment

Risk of bias and *threat to internal study validity* refer to the extent to which the design and conduct of a study are likely to have introduced bias into the study results.¹¹ Studies with significant risk of bias have been shown to overestimate or underestimate treatment effects.^{12,13}

The risk of bias of each eligible study is assessed by a single reviewer to determine the potential differences in the 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. Based on a review of prior systematic reviews^{14,15} and an internal Health Quality Ontario assessment of individual risk-of-bias assessment tools, we use the tools presented in [Appendix 2](#), which were selected based on study type, methodological comprehensiveness, and pragmatic considerations. We review and update these risk-of-bias assessment tools as the area of assessing risk of bias continues to evolve.

2.2.1.9 Data Synthesis

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

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. We provide a narrative synthesis of results when meta-analysis is inappropriate owing

to clinical or methodological heterogeneity. Narrative synthesis involves describing study findings and may also be used to supplement results from meta-analysis.

2.2.1.10 Meta-analysis

Meta-analysis refers to the statistical method used to combine quantitative results for an individual outcome 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 perform a meta-analysis to better estimate the effect of an intervention using information from individual studies. We follow the general methodological principles outlined in the *Cochrane Handbook for Systematic Reviews*¹⁶ when performing meta-analyses of patient-important and clinical outcomes for health technologies. We use standard statistical software (e.g., R,¹⁷ Review Manager,¹⁸ Stata¹⁹) to perform meta-analyses.

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 Diagnostic Test Accuracy Reviews*.²⁰

2.2.1.11 Quality of Evidence Assessment

A single reviewer assesses the quality of the body of evidence (i.e., the studies included in the clinical evidence review) for each outcome of interest according to the *Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Handbook*.²¹

The *GRADE Handbook* criteria provide a transparent, structured process for rating the quality of a body of evidence. The general approach begins by considering the study design (randomized controlled trials starting with a rating of high quality, and observational studies starting with a rating of low quality), followed by assessing five factors that may reduce (rate down) the quality of evidence:

- Risk of bias (internal validity)
- 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 analysis, 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 in, or how certain we are, in the effect estimate (the result) of the meta-analysis of a certain outcome.

Specific modifications to the GRADE approach are applied to diagnostic accuracy reviews,²²⁻²⁴ prognostic reviews,²⁵ and network meta-analyses.²⁶

2.2.1.12 Contextualizing the Evidence

Expert consultation provides context to the clinical evidence review process. Relevant experts may include the HTA applicant, patients, clinicians, researchers, OHTAC or OGAC members, industry representatives, or other people with expertise in the health condition or health technology. We aim to contact experts from a variety of health care settings across Ontario to account for potential variations in populations and practice patterns.

In addition to providing feedback during the scope development and clinical evidence review phases, experts may help contextualize the results of the clinical evidence review for Ontario.

2.2.2 Economic Evidence

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

1. An economic evidence review to summarize the evidence from the available economic literature on the health technology
2. A primary economic evaluation to estimate the cost-effectiveness (value for money) of the health technology
3. A budget impact analysis to assess the affordability of the health technology

2.2.2.1 Economic Project Plan

At the beginning of the economic assessment, we develop 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 engage economic and clinical experts, as well as the Ministry of Health and Long-Term Care, in the development and review of the economic project plan to ensure the plan is relevant to the Ontario context.

We continually update the economic project plan throughout the economic assessment to reflect revisions in methodology over the course of the developing HTA.

2.2.2.2 Economic Evidence Review

2.2.2.2.1 Objective and Research Question

The objective of the economic evidence review is to summarize and critically appraise the available economic literature relevant to the health technology. We align our research question with the clinical evidence review, ensuring to specify, at minimum, the population, intervention, and comparator of interest. This process ensures harmonization across the HTA.

2.2.2.2.2 Literature Search Strategy and Methods

We conduct a systematic search of published evidence on the cost-effectiveness of the health technology using an economic filter applied to the clinical literature search strategy. See [section 2.2.1.4](#) for more details on methods used.

2.2.2.2.3 Study Selection Criteria

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.

2.2.2.2.4 Study Screening

We screen the literature and report the results of the literature review process within the HTA report through a PRIMSA flow diagram.²⁷ Within the flow diagram, we provide reasons for study exclusion at the full-text review stage.

2.2.2.2.5 Data Extraction

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.

2.2.2.2.6 Study Applicability and Quality-of-Evidence Assessment

We determine the applicability of each identified study to the Ontario context by applying a modified applicability checklist for economic evaluations originally developed by the National Institute for Health and Care Excellence in the United Kingdom ([Table 1](#)).²⁸ The checklist considers the applicability of the literature to the current decision problem through the examination of several factors, including the target population, interventions, comparators, context, clinical inputs, and cost inputs. We also consider date of publication when assessing applicability, and we evaluate new clinical evidence that becomes available during the economic evidence review process.

Table 1: Study Applicability Appraisal Checklist

Question	Possible Responses
Is the study population similar to the question?	Yes/Partially/No/Unclear/NA
Are the interventions similar to the question?	Yes/Partially/No/Unclear/NA
Is the health system in which the study was conducted similar to the current Ontario context?	Yes/Partially/No/Unclear/NA
Was/were the perspective(s) clearly stated, and what were they?	Yes/Partially/No/Unclear/NA
Are estimates of treatment effect from the best available source?	Yes/Partially/No/Unclear/NA
Are all future costs and outcomes discounted?	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

Source: Adapted from the National Institute for Health and Care Excellence.²⁸

When studies conducted outside Ontario are identified, we assess their generalizability to the Ministry of Health and Long-Term Care context. *Generalizability* refers to “the problem of whether one can apply or extrapolate results obtained in one setting or population to another.”²⁹ We consider several factors when determining generalizability, including the following³⁰:

- Population demography
- Disease epidemiology
- The availability of health care resources
- Variations in clinical practice
- Incentives to health care professionals and institutions
- Relative costs
- Health state preferences

We next critically assess the quality of studies deemed applicable to the research question. This process typically includes assessing the following:

- The structure and assumptions of the models used in the studies
- The clinical evidence used
- The costs and consequences included
- The methods used to account for uncertainty

Generally, we classify studies based on their degree of limitation (i.e., minor, potentially serious, or very serious limitations).

2.2.2.2.7 Summary and Contextualization of Existing Economic Evidence

We summarize the results, strengths, and limitations of the existing economic literature with regard to the Ontario context and the scope of the HTA. Based on the results of the clinical and

economic evidence reviews, we determine if there is a need to develop a primary economic evaluation. A primary economic evaluation may be omitted in one of two cases:

- When there is limited clinical evidence or the evidence doesn't support similar or differential health outcomes between the health technology and its comparator(s)
- When the economic evidence review identifies a recent study without major limitations that is specific to the context of Ontario or Canada and is judged to be highly applicable to the HTA

When we assess a study to be highly applicable, its conclusions provide information about the potential cost-effectiveness of the health technology compared with its alternative(s). In certain circumstances, studies done in other contexts may be applicable to the HTA. In these cases, we may request or rebuild the model, adapting it to the Ontario context and conducting updated analyses.

2.2.2.3 Primary Economic Evaluation

2.2.2.3.1 *Objective and Research Question*

The objective of the primary economic evaluation is to assess the cost-effectiveness (costs and health outcomes) of the health technology in Ontario given a specific patient population, comparator(s), and perspective. We develop a specific research question that aligns with our objective to guide the data inputs and methodologies used in our analysis.

2.2.2.3.2 *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 of 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). Where utility data are available, we prefer to use cost-utility analyses, since they allow results to be compared across diverse disease areas.

2.2.2.3.3 *Modelling Considerations*

Decision analytic models are commonly used in health care research to represent a series of possible consequences that may flow from a set of alternative options being evaluated.³¹ Our modelling methods are based on the Canadian Agency for Drugs and Technologies in Health (CADTH) guidelines for the economic evaluation of health technologies,³² the Agency's guidance document for the costing of health care resources,³³ and reports by the International Society for Pharmacoeconomics and Outcomes Research–Society for Medical Decision Making (ISPOR-SMDM) Modelling Good Research Practices Task Force.³⁴⁻³⁸ Our reporting methods follow the Consolidated Health Economic Evaluation Reporting Standards Statement ([Appendix 3](#)).³⁹

2.2.2.3.3.1 Target Population

Our target population 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. Depending on the available data, this includes both the reference case (most likely) characteristics and the variability of characteristics within the population. We typically define cohorts by some or all of the following criteria:

- Demographic features (e.g., age, sex, socioeconomic status)
- Specific condition
- Disease severity
- Comorbidities
- Risk factors

Cohorts may further be defined by some or all of the following factors:

- Environmental setting (e.g., community, hospital)
- Geographic location
- Adherence rates
- Treatment patterns
- The expected application of the health technology (e.g., replacement for current therapy, adjunct to current therapy, use in nonresponders, use in those contraindicated to current therapy)

Throughout our analyses, we may stratify the target population into smaller, more homogeneous subgroups to reflect variations in clinical effectiveness, natural histories, and/or treatment pathways.

