Rapid Synthesis

Examining the Public Provision and Funding of Clinical Genetic Tests

5 September 2017

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Rapid Synthesis:
Examining the Public Provision and Funding of Clinical Genetic Tests
30-day response

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McMaster Health Forum

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Timeline

Rapid syntheses can be requested in a three-, 10- or 30-business day timeframe. This synthesis was prepared over a 30-business day timeframe. An overview of what can be provided and what cannot be provided in each of the different timelines is provided on the McMaster Health Forum's Rapid Response program webpage (http://www.mcmasterhealthforum.org/policymakers/rapid-response-program).

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Conflict of interest

The authors declare that they have no professional or commercial interests relevant to the rapid synthesis. The funder played no role in the identification, selection, assessment, synthesis or presentation of the research evidence profiled in the rapid synthesis.

Merit review

The rapid synthesis was reviewed by a small number of policymakers, stakeholders and researchers in order to ensure its scientific rigour and system relevance.

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KEY MESSAGES

Questions

- In comparator jurisdictions, what clinical genetic tests are publicly offered and what payment models are used to support their delivery?
- What does the evidence say about the processes or criteria for determining whether and when clinical genetic tests should be publicly available, and how this has been implemented in comparator jurisdictions?

Why the issue is important

- Since the completion of the Human Genome Project in the 1990s, there have been rapid advances of research in the area of genetics and genomics.
- When combined with evolving medical technologies this has meant that the use of genetic testing and screening are increasingly common in the health system.
- Despite clinical genetic tests having been commonly used in the health system for more than two decades, many jurisdictions around the world still do not have a systematic approach to evaluating these tests or for reaching decisions regarding what to publicly fund.
- In response to this challenge, this rapid synthesis aims to identify what genetic tests are currently funded in comparator jurisdictions, and what frameworks and decision-making criteria have been used to support resource allocation for clinical genetic testing.

What we found

- We identified a total of 19 documents including: one systematic review, three non-systematic reviews, four primary studies, and 11 theoretical frameworks for decision-making with regards to clinical genetic tests.
- In addition, we undertook a scan of 16 comparator jurisdictions (each Canadian province other than British Columbia which is where the synthesis was requested from, Australia, New Zealand, the United Kingdom and four large Health Maintenance Organizations (HMOs)– Anthem, Blue Cross Blue Shield, Cigna and United Healthcare – in the United States) to determine what genetic tests are publicly provided, for whom, and how they are paid for.
- Relatively little information was found for each jurisdiction, however in most jurisdictions genetic testing is covered when it is deemed medically necessary by a qualified health professional, when no other alternative exists, and when the results of the genetic test have an impact on clinical decision-making.
- In all jurisdictions that we reviewed, genetic tests are paid for in full under public insurance plans when medically necessary, but the HMOs reviewed in the United States require the payment of a deductible or co-pay for all eligible individuals.
- One primary study conducted interviews with those involved in making funding decisions for genetic testing in Canada and found the clinical utility of the test was rated as being the most important criteria in decision-making.
- Another primary study examined 55 coverage decisions of newborn genetic screenings, and found that stakeholder participation and transparency improved decision-making processes for determining what genetic tests to fund.
- Each of the 11 decision-making frameworks that we identified call for the use of randomized control trials (RCTs) as the primary evidence base for evaluating genetic tests.
- Common elements of the identified frameworks include: analytical validity; clinical validity; clinical utility; ethical, social and legal implications; and economic considerations.
- Two primary limitations for the application of these frameworks were identified: 1) each have different scopes of genetic tests or health technologies for which they can be used; and 2) most of the frameworks do not provide guidance on how to make value judgments on what to fund.

QUESTIONS

- In comparator jurisdictions, what clinical genetic tests are publicly offered and what payment models are used to support their delivery?
- What does the evidence say about the processes or criteria for determining whether and when clinical genetic tests should be publicly available, and how this has been implemented in comparator jurisdictions?