2.2.2.3.3.2 Study Perspective

We primarily adopt the perspective of the publicly funded health system (i.e., the Ontario Ministry of Health and Long-Term Care). The perspective chosen informs the viewpoint from which we capture costs and health benefits. Other perspectives may also be undertaken; for example, that of an institution (e.g., hospital). We may also undertake a secondary societal perspective 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, savings in out-of-pocket costs).

2.2.2.3.3.3 Model Structure

We determine the appropriate model type and structure based on the stated objectives, 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. Two common model types are decision tree and state-transition (e.g., Markov model, microsimulation). The software programs we use to build models and run analyses include TreeAge Pro,⁴⁰ Excel,⁴¹ and R.¹⁷

2.2.2.3.3.4 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 are considered potential comparators. In principle, the comparator is standard of care, which is the current treatment used in Ontario for the health condition. We often solicit opinions from clinical experts to understand all likely alternatives. Where relevant, we also anticipate the entry of future comparators into the market.

2.2.2.3.3.5 Time Horizon

We select the model's time horizon (time period), over which we will 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. 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) or 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). 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., in the case of nondisplaced fractures). We may also explore the impact of different time horizons on the results in scenario analyses. The time horizon may differ from the duration of treatment (since treatment may have a long-term impact on disease outcome).

2.2.2.3.3.6 Cycle Length

In a state-transition (Markov) model (which describes a clinical situation in terms of different states, such as "well" or "sick," and how individuals move between such states), cycle length is the minimum interval over which the pathology, symptoms, or resource use associated with a health condition are expected to change.³² We choose cycle length based on the natural history of the health condition and its treatment trajectory. We typically use a half-cycle correction, a modeling adjustment strategy to simulate real-world accumulation of costs and health outcomes, on all transitions in state-transition models.

2.2.2.3.3.7 Discount Rate

Various costs and health outcomes may occur at different points in time. To account for this, we typically discount costs and health outcomes 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).³² We use an annual discount rate of 1.5% as per the most recent CADTH guidelines for

economic evaluations.⁴² In our sensitivity analyses, we also assess different discount rates (e.g., 0%, 3%).

2.2.2.3.3.8 Assumptions

It is impossible to capture all the complexities and variation 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 Ministry of Health and Long-Term Care, or other health system partners where relevant. Assumptions are a vital source of information required to understand the model structure and dynamics. We include a description of and justification for all assumptions used to build and run the 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 [section 2.2.2.3.6](#)).

2.2.2.3.4 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., from 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. Calibration methods (used to estimate unknown model parameters by matching model outputs with other sources of data) may be used to estimate or adjust input values.³⁴ To ensure transparency, we provide the sources of our data along with our methods for identifying data.

2.2.2.3.4.1 Clinical Inputs

2.2.2.3.4.1.1 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 use inputs to model the natural history that represent the Canadian context.

2.2.2.3.4.1.2 Clinical Effectiveness

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

We want our economic evaluations to be generalizable to the real world. Ideally, our analyses are based on real-world performance (effectiveness) data. However, high-quality sources that offer a measure of effectiveness are often unavailable. Therefore, we typically use data obtained from randomized controlled trials (efficacy). When identifying inputs, we

simultaneously consider the quality (lack of bias), comprehensiveness, and relevance of the literature.

We typically obtain treatment effects from the clinical evidence review section of the HTA. The clinical evidence review captures the quality of the evidence according to the *GRADE Handbook* criteria.²¹ 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 possible, the clinical evidence review includes a systematic review and meta-analysis of the literature. When available, meta-analyses of high-quality studies directly comparing the health technology with its relevant comparator(s) are typically preferred for reference-case estimates.⁴³ A single study may be used in cases where there is sparse clinical literature, where only a single 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. To assess the relevance of data published in the literature, we consider how similar the situation we are evaluating is to those in which the clinical studies were conducted (e.g., by considering such factors as similarity to real-world settings and consistency with model structure, model inputs, and target population).³⁰

Acquired treatment effect estimates may be based on short-term data obtained from comparative studies. If our time horizon extends beyond those used in the studies reviewed, we may extrapolate to estimate longer-term outcomes. The extrapolation methods used depend on the data available and the plausibility that the intervention's relative effectiveness will be maintained over a longer period of time.

Proxy measures or intermediate endpoints may also be used, but only when there is an established link with patient-important outcomes.³⁰ 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.

2.2.2.3.4.1.3 *Clinical Harms*

Our assessment takes into consideration complexities specific to the effectiveness of the health technology and its comparator(s), such as surgical expertise and adverse events.³² We try to capture episodes of care rather than solely the health technology's performance on key clinical outcomes. We do so by modifying the model structure to include potential clinical harms such as imperfect procedures and adverse events.

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 for this.

2.2.2.3.4.2 Cost Inputs

Costing depends on the perspective used in the model. We perform costing according to standard guidelines for economic evaluation and costing of health care resources.^{33,44} We systematically identify, measure, and value all costs relevant to the Ministry of Health and Long-Term Care. Only costs that are identical (both unit cost and resource quantities) between the intervention and comparator may be excluded, as, in effect, they will cancel each other out. Examples of typical costs included in the model include those associated with the following:

- Use of the health technology
- Prescription drugs covered under provincially funded plans
- Physician and/or health care staff services
- Diagnostic and/or laboratory tests
- Medical procedures
- Hospitalization
- Outpatient clinic visits
- Rehabilitation
- Home care
- Long-term care
- Assistive devices

We include both capital and overhead costs in our analysis.

Several approaches for costing may be used depending on the treatment pathway of interest 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., a Canadian Institute for Health Information database, the Discharge Abstract Database, an IntelliHealth Ontario database, the National Ambulatory Care Reporting System, the Ontario Health Insurance Plan claims database), or the broader literature. Unit costs may also be derived from public websites, administrative databases, published literature, the device manufacturer, or clinical experts.

The length of time over which costs are monitored varies depending on the time horizon of the analysis. Often, we track costs for the lifetime of the intervention (including the device or health service maintenance and downstream treatment costs), although the value of future costs in such cases will be lessened because of discounting to present values.

2.2.2.3.4.2.1 *Currency, Price Date, and Conversion*

Because prices change over time, it is necessary to report dates with prices. When prices of health care goods or services are unavailable for the current year, we inflate them using the

health care component of the Statistics Canada Consumer Price Index.⁴⁵ 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. We then convert the foreign currency to Canadian dollars (e.g., through purchasing power parities).

2.2.2.3.4.3 Valuing Health Outcomes

Health outcomes are the measures of benefit in the economic evaluation and may be expressed in natural units (e.g., myocardial infarctions avoided, life years gained) or quality-of-life measures (e.g., quality-adjusted life-years).³⁰ Generally, we use quality-of-life measures; however, natural units may be used when there are certain data limitations (e.g., when no utility values are available).

Our economic evaluations typically use the quality-adjusted life-year (QALY), which is a comprehensive measure of health that considers both length of life and health-related quality of life, and which can be applied across different patient populations and disease areas. QALY weights (utilities) for health states are typically measured on an interval scale with death set at 0 and perfect health set at 1.³⁰ QALYs are calculated by multiplying the utility weight by the time spent in the health state being evaluated. The weights for a given health state are best elicited through preference-based measures (e.g., standard gamble, time-trade-off). We commonly use multi-attribute health status classification scales, which are preference based. These may be disease-specific or generic tools.³⁰ Disease-specific quality-of-life measures focus on the quality-of-life dimensions most pertinent to a particular disease, health condition, or patient population. Generic measures of quality of life, such as the EuroQol–Five Dimensions (EQ-5D) and the 36-Item Short Form Survey (SF-36), capture outcomes in broad areas, including physical functioning, self-care, psychological status, pain, and social integration.³⁰ When possible, we prefer to use utility values that reflect the Canadian population. For additional reading on these methods, please refer to Drummond et al.³⁰

We typically obtain utility values (QALY weights or patient preferences) 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.⁴⁶ No database auto-alerts are run. Preference is given to studies with representative, generalizable patient populations and preference-based elicitation techniques.

2.2.2.3.5 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.⁴⁷ 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 [section 2.2.2.3.6](#)), and we calculate the costs and 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 are presented for costs and outcomes. Typically, we calculate the incremental cost-effectiveness ratio (ICER) of the intervention versus each comparator ([Equation 1](#)). 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.