WHY THE ISSUE IS IMPORTANT

Since the completion of the Human Genome Project in the 1990s, there have been rapid advances of research in the area of genetics and genomics.(1) When combined with evolving medical technologies this has meant that the use of genetic testing and screening are increasingly common in the health system. Genetic tests can offer benefits for the diagnosis and treatment of conditions, identification of predisposition to a genetic disease, and even the tailoring of drugs and therapies to an individual's genetic profile. In recent years however, there has been a large increase in the use of genetic tests, largely as a response to both the improved accuracy and availability of these tests, as well as to patient demands for enhanced personalized health information.(2)

However, there are also a number of possible individual and societal risks associated with increased use of genetic testing. On an individual level, genetic testing can pose undue emotional and psychological harm as a result of revealing unexpected information, or as a result of testing errors (e.g., false negatives or false positives). Testing may also have unforeseen consequences for family members of those who have undergone screening (e.g., by potentially being unprepared to discover that they too are at risk for a disease). On a societal level, increased genetic testing raises a number of questions regarding additional resource use, genetic discrimination, eugenics, and balancing how to maintain individual privacy against the duty to disclose.(2)

While these tests represent a new source of data in the health system and a step towards personalized medicine, they also offer a unique challenge given the need to weigh benefits and harms, as well as complex ethical, legal and social implications.

Box 1: Background to the rapid synthesis

This rapid synthesis mobilizes both global and local research evidence about a question submitted to the McMaster Health Forum's Rapid Response program. Whenever possible, the rapid synthesis summarizes research evidence drawn from systematic reviews of the research literature and occasionally from single research studies. A systematic review is a summary of studies addressing a clearly formulated question that uses systematic and explicit methods to identify, select and appraise research studies, and to synthesize data from the included studies. The rapid synthesis does not contain recommendations, which would have required the authors to make judgments based on their personal values and preferences.

Rapid syntheses can be requested in a three-, 10- or 30-business-day timeframe. An overview of what can be provided and what cannot be provided in each of these timelines is provided on the McMaster Health Forum's Rapid Response program webpage (http://www.mcmasterhealthforum.org/policymakers/rapid-response-program).

This rapid synthesis was prepared over a 30-business day timeframe and involved four steps:

1) submission of a question from a health system policymaker or stakeholder (in this case, the Ministry of Health of British Columbia);
2) identifying, selecting, appraising and synthesizing relevant research evidence about the question;
3) drafting the rapid synthesis in such a way as to present concisely and in accessible language the research evidence; and
4) finalizing the rapid synthesis based on the input of at least two merit reviewers.

Despite clinical genetic tests having been commonly used in the health system for more than two decades, many jurisdictions around the world still have no systematic way of evaluating them or reaching decisions regarding what to publicly fund. Therefore, policymakers and public-health officials are asked to examine many different risks and benefits to ensure that genetic-testing programs best fit the public interest. Without a structure in place to make these decisions, these assessments are frequently conducted reactively when a pressing health issue emerges, or when a new technology enters the market, rather than using a set of consistent decision-making criteria.(3) In addition, considering which tests to fund is also important as all publicly funded healthcare systems have finite resources. As such, these systems are forced to consider the opportunity costs of providing increased genetic tests.

In response to this challenge, this rapid synthesis aims to identify what genetic tests are currently funded in comparator jurisdictions, and what frameworks and decision-making criteria have been used to support resource allocation for clinical genetic testing.

Box 2: Identification, selection and synthesis of research evidence

For the first question, we undertook a purposeful sampling of websites of the governments and agencies involved in genetic testing in each of the jurisdictions. For the second question, we identified research evidence (systematic reviews and primary studies) by searching (in July 2017) Health Systems Evidence (www.healthsystemsevidence.org) and PubMed. In Health Systems Evidence, we searched for genetic AND (test* OR screen*) in the title, abstract and keywords fields. In PubMed, we searched for (genetic OR genomic) AND (insur* OR public* fund OR public* finance* OR public* coverage) AND (decision*making OR resource allocation OR ration*)

The results from the searches were assessed by one reviewer for inclusion. A document was included if it fit within the scope of the questions posed for the rapid synthesis.

For each systematic review we included in the synthesis, we documented the focus of the review, key findings, last year the literature was searched (as an indicator of how recently it was conducted), methodological quality using the AMSTAR quality appraisal tool (see the Appendix for more detail), and the proportion of the included studies that were conducted in Canada. The methodological quality of primary studies and non-systematic reviews was not appraised due to the shortened timeframe required to conduct a rapid synthesis. We have, however, documented the focus of the study, methods used, a description of the sample, the jurisdiction(s) studied, key features of the intervention, and key findings. We then used this extracted information to develop a synthesis of the key findings from the included reviews and primary studies.

WHAT WE FOUND

We identified a total of 19 relevant documents by searching two databases (Health Systems Evidence and PubMed), with the search strategy for these databases detailed in Box 2. We identified one systematic review, three non-systematic review, four primary studies, and 11 frameworks for decision-making for clinical genetic tests. In addition, we undertook a scan of 16 comparator jurisdictions that were pre-determined by the requestor. These included each Canadian province (other than British Columbia which is where the synthesis was requested from), Australia, New Zealand, the United Kingdom and four of the largest HMOs in the United States (Anthem, Blue Cross Blue Shield, Cigna and United Healthcare). For these jurisdictions we identified (where possible) what genetic tests are publicly provided, for whom, and how they are paid for. To conduct the scan, we purposefully sampled websites from each of the jurisdictions. This included reviewing the websites of the government agency responsible for health in each jurisdiction, as well as key agencies or organizations involved in providing insurance for or delivering genetic-testing services in each jurisdiction to identify the schedule of benefits. For the purpose of this rapid synthesis, we have conceptualized genetic testing as the provision of a test that can identify changes in chromosomes, genes or proteins, which may be related to a genetic condition or genetic disorder.(4) We provide more details about each of the reviews and primary studies in Appendix 1 and 2, respectively.

In comparator jurisdictions, what clinical genetic tests are publicly offered and what payment models are used to support their delivery?

We provide a summary of the results of the jurisdictional scan in Table 1 in terms of what genetic tests are publicly provided, for whom, and how they are paid for in each jurisdiction. Given that our scan consisted of a purposeful sampling of key websites in each jurisdiction (as described above), Table 1 may not provide a comprehensive overview of clinical genetic testing, but rather a broad outline of key characteristics.

While some information was found about public coverage for clinical genetic testing for specific conditions or populations (e.g., prenatal testing for pregnant women), relatively little information was found about exactly what tests are covered and under what circumstances. The challenge of finding information may be indicative of a broader problem across health systems of not consistently sharing information on what genetic tests are publicly funded and how the funding decisions have been made. This may be a result of the decisions about what genetic tests to fund being closely linked to priorities in funding research protocols, such as research being undertaken at the B.C. Cancer Agency or B.C. Women's Hospital and Health Centre. While tests being conducted as part of this research may account for a large proportion of genetic tests being conducted in the province, examining these research grants was beyond the scope of this rapid synthesis and have therefore not been included in our findings.

In most jurisdictions, genetic testing is covered when it is deemed medically necessary by a qualified health professional, when no other alternative exists, and when the results of the genetic test have an impact on clinical decision-making. In most cases this includes both predictive (or susceptibility) testing which is used to identify which people have a higher change of getting a disease before symptoms appear (e.g., BRAC 1/2 gene testing).(5) However, an exact definition for what is considered medically necessary has not been provided by any of the sources reviewed for this rapid synthesis. A report developed as a part of the Commission on the Future of Health Care in Canada provides some insights into a definition, including that medically necessary services are those that will improve the health of an individual. In terms of the qualified health professional, this is considered to be a referral from a family physician or specialist to a genetic counsellor who in most jurisdictions acts as the gatekeeper to genetic tests and relays results.

Compared to the other jurisdictions, the four large HMOs in the United States that we reviewed (Anthem, Blue Cross Blue Shield, Cigna and United Healthcare) provided more information than other jurisdictions about what tests are covered and for what populations.

In all jurisdictions that we reviewed, genetic tests are paid for in full under public insurance plans when medically necessary, but the HMOs reviewed in the United States require the payment of a deductible or co-pay for all eligible individuals. Genetic tests that are not medically necessary, or for which no referral has been made, are paid for either entirely out-of-pocket, or may be covered in part by private or employer-based insurance. Non-medically necessary genetic tests include those to determine food sensitivities, genetic testing for fertility treatments (with the exception of some availability in the U.K.), or direct-to-consumer personal genetic tests.

Despite not identifying comprehensive lists of genetic services available in each jurisdiction, Table 1 presents the information we were able to retrieve about what tests may be publicly covered in each comparator jurisdiction, for whom, and how they are paid for.