Equation 1:

$$ICER = \frac{Cost_{INTERVENTION} - Cost_{COMPARATOR}}{QALY_{INTERVENTION} - QALY_{COMPARATOR}}$$

The calculated ICER may be compared to different threshold values. If the ICER is below a particular threshold value, the health technology may be considered cost-effective. For transparency, we typically present results over a range of threshold values.

Several approaches for considering cost-effectiveness thresholds have been proposed, including selecting thresholds based on per capita gross domestic product (GDP),⁴⁸ league tables,^{48,49} and benchmark interventions.^{48,50} However, given limitations to these methods,⁴⁸ OHTAC has not adopted a defined willingness-to-pay threshold at which a health technology would be deemed to provide either poor or good value for money.

2.2.2.3.6 *Uncertainty and Variability*

We consider three key types of uncertainty: parameter, structural, and methodological. Parameter uncertainty refers to the precision of input parameters and their estimation. Structural uncertainty pertains to whether the model and its assumptions are specified correctly. Methodological uncertainty refers to unresolved questions about methods in the field (i.e., discount rate, utility algorithm).

To explore uncertainty, we use several methods:

- We use **probabilistic sensitivity analyses** to examine the joint effects of uncertainty in all input parameters simultaneously. We perform many Monte Carlo simulations, in which we calculate the expected values of total costs, total effects, and the resulting ICERs. 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).³⁰ We present these results in the form of a cost-effectiveness acceptability curve, where the proportion of simulations in which each treatment alternative was preferred is shown at a range of willingness-to-pay thresholds. This curve represents the probability that the health technology is cost-effective at a particular threshold compared with the existing alternative(s). The curve reflects the robustness of the model and our confidence in its conclusions.
- We use **one-way deterministic sensitivity analyses**, varying estimates 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 effect outcomes.³² We also perform multiway sensitivity analyses to examine the effects of simultaneously varying the values of more than one parameter in the model.

- We use **scenario analyses** to 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. Typically, the scenarios include the reference case (“best guess”), ideal case (“best case”), and pessimistic case (“worst case”). We alter values to reflect these cases, and we calculate the overall costs, effects, and ICERs. Other relevant scenarios may also be applied.

If probabilistic sensitivity analyses are conducted, and if decision uncertainty (the risk of making the wrong decision) is of major concern, we may consider using value-of-information analysis (e.g., expected value of perfect information [EVPI] and expected value of partial perfect information [EVPPPI]).^{31,44} For instance, EVPPPI can inform the contribution of each parameter or groups of parameters and can estimate the expected value of conducting more research to support a decision.³¹

In addition to uncertainty, there may be variability in the target population (either owing to differences in clinical practice or patient heterogeneity). We address variability in practice by conducting specific scenario analyses. We assess variability owing to patient heterogeneity by conducting subgroup analyses. Important patient subgroups are identified in the clinical review or at the beginning of the economic evaluation as appropriate.

2.2.2.3.7 Other Methodologic Considerations

2.2.2.3.7.1 Validation

Our models are subjected to rigorous internal validation. We validate our evaluation by verifying the model and its equations, 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.

2.2.2.3.7.2 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.

2.2.2.3.7.3 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.⁴⁴ As recommended by the 2017 CADTH guidelines,⁴⁴ 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”), whereas vertical equity justifies the differential treatment of people with different characteristics (“unequal treatment of unequals”).⁵¹

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.⁵² 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.⁴⁴

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.

2.2.2.3.8 Summarizing Economic Evaluation Results

We report the results of our primary economic evaluation following standard guidelines for economic evaluations.³² To provide a clear understanding of both the cost-effectiveness of the health technology and the certainty of our conclusions, we present our probabilistic reference case results as an ICER. We provide a cost-effectiveness acceptability curve ([Figure 1](#)), as described above, and a scatter plot of ICER simulations on the cost-effectiveness plane ([Figure 2](#)). The scatter plot illustrates the proportion of simulations, given a certain threshold value, that are cost-effective. 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.

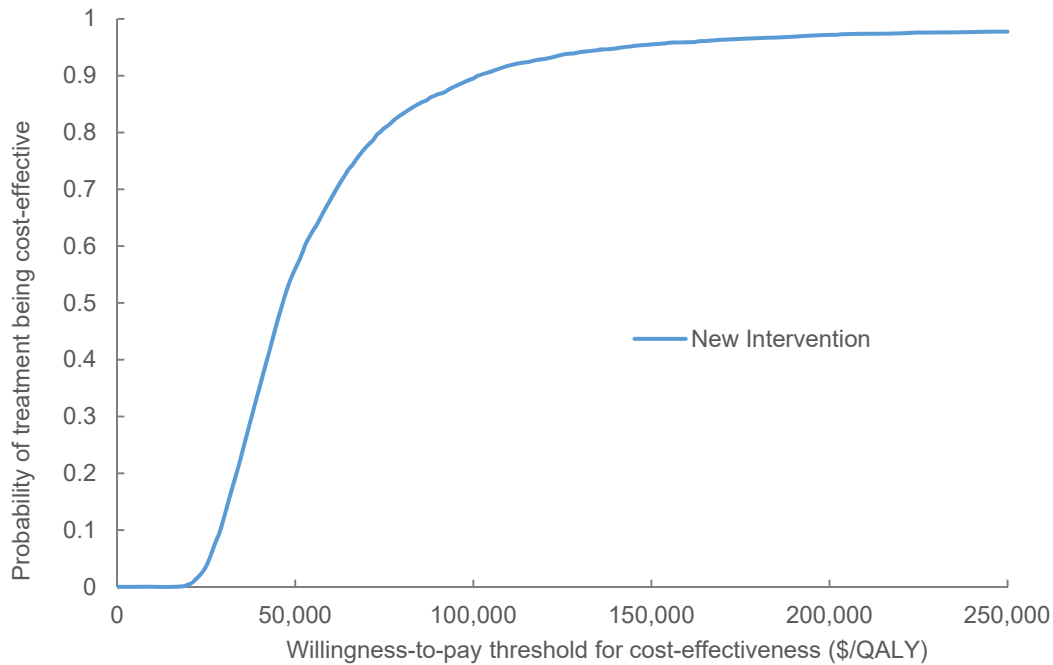


Figure 1: Cost-effectiveness acceptability curve showing the probability of a new intervention being cost-effective at different threshold values

Abbreviation: 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 incremental cost-effectiveness ratio (ICER) below a certain threshold value. For example, the line in the graph indicates that at a willingness-to-pay threshold of \$50,000/QALY, 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 threshold of \$50,000/QALY.

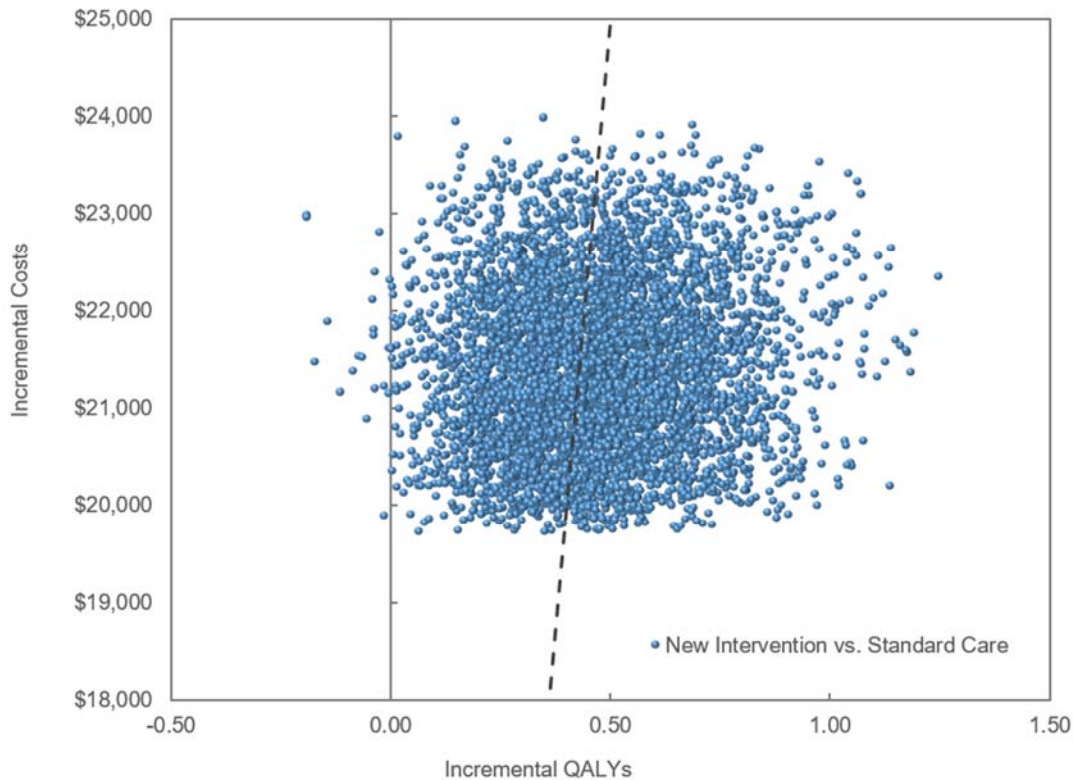


Figure 2: Monte Carlo simulation results on the cost-effectiveness plane

Abbreviation: 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 line with a slope equal to \$50,000/QALY.