Table 1: Jurisdictional scan of public coverage for genetic tests

Jurisdiction	What is covered?	For who?	How is it paid for?
Canada			
• Alberta	• Genetic testing is generally covered by provincial health plans (6-8) • Genetic tests that may be publicly covered include predictive testing, prenatal and newborn screening, late-onset disease testing, diagnostic testing, and individual pharmacogenomic testing (8-10)	• Genetic testing is generally covered by provincial health plans for those who meet test-specific conditions, and where a recommendation has been made by a physician (11) • The Alberta Newborn Metabolic Screening Program covers all babies born in Alberta (9)	• When eligibility requirements are met the cost of the genetic testing is paid in full through the Alberta Health Care Insurance Plan (6) • In some instances, private genetic services may be purchased by individuals paying the cost entirely out-of-pocket or, in some select cases, through private or employer-based insurance
• Saskatchewan	• Genetic testing is generally covered by provincial health plans (12) • Genetic tests that may be publicly covered include predictive testing, genetic testing for cancer, prenatal testing, and preconception genetic testing or counselling for individuals at high risk of a genetic mutation (13) • Pre-symptomatic testing for adult onset conditions and carrier testing are not offered to those under the age of 18 (12)	• Genetic testing is generally covered by provincial health plans for those who meet specific referral guidelines for genetic testing and have a referral from a qualified health professional (12) • Prenatal screening is available to all pregnant women in Saskatchewan (12;13)	• When eligibility requirements are met, the cost of the genetic testing is paid in full through Saskatchewan Health (12) • In some instances, private genetic services may be purchased by individuals paying the cost entirely out-of-pocket or, in some select cases, through private or employer-based insurance (14)
• Manitoba	• Genetic testing and counselling are generally covered by the provincial health plan • Genetic tests that may be publicly covered include predictive testing, diagnostic testing, prenatal testing, genetic testing for metabolic conditions, and testing for hereditary cancers (15;16) • Pre-natal screening offered to all pregnant women includes a Maternal Serum Screen as well as an amniocentesis (15)	• Genetic testing is generally covered by provincial health plans for those who meet specific referral guidelines for genetic testing and have a referral from a qualified health professional (15;16) • Prenatal screening is available to all pregnant woman in Manitoba, with additional screening available for those who meet the necessary criteria (15)	• When eligibility requirements are met the cost of genetic testing is paid in full through Manitoba Health • In some instances, private genetic services may be purchased by individuals paying the cost entirely out-of-pocket or, in some select cases, through private or employer-based insurance
• Ontario	• Genetic testing and counselling are covered by the provincial health plan (OHIP) (17) • Genetic tests that may be publicly covered include predictive testing, diagnostic testing, prenatal testing, genetic testing for metabolic conditions, and testing for hereditary cancers (18)	• Genetic testing is covered for all residents of Ontario carrying a valid OHIP card when deemed medically necessary. • Extended prenatal screening and prenatal diagnostic testing are covered for those that meet certain risk-based	• When eligibility requirements are met, the Ontario Health Insurance Program and other programs such as Multiple Marker Screening Program cover the cost of genetic testing in full (23) • In some instances, private genetic services may be paid for out-of-pocket or, in some select cases, through private or employer-based insurance

	• Predictive or susceptibility tests such as the BRCA1/2 breast cancer genetic test are covered if individuals meet specific criteria regarding personal medical history or family history (19) • Genetic testing for fertility treatments are not covered by OHIP (20)	criteria, like the age of the mother and family history, or have abnormal ultrasound findings (21;22)	
• Quebec	• Genetic testing and counselling are covered by provincial health plans • Genetic tests that may be publicly covered include predictive testing, diagnostic testing, prenatal testing, and testing for hereditary cancer (24) • The Quebec Newborn Blood Screening Program screens for type 1 tyrosinemia, phenylketonuria, congenital hypothyroidism, and medium-chain acyl-CoA dehydrogenase deficiency (25) • When a genetic test has been recommended by a physician but is not available in Quebec, individuals are eligible to submit a request for the test to be covered and provided (24)	• Genetic testing is covered for all residents of Quebec when deemed medically necessary (25) • The Quebec Newborn Screening Program is for all newborns and adopted children of parents covered by the Quebec Health Insurance Plan (25) • Genetic screening tests for tyrosinaemia, congenital lactic acidosis, hereditary motor and sensory neuropathy, recessive spastic ataxia of Charlevoix Saguenay, and cystic fibrosis are covered for individuals who already have a known case in their family or has a partner known to be a carrier (26)	• When eligibility requirements are met, the cost of genetic testing is paid in full through l'assurace maladie Quebec • In some instances, private genetic services may be paid for out-of-pocket or, in some select cases, through private or employer-based insurance
• Nova Scotia	• Genetic testing and counselling are covered by provincial health plans • Genetic tests that may be publicly covered include predictive testing, diagnostic testing, prenatal and pediatric testing, testing for metabolic disorders, and testing for hereditary cancer (27) • Newborn screening is offered for 15 or more inherited disorders (28)	• Genetic testing is generally covered for all residents of Nova Scotia when deemed medically necessary	• When eligibility requirements are met the cost of genetic testing is paid in full through Nova Scotia's Medical Services Insurance • In some instances, private genetic services may be paid for entirely out-of-pocket or, in some select cases, through private or employer-based insurance.
• New Brunswick	• Details not identified from publicly available sources on websites reviewed	• Details not identified from publicly available sources on websites reviewed	• Details not identified from publicly available sources on websites reviewed
• Prince Edward Island	• Details not identified from publicly available sources on websites reviewed	• Details not identified from publicly available sources on websites reviewed	• Details not identified from publicly available sources on websites reviewed
• Newfoundland and Labrador	• Details not identified from publicly available sources on websites reviewed	• Details not identified from publicly available sources on websites reviewed	• Details not identified from publicly available sources on websites reviewed