We validate our evaluation by verifying the model and its equations, communicating with clinical experts to ensure the model has face validity, and cross-validating the results with previously published economic evaluations addressing similar decision problems.

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.

2.2.2.3.9 Considerations in the Economic Evaluation of Medical Genetic Technologies

Most methods for the economic evaluation of genetic technologies are the same as those for evaluating all health technologies. However, methods used for genetic economic evaluations do have some unique features, including the following:

- **Target population:** Our research question guides the definition of the target 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 test may be influenced by the quality of the technology and the laboratory setting in which the test is conducted. Sensitivity and specificity respectively reflect the percentage of positive and negative cases correctly identified by a given genetic test.⁵³ We model test results as true positives, false positives, true negatives, and false negatives where necessary. Modelling may also capture 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 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.^{54,55}
- **Effectiveness and outcome measures:** The results of a genetic 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 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. When possible, we use utilities reflecting the Canadian context.

2.2.2.4 Budget Impact Analysis

Our reporting methods for budget impact analyses follow a checklist developed by Health Quality Ontario, adapted from the report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force ([Appendix 4](#)).⁵⁶

2.2.2.4.1 Objective and Research Question

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 adopt the perspective of the Ontario Ministry of Health and Long-Term Care). We develop a specific research question that aligns with our objective to guide the data inputs and methodologies used in our analysis.

2.2.2.4.2 Analytic Considerations

Our budget impact methods are adapted from standards set by the International Society for Pharmacoeconomics and Outcomes Research.⁵⁶ 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).⁵⁶ As shown

in [Figure 3](#), 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 (see [section 2.2.2.3](#)). We conduct our budget impact analyses from the perspective of the Ministry of Health and Long-Term Care, typically over a five-year time horizon.

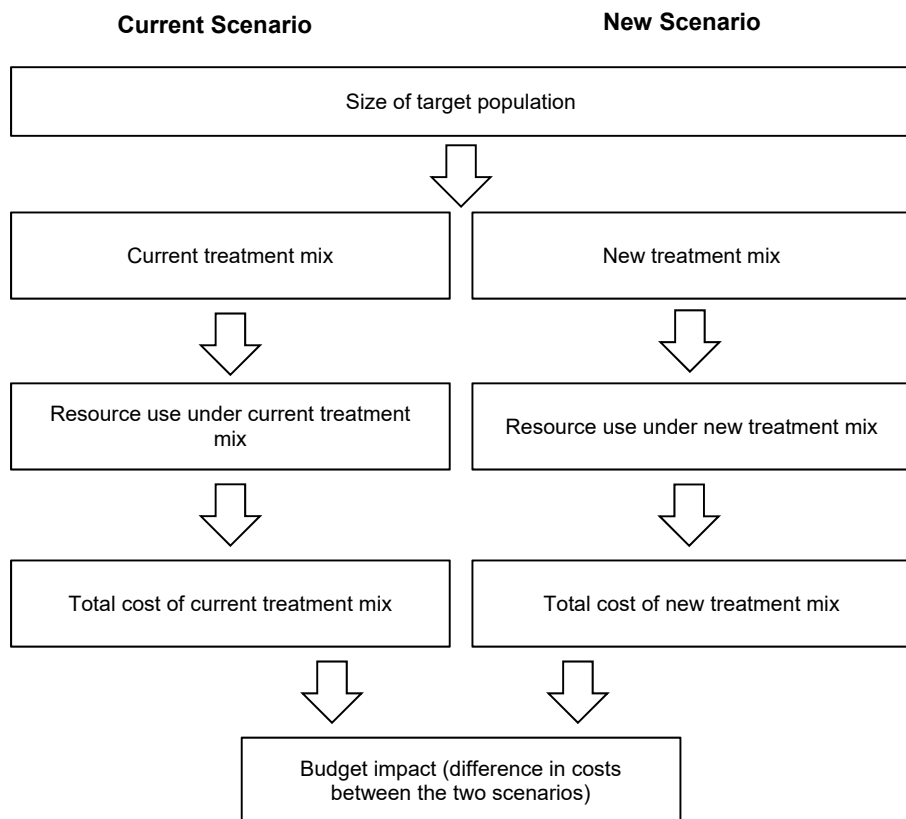


Figure 3: Budget impact model schematic

2.2.2.4.3 Capturing the Size of the Target Population

Our target population consists of all people in Ontario eligible to receive the health technology. The current size of the target population can be estimated based on either population data or claims data.⁵⁷ When using population data, the size of the target population can be estimated using epidemiological inputs, such as the prevalence and incidence of the disease being evaluated. We also include predicted changes in the target population and disease severity mix over the model time horizon, when applicable. If claims data are available through administrative databases (e.g., the Ontario Health Insurance Plan claims database), the size of the target population can be forecasted using the number of claims. The target population may also be informed by expert opinion or the Ontario Ministry of Health and Long-Term Care.

2.2.2.4.4 *Determining the Intervention Mix*

Often, multiple interventions are available in the health system at the same time but are used at different rates (a situation referred to as the intervention mix). In budget impact analyses with a companion cost-effectiveness analysis (in which a primary economic evaluation is conducted), the technologies are the comparators included in the primary economic evaluation. We therefore estimate the current mix of interventions and the potential new mix of interventions. The new intervention mix depends on how quickly we expect the new intervention to be adopted (i.e., the uptake rate) and the extent to which it will replace the current intervention (typically standard care). The uptake rate may depend on the current capacity of the system. The intervention mix and the uptake rate of the new intervention may be extrapolated from currently available data, informed by external stakeholders (e.g., clinical experts, the device manufacturer, the Ontario Ministry of Health and Long-Term Care), or modelled after other jurisdictions (Canadian jurisdictions when possible).

2.2.2.4.5 *Resource Use and Costs*

We estimate resource use and the associated health system costs associated with adopting the new health technology. Depending on the objective of the analysis and the indication of the intervention, the associated costs of resource use may include those of the health technology, related procedures, monitoring, treatment-related adverse events, and disease progression. In standalone budget impact analyses, in which there is insufficient clinical evidence to conduct a primary economic evaluation, we typically focus on costs associated with the health technology. In budget impact analyses with a companion cost-effectiveness analysis, we include both health technology–associated and disease-associated costs. For disease-associated costs, we run companion cost-effectiveness analyses over the time horizon of the budget impact analysis to obtain the relevant costs.

2.2.2.4.6 *Analyses*

We calculate the annual budget impact of the new intervention by subtracting the costs of the current scenario (current practice) from the costs of the new scenario (practice with new intervention) (see [Figure 3](#)).

2.2.2.4.6.1 *Uncertainty*

Similar to our primary economic evaluation, we conduct sensitivity analyses to test key parameter input values and their impact on the annual budget, and we evaluate the structural uncertainty of the assumptions made in the analysis. Typically, we examine the impact of the price of the new intervention, the market share of each comparator, and the size of the target population. We apply various additional sensitivity analyses depending on the nature of the modelling framework and analyses.

2.2.2.4.7 *Summarizing Budget Impact Results*

We present the number of patients and costs for both the current scenario and the new scenario for each year of the budget impact analysis. For costs, we present both total costs and

disaggregated costs by costing components (e.g., costs associated with the device, health service, or genetic test, treatment, administration, and changes in health outcome over the time horizon).

We discuss the results of our budget impact analysis, describing our main findings and clinical relevance, and 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.

2.2.3 Evaluating Patient Preferences and Values

We examine patient preferences and values by seeking to understand patients' lived experience with a health condition, including the impact the condition and its treatment has on themselves, their families, and caregivers. This evidence allows us to examine the needs, priorities, preferences, and values of people living with the health condition and receiving care via standard care or the health technology being evaluated. Additionally, lived experience provides an understanding of people's perspectives on the ethical and societal values implications of a health technology. Lived experience provides a unique source of evidence about the personal impact of a health condition and how that condition is treated, including what it is like to navigate the health system with the condition and how the health technology being reviewed may or may not make a difference in people's health care and quality of life. Information acquired from lived experience can also identify gaps or limitations in the published literature (e.g., outcome measures that do not reflect what is important to those with lived experience of a health condition).⁵⁸⁻⁶⁰

Information about patient preferences, values, and lived experience 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 developing; current methodologies are guided in part by a report of the OHTAC Public Engagement Subcommittee.^{60,61}

2.2.3.1 Direct Patient Engagement

Patient engagement seeks to understand the lived experience of a wide sampling of the relevant patient population, 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 if relevant.