• United Kingdom	• Genetic testing and counselling are covered under National Health Insurance • Genetic tests that may be publicly covered include diagnostic testing, predictive testing at all ages, prenatal testing, targeted investigations for risk-assessment and management of conditions, genetic testing and familial counselling for hereditary conditions (29)	• Clinical genetics provides services for any individual or family affected by, or at risk of, a genetic disorder or congenital abnormality (29) • Specifically, the services will cover any patient (adult or child) referred to a Clinical Geneticist or an appropriately registered Genetic Counsellor who meets agreed referral pathway or standards (29)	• When eligibility requirements are met, the cost of genetic testing is paid in full through U.K. National Health Service (29) • In some instances, private genetic services may be paid for entirely out-of-pocket or, in some select cases, through private or employer-based insurance.
• Australia	• Most genetic testing and counselling are covered under the Medicare Benefits Schedule • For prenatal testing, these include cytogenetics, alpha feto protein and related biochemical markers, and ultrasound derived nuchal translucency (30) • For DNA genetic tests the schedule of benefits funds four items, including testing for haemochromatosis, Factor V Leiden, protein C or S deficiencies, and antithrombin 3 deficiency (30)	• Medical genetic testing typically requires referral from a medical practitioner as well as pre-test and post-test counselling (31) • Diagnostic testing is typically covered for those referred to a laboratory to confirm a clinical observation, or those that are descendant from an individual known to have a hereditary condition (31) • The request pathway for kinship testing is less regulated, and is generally available without referral or counselling (31) • Genetic tests purchased online are not covered by Medicare (31)	• When eligibility requirements are met, the cost of genetic testing is paid in full through Medicare • In some instances, particularly for genetic tests to confirm kinship or where a referral has not been provided, private genetic services may be paid for entirely out-of-pocket or, in some select cases, through private or employer-based insurance
• New Zealand	• Genetic tests that may be publicly covered include diagnostic testing, predictive or susceptibility testing, presymptomatic testing, preconception and carrier testing, prenatal testing, preimplantation screening, and testing for somatic mutations in pathological tissues from cancer patients (32;33)	• Genetic tests are covered for individuals of all ages provided the individual meets the eligibility requirements and has been referred by a qualified health professional (34)	• When eligibility requirements are met, the cost of genetic testing is paid in full through the National Health Board (34) • In some instances, private genetic services may be paid for entirely out-of-pocket or, in some select cases, through private or employer-based insurance
United States			
• Blue Cross Blue Shield	• Coverage is state-, plan- and test-specific • Genetic tests that may be covered include diagnostic testing, susceptibility testing, pre-symptomatic testing, carrier testing, prenatal testing, companion testing, pre-implantation	• Individuals being tested must meet a set of indication/disease-specific criteria (e.g., close relative has disorder), and the results of the test must have an impact on the treatment	• Payment for genetic tests is dependent on the insurance plan that is chosen by the individual, with most medically necessary genetic tests covered after co-pays and deductibles

	screening, and testing for somatic mutations in pathological tissues from cancer patients (35-38) • General population screening and self-testing kits are not covered (35; 36; 38)	or outcomes of the individual or their offspring • Genetic testing is covered only when the test is considered medically necessary • Tests are not medically necessary if they are not appropriate for the disease, are performed for convenience, or if results can be determined through other conventional tests (35; 37; 38)	
• Anthem	• Coverage of genetic tests varies by condition and plan • Individuals are potentially eligible for diagnostic testing, susceptibility testing, pre-symptomatic testing, carrier testing, prenatal genetic testing, companion testing, pre-implantation screening, and testing for somatic mutations in pathological tissues from cancer patients (39-41)	• Individuals being tested must meet indication/disease- and test-specific criteria • To be eligible