2.2.3.2 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 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.

2.2.3.3 Engagement Plan

If the needs assessment concludes that direct patient engagement would be useful, 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 outreach is needed to target 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. Recruitment is purposeful, and we make an effort to reach out to key informants who can help us connect with people with relevant lived experience.⁶² Key informants may be clinical experts, representatives of advocacy organizations, care delivery or clinic staff, or patient advisory network staff. For projects with an equity component, we recruit people by reaching out through online forums, social media, and via clinicians who care for disadvantaged patients.

The questions we ask relate to the lived experience of the health condition, people's experiences of different treatments, and, when possible, the health technology being evaluated.⁶³ We coordinate our engagement 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 Health Quality Ontario's offices, on the phone, and online. We provide participants with a letter of information and a consent form 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. Consultations with privacy and ethics experts have informed us that Health Quality Ontario's direct patient engagement activities are designed for quality improvement purposes (i.e., to improve health care in Ontario) and not to test research hypotheses. As such, our patient engagement work is exempt from research ethics review.⁶⁴

Our outreach methodology follows good practice to protect people’s privacy. We inform peer support groups and health care providers about our projects and ask them to spread the word about our engagement activities. After learning about a particular project, people interested in participating contact Health Quality Ontario directly.

2.2.3.4 Summarizing the Findings

We typically transcribe relevant sections of participant interviews, which enables us to code and explore themes in the resulting transcripts using a modified version of grounded theory.⁶⁵⁻⁶⁷ Survey responses are also coded. We use the qualitative data analysis software NVivo⁶⁸ to identify and compare themes using a constant comparative analysis approach. We also select illustrative quotes from participants to bring to life the impact of the health technology on patients’ quality of life. Lived experience evidence provides an in-depth picture of patient needs, priorities, preferences, values, and quality of life with respect to the health condition and health technology.

2.3 Phase 3: Making a Recommendation

The [Ontario Health Technology Advisory Committee](#) (OHTAC) reviews the findings of HTA reports on medical devices and health services and, through a deliberative process, makes recommendations to Health Quality Ontario regarding public funding.

The [Ontario Genetics Advisory Committee](#) (OGAC), a subcommittee of OHTAC, reviews the findings of HTAs of genetic tests and, through a deliberative process, makes recommendations to OHTAC regarding public funding for the genetic tests reviewed. OHTAC then makes recommendations to Health Quality Ontario regarding public funding.

The process for developing recommendations regarding publicly funding genetic tests follows the process outlined in [section 2.3.6](#).

2.3.1 Health Quality Ontario 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 ([Table 2](#)).⁶⁹ This framework provides considerations for developing a recommendation within four domains:

- Overall clinical benefit
- Consistency with expected societal and ethical values
- Value for money
- Feasibility of adoption into Ontario’s health system

These determinants do not have a hierarchy, and the relative weight of each domain is specific to the individual health technology being assessed. Updates to this framework will address the specificity of domain names and the operationalization of the framework. We will update this methods and process guide when those revisions are incorporated into OHTAC’s processes.

Table 2: Decision Determinants Framework⁶⁹

Domain	Subcriteria	Definitions
Overall clinical benefit	Effectiveness	The potential health impact of the technology compared with the available alternatives, measured in terms of relevant patient outcomes such as mortality, morbidity, and quality of life. Magnitude and direction of effect should be considered.
	Safety	The frequency and severity of adverse effects associated with the technology compared with the available alternatives.
	Burden of illness	Incidence, prevalence, or other measure of disease burden .
	Need	The availability of an effective alternative to the technology.
Consistency with expected societal and ethical values	Expected societal values	Broadly shared values in society that bear on the appropriate use of the technology.
	Expected ethical values	The potential ethical issues inherent in using or not using the technology. Relevant ethical issues should be listed.
Value for money	Economic evaluation	A measure of the net cost or efficiency of the technology compared with available alternatives expressed as an incremental cost effectiveness ratio (ICER)
Feasibility of adoption into the health system	Economic feasibility	The net budget impact of the technology derived by determining all relevant costs and savings to the health system.
	Organizational feasibility	The ease with which the health technology can be adopted is evaluated by assessing the health system enablers and barriers to diffusion within the health system infrastructure (operational, capital, human resources, legislative, and regulatory).

2.3.2 Overall Clinical Benefit

The evaluation of overall clinical benefit includes assessing the effectiveness and safety of the health technology being reviewed, the burden of illness experienced by people with the target health condition, and the need for the health technology. Evidence from the clinical and lived experience reviews provides the foundation for assessing the overall clinical benefit of the health technology.

2.3.3 Consistency With Expected Societal and Ethical Values

The evaluation of expected societal and ethical values involves considering the broadly shared values in society that may impact the use of the health technology. This domain also considers any potential ethical issues inherent in using and not using the health technology, as well as any equity concerns. Evidence from the clinical and lived experience reviews (including patient, family, and caregiver perspectives) provides the foundation for examining the actual or potential societal and ethical impact of the health technology.

2.3.4 Value for Money

The evaluation of value for money includes assessing whether the cost of the health technology is an efficient use of resources compared with an alternative treatment for the same health condition. The findings from the economic evaluation and/or the review of the economic literature typically inform this evaluation. Health Quality Ontario does not currently have a single explicitly defined willingness-to-pay threshold at which a health technology would be considered either poor or good value for money (see [section 2.2.2.3.5](#)).

2.3.5 Feasibility of Adoption Into the Health System

Evaluating the feasibility of adopting a new health technology into Ontario's health system involves assessing the impact of adopting the health technology on currently available health care resources, as well as any resource gaps that would need to be addressed or system-level changes (e.g., fee schedule changes) that would need to be made for the health technology to be successfully adopted. Where many system-level changes would need to be made and/or where there are numerous resource gaps, adoption is likely to be difficult; where there are few barriers, adoption is likely to be easier.

In keeping with Health Quality Ontario's guiding principle of transparency, OHTAC provides Health Quality Ontario with a rationale for each of its recommendations. The decision determinants framework does not explicitly guide the development of recommendations for health technologies involving rare conditions or situations of disinvestment. However, each health technology is considered on a case-by-case basis, and the relevance of each criterion and the overall weight each criterion has in the final recommendation are unique to each situation.

2.3.6 Health Quality Ontario Recommendation

Following deliberations on the findings of an HTA, OHTAC prepares a draft recommendation for Health Quality Ontario regarding public funding for the health technology.

The recommendation consists of a declarative statement and a rationale for the recommendation. Recommendations typically take the form of one of the following:

- *For new health technologies not currently publicly funded*
 - Health Quality Ontario, under the guidance of the Ontario Health Technology Advisory Committee, recommends publicly funding [health technology] for [health condition]
 - Health Quality Ontario, under the guidance of the Ontario Health Technology Advisory Committee, recommends against publicly funding [health technology] for [health condition]

- *For existing health technologies that are currently publicly funded*
 - Health Quality Ontario, under the guidance of the Ontario Health Technology Advisory Committee, recommends the continued public funding of [health technology] for [health condition]
 - Health Quality Ontario, under the guidance of the Ontario Health Technology Advisory Committee, recommends that public funding of [health technology] be discontinued for [health condition]

OHTAC may also add supplementary recommendations that provide additional guidance to the Ministry of Health and Long-Term Care.

The completed HTA report and draft recommendation are posted for feedback on the Health Quality Ontario website for three weeks. OHTAC considers all feedback before issuing a final recommendation.

Recommendations, including recommendations regarding genetic tests originating with OGAC, require final approval by the Health Quality Ontario board of directors. Once approved by the board, recommendations are sent to the Minister of Health and Long-Term Care.

The HTA report is published in the journal *Ontario Health Technology Assessment Series*, which is indexed in MEDLINE, EMBASE, and the Cochrane Library. Both the HTA report and final Health Quality Ontario recommendation are published on the Health Quality Ontario website.

3 KEY ELEMENTS OF THE HEALTH TECHNOLOGY ASSESSMENT PROCESS

3.1 Health Technology Assessment Process Overview

Section 3 of this guide describes the key process elements and roles involved in developing HTA reports at Health Quality Ontario.

3.2 Timelines

The time to complete an HTA report varies depending on topic complexity, but in general projects adhere to the timeline shown in [Table 3](#).

Table 3: HTA 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 Ministry of Health and Long-Term Care of draft recommendation; post HTA report and recommendation for public feedback; OHTAC finalizes recommendation (OGAC finalizes genetic test recommendation which is then reviewed by OHTAC)	6–6.5 months
Recommendation approval	Present HTA report and recommendation to Health Quality Ontario's board of directors for approval; once approved, share HTA report and recommendation with Minister of Health and Long-Term Care	0.5 months
Final web posting	Post approved and finalized HTA report and HQO board-approved recommendation on Health Quality Ontario website	0.5 months
Total project duration		~13–14 months

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

3.3 Roles and Responsibilities

[Table 4](#) presents the roles and responsibilities of those involved in the development of an HTA report and Health Quality Ontario recommendation.

Table 4: Roles and Responsibilities of Those Involved in the Development of an HTA Report and Health Quality Ontario Recommendation

Role	Responsibilities
Health Quality Ontario HTA team	Receives HTA applications; supports OHTAC and OGAC in topic prioritization process; completes clinical, economic, and patient preferences and values evidence reviews; prepares draft HTA reports; manages HTA report production and approval process
Ontario Health Technology Advisory Committee (OHTAC)	Prioritizes HTA topics; reviews draft HTA reports; reviews public feedback received; makes draft and final recommendations; provides recommendations to Health Quality Ontario board of directors for approval; reviews and approves OGAC recommendations; provides OGAC recommendations to Health Quality Ontario board of directors for approval
Ontario Genetics Advisory Committee (OGAC)	A subcommittee of OHTAC; prioritizes genetic HTA topics reviews draft HTA reports; reviews public feedback received; makes draft recommendations; provides draft recommendations to OHTAC for approval
Expert consultants (e.g., patients, clinicians, industry representatives)	Provides contextualization for the HTA
External stakeholders (e.g., clinicians, researchers, industry representatives, patients, caregivers)	Provides feedback on draft HTA reports and Health Quality Ontario recommendations through the open-for-feedback process
Health Quality Ontario board of directors	Approves final Health Quality Ontario recommendations
Ministry of Health and Long-Term Care	Participate in prioritization of HTA topics, Reviews draft HTA reports and provides feedback on clinical and economic plans; receives Health Quality Ontario recommendations; uses Health Quality Ontario 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.

3.4 Health Technology Assessment Process

3.4.1 Process Flowchart: All Phases

[Figure 4](#) presents a flowchart illustrating the typical process phases for an HTA at Health Quality Ontario. The grey bars indicate the overarching phases of the process, and the elements below each bar indicate the steps involved in each phase.

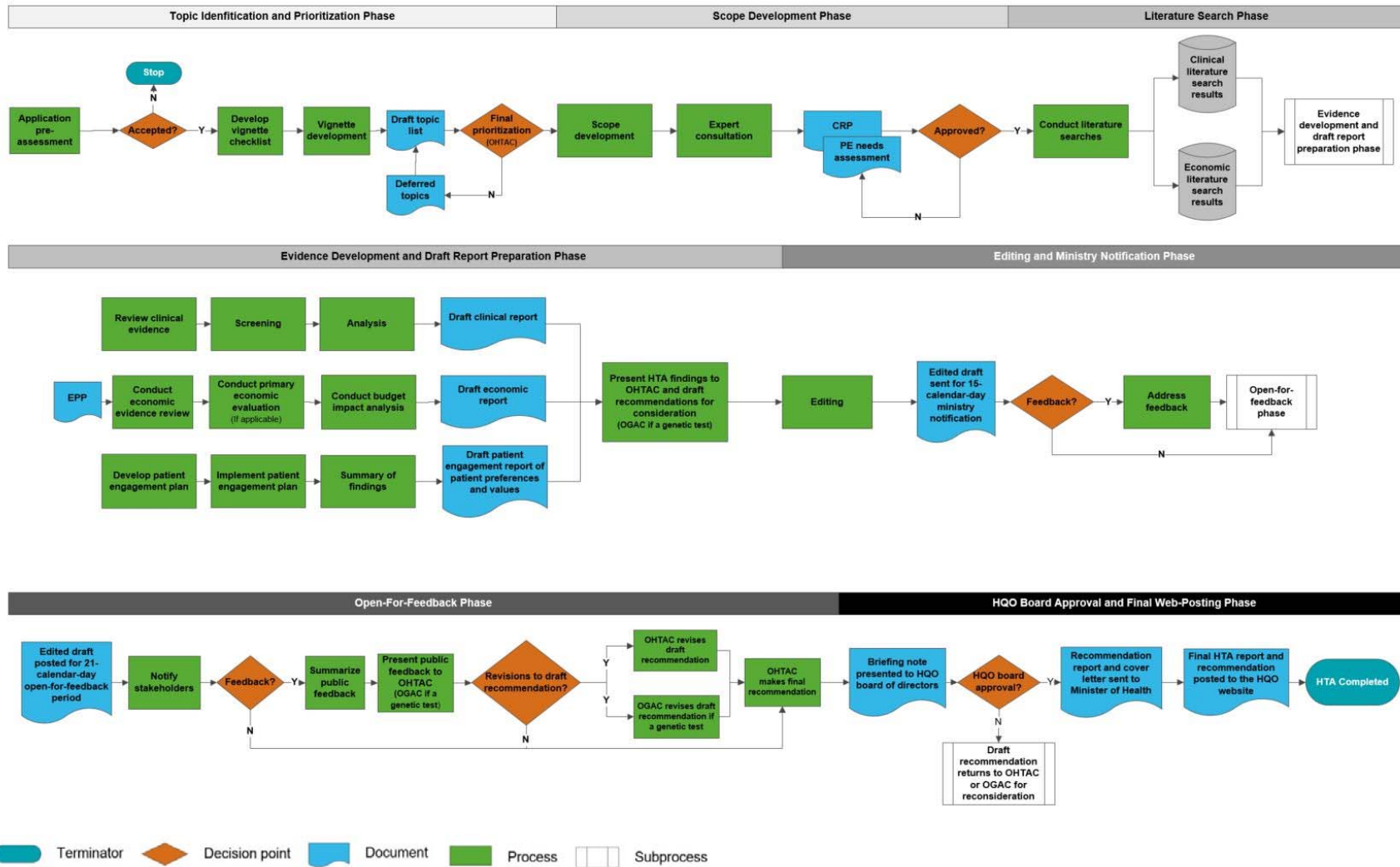
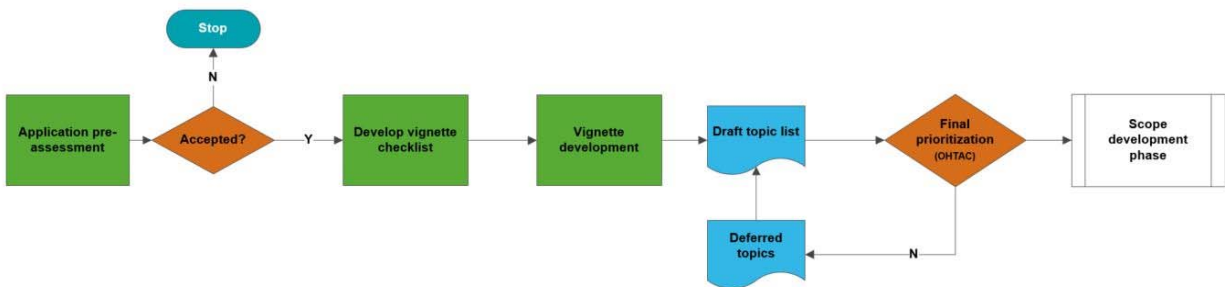


Figure 4: HTA Process Flowchart

Abbreviations: CRP, clinical review plan; EPP, economic project plan; HQO, Health Quality Ontario; HTA, health technology assessment; OGAC, Ontario Genetics Advisory Committee; OHTAC, Ontario Health Technology Advisory Committee; PE, patient engagement; PPV, patient preferences and values.

3.5 Process Detail: Topic Identification and Prioritization Phase



3.5.1 Application Pre-assessment

Suggested topics for HTAs are typically received online through Health Quality Ontario's [open application process](#). The applications are reviewed by the HTA program director and either accepted or rejected for prioritization according to the director's assessment of fit with Health Quality Ontario's mandate.

3.5.2 Vignette Development

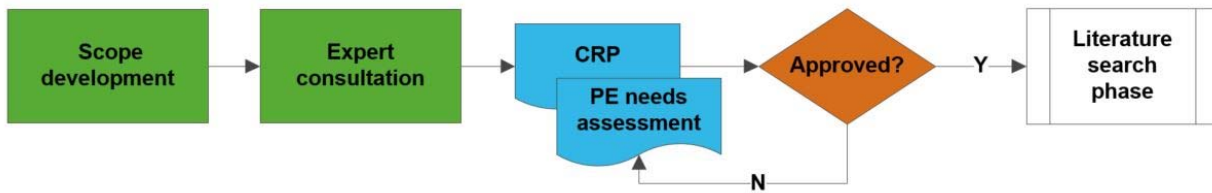
Following pre-assessment, the HTA team develops a vignette checklist of relevant references. After preliminary scoping of suggested topics, the HTA team then develops a vignette for each. The vignette includes information about the topic with regard to the prioritization criteria ([Appendix 1](#)). The HTA team then creates a draft list of HTA topics in order of priority for HTA development for consideration by OHTAC.

3.5.3 Final Prioritization

The draft priority list of HTA topics is presented for consideration at an OHTAC meeting, during which the committee deliberates and finalizes the order in which HTAs should be completed. Deferred topics are considered in subsequent prioritization meetings. Health Quality Ontario prioritizes HTA topics twice a year, typically in November and May.

Under the advisement of OGAC, we are currently developing a framework for the prioritization of genetic topics.

3.6 Process Detail: Scope Development Phase



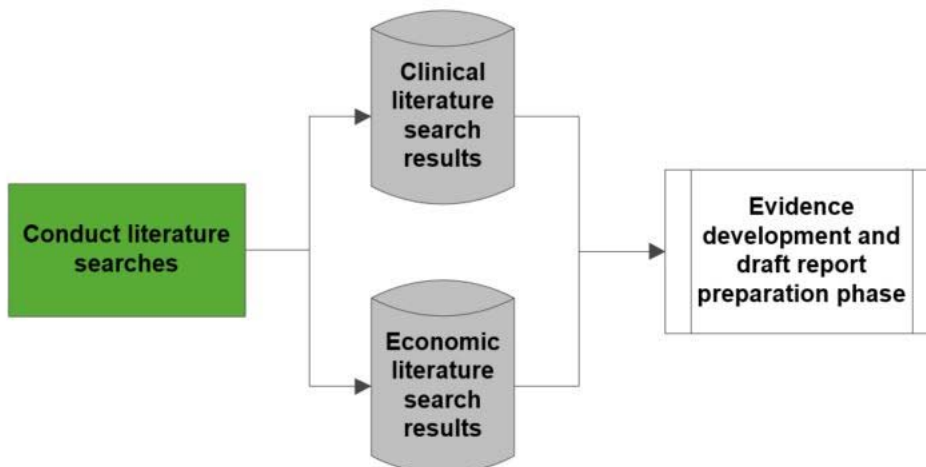
3.6.1 Expert Consultation

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

3.6.2 Clinical and Patient Engagement Review Plan Development

HTA team members develop the clinical review plan and patient preferences and values engagement plan (if required). The HTA team works collaboratively to ensure the alignment of scope, research questions, and literature search strategies. The clinical review plan is approved by the manager of Clinical Reviews, and the patient preferences and values engagement plan is approved by the director of Patient, Caregiver, and Public Engagement. The economic project plan is developed later in the HTA process.

3.7 Process Detail: Literature Search Phase



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

3.8 Process Detail: Evidence Development and Draft Report Preparation Phase



3.8.1 Review of Clinical Evidence, Screening, and Analysis

During this phase, we screen the literature search results to determine which studies are relevant to the research question(s). Relevant studies are included in the clinical evidence review. Findings are summarized in the draft clinical report.

3.8.1.2 Economic Evidence Review, Primary Economic Evaluation, and Budget Impact Analysis

We develop 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. Following this, we conduct an economic evidence review. 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.

3.8.1.3 Develop Patient Engagement Plan, Plan Implementation, and Summary of Findings

The HTA team conducts a needs assessment regarding the need for 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 director of Patient, Caregiver, and Public Engagement, then decides whether to proceed with direct patient engagement activities. If it is decided to undertake direct patient engagement, the Patient, Caregiver, and Public Engagement team decide on the most appropriate engagement activity to pursue.

Typically, two scenarios exist for assessing patient preferences and values: a review of the qualitative and quantitative published literature on the topic or direct patient engagement (i.e., via interviews, focus groups, and/or surveys). The decision to undertake direct patient engagement depends on the needs of the HTA and is made on a case-by-case basis. For direct patient engagement, the HTA team prepares and then executes an engagement strategy defining the types of patient 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

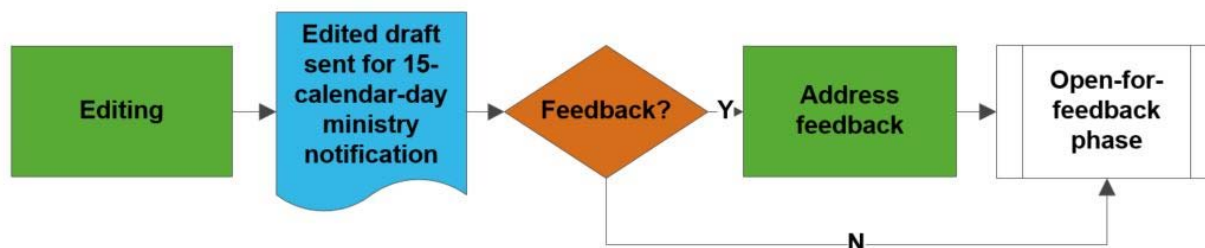
qualitative and/or quantitative literature review and direct engagement may be conducted. Findings are summarized in the draft patient preferences and values report.

3.8.2 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 [Table 2](#)).

The draft recommendation and draft clinical, economic, and patient preferences and values reports are then submitted for editing.

3.9 Process Detail: Editing and Ministry Notification Phase



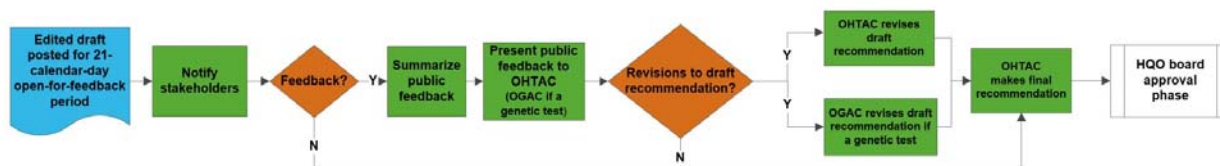
3.9.1 Editing

In this phase, the draft clinical, economic, and patient preferences and values reports are merged into a single document, the HTA report, and the merged document is edited by a medical editor. The draft recommendation is also edited at this time.

3.9.2 Ministry Notification

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

3.10 Process Detail: Open-for-Feedback Phase



3.10.1 Open-for-Feedback Posting

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

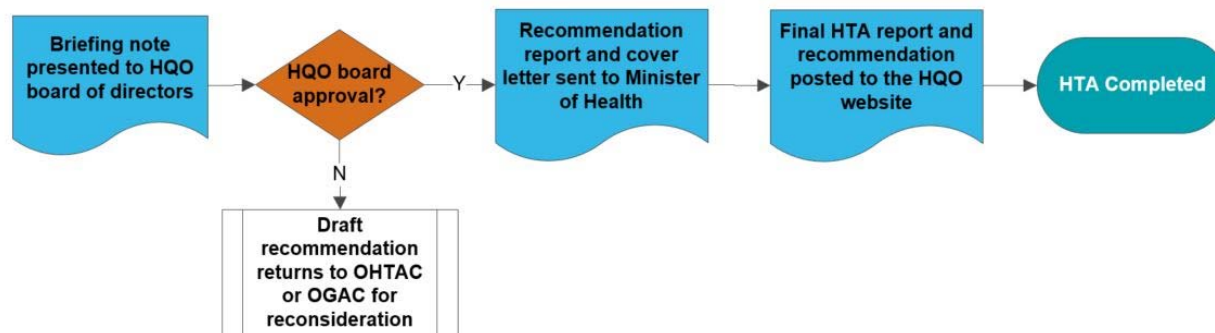
3.10.2 Notifying Stakeholders

Once the draft recommendation and HTA report are posted on the Health Quality Ontario 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.

3.10.3 Summarizing and Addressing Public Comments

Following the open-for-feedback period, the HTA team assesses, summarizes, and then presents all feedback at the next OHTAC meeting or OGAC meeting (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 submitting the finalized recommendation and HTA report to the Health Quality Ontario board of directors for approval.

3.11 Process Detail: Health Quality Ontario Board of Directors Approval and Final Web-Posting Phase



3.11.1 Briefing Note

The HTA team prepares a briefing note for consideration by Health Quality Ontario's board of directors. The briefing note describes the final recommendation, OHTAC's or OGAC's rationale for the recommendation, and relevant background information on the HTA topic. The OHTAC chair presents the briefing note to the Health Quality Ontario board of directors at the board's next scheduled meeting.

3.11.2 Letter to the Minister of Health and Long-Term Care

The approved final HTA report and Health Quality Ontario recommendation are sent to the Minister of Health and Long-Term Care via email.

3.11.3 Final Posting to Health Quality Ontario Website

The approved HTA report and final Health Quality Ontario recommendation are posted to the Health Quality Ontario website. Final recommendation documents are provided in English and French.

APPENDICES

Appendix 1: Health Quality Ontario Health Technology Assessment Topic Prioritization Guide^a

Criteria	Rating Categories			Rating
	A = 3	B = 2	C = 1	
1. Potential to improve health outcomes relative to existing alternatives	Potential benefit	Likely equivalent benefit or no evidence identified	Inferior benefit	
2. Number of patients likely to use the health technology	> 10,000	5,000–10,000	< 5,000	
3. Potential to reduce harm relative to existing alternatives	Potential reduction in harm	No likely reduction in harm	Potential for increased harm	
4. Patients accessing health technology by going out of province or out of country	High degree of out-of-province or out-of-country demand	Some demand	No demand	
5. Implementation feasibility/system readiness	Significant feasibility to implement	Moderate feasibility to implement	Significant challenges to or uncertainty in feasibility of implementation	
6. Stakeholder demand	Clinical stakeholders or member of the public	Industry with clinical stakeholders or industry with member of the public	Industry only	
7. Potential unmet need	Significant	Some	No	
8. Equity impact	Major potential to improve equity	No expected change in equity	Potential to increase inequity	
9. Potential cost-effectiveness	Likely good value for money	Uncertain	Likely poor value for money	
10. Potential savings to the health system	Yes	Uncertain	No	

^aThe prioritization guide for genetic topics is currently in development.

Appendix 2: Risk-of-Bias Assessment Tools

Study Type	Suggested Risk-of-Bias Assessment Tool(s)
Randomized controlled trial	<ul style="list-style-type: none"> • Cochrane Risk of Bias Tool⁷⁰
Observational study	<ul style="list-style-type: none"> • SIGN Checklist 3: Cohort Studies⁷¹ • SIGN Checklist 4: Case-Control Studies⁷² • ISPOR questionnaire⁷³ • Effective Practice and Organisation of Care (EPOC)⁷⁴ • Newcastle–Ottawa Assessment Scale (NOS) for cohort and case-control studies⁷⁵ • Good ReseArch for Comparative Effectiveness (GRACE) Checklist⁷⁶ • Downs and Black Checklist⁷⁷ • Risk of Bias Assessment Tool for Nonrandomized Studies (RoBANS)⁷⁸ • Cochrane Risk of Bias in Non-Randomized Studies—of Interventions (ROBINS-I)⁷⁹
Diagnostic accuracy study	<ul style="list-style-type: none"> • Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2)⁸⁰
Systematic review	<ul style="list-style-type: none"> • Risk of Bias in Systematic Reviews (ROBIS)⁸¹

Abbreviations: ISPOR, International Society for Pharmacoeconomics and Outcomes Research; SIGN, Scottish Intercollegiate Guidelines Network.

Appendix 3: Modified Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Checklist

Question	Yes/No/NA
Title and abstract	
1. Does the abstract summarize the following? <ul style="list-style-type: none"> • Objective • Perspective • Setting • Methods (including study design and inputs) • Results (including base case and uncertainty analyses) • Conclusions 	
Introduction	
2. Is there a statement on the broader context of the study?	
3. Is the study question presented, as well as its relevance for health policy or practice decisions?	
Methods	
4. Are characteristics of the reference case population and subgroups described, including why they were chosen?	
5. Is the setting and location specified? (Ontario)	
6. Is the perspective of the study provided, and does it relate to the costs being evaluated?	
7. Are the comparators (i.e., interventions/strategies) described and their choice explained?	
8. Is the time horizon stated and explained?	
9. Is the discount rate reported, and is it used for costs and outcomes?	
10. Are the outcomes described, and are any used as a measure of benefit in the evaluation?	
11. Are the outcomes relevant for the type of analysis performed?	
12. Are approaches to estimate resource use and cost from data sources described?	
13. Are the dates of resource quantities and unit costs reported?	
14. Are the methods for adjusting costs to the desired year or common currency base described?	
15. Is the choice of model explained, and is a figure of the model structure provided?	
16. Are structural and other assumptions of the decision-analytical model described?	
17. Are analytical methods that support the evaluation described? For example: <ul style="list-style-type: none"> • Methods to deal with skewed, missing, or censored data • Extrapolation methods • Methods for pooling data • Approaches to validate or make adjustments (half-cycle correction) to a model • Methods for handling population heterogeneity and uncertainty 	
Results	
18. Are all study parameters reported (preferably in table format)?	
19. Are sources/distributions explained when used to represent uncertainty?	
20. Are mean values for costs and outcomes provided for each intervention (as well as differences)?	
21. Are incremental cost-effectiveness ratios reported?	
22. Does the study describe the effects of uncertainty for all input parameters on the results?	
23. Does the study describe the uncertainty related to the model structure/assumptions?	
24. Does the study describe differences in outcomes that can be explained by variations between patient subgroups?	
Discussion	
25. Are the study findings summarized?	
26. Are limitations and the generalizability of the findings outlined?	

Question	Yes/No/NA
Other	
27. Is the source of funding provided, as well as the funder's role in the study?	
28. Are conflicts of interest outlined (where required)?	

Source: Husereau et al, 2013.³⁹

Appendix 4: Health Quality Ontario Budget Impact Analysis Reporting Checklist

Question	Yes/No/NA
General	
1. Does the study indicate whether it is a companion (conducted along with a primary economic evaluation) or a standalone budget impact analysis?	
Methods	
2. Is the perspective of the study provided, and does it relate to the costs being evaluated? (Ontario Ministry of Health and Long-Term Care, hospital, etc.)	
3. Is the time horizon stated and relevant to the budget holder? (usually 5 years)	
4. Is the target population size determined using data specific to Ontario? If not, is justification provided.	
5. Are included subgroups described? (optional)	
6. Are indications for the technology and market effects described with respect to the target population? Consider: <ol style="list-style-type: none"> Approved indication of the technology Planned restriction on use or reimbursement Possible “leakage” (possibility of the technology being used beyond the restriction) Possible market expansion (previously untreated patients may now seek treatment because the new intervention has improved outcomes, greater convenience, or fewer side effects) 	
7. Does the study state if the target population changes over time (with and without the intervention)?	
8. Are the current scenario and new scenario clearly defined?	
9. Is the intervention mix in the current scenario described? Are sources reported?	
10. Is the uptake rate of the new technology reported? Are sources reported?	
11. Is the intervention mix in the new scenario described? Are sources reported? Consider: <ol style="list-style-type: none"> Is the new intervention a substitution (replacing current intervention), combination (add-on to current intervention), or expansion of the current intervention? Are changes within subgroups reported? 	
12. Are all relevant costs considered in the budget impact analysis? Are sources reported? Consider (where applicable): <ol style="list-style-type: none"> Technology costs (including capital costs, maintenance, consumables, required diagnostics) Cost savings (owing to change in outcomes, treatment administration, etc.) Labour costs Administrative or monitoring costs Disease-related and complication-related costs 	
13. Are costs Ontario specific where possible?	
14. Are assumptions reported?	
15. Are sensitivity analyses described and conducted? Consider: <ol style="list-style-type: none"> Changes in the target population Input parameters (e.g., costs, effectiveness, intervention mix, uptake rates) Relevant scenario analyses 	
Results	
16. Are results presented as undiscounted costs?	
17. Are the annual costs per person included for the current and new scenarios reported (if applicable)?	
18. Are the annual aggregate costs included for the current and new scenarios reported?	
19. Is the net budget impact (new scenario costs – current scenario costs) reported?	
20. Are cost breakdowns presented (technology-related and disease-related costs at minimum)?	
Discussion	
21. Are the study findings summarized?	
22. Are limitations and the generalizability of the findings outlined?	

Source: Adapted from Sullivan et al, 2014.⁵⁶

Appendix 5: Health Quality Ontario 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)

Criteria for Assessing the Need for Direct Patient Engagement

	Increasing Need for Conducting an Engagement Activity →		
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 Ministry of Health and Long-term Care? 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 caregiver burden
 - Understand the impact of the side effects of the health technology
 - Understand the 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.

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

ABBREVIATIONS

CADTH, Canadian Agency for Drugs and Technologies in Health

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

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 process that systematically assesses the clinical benefit, value for money, and patient preference and values of a health technology, usually to inform decision-making about the technology.
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.
Morbidity	The occurrence of a disease or condition in a population. Generally expressed as a quantity, the morbidity rate.
Point estimate	A specific number that is taken to be the best estimate of some aspect of a sampled population.
Probabilistic sensitivity 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.

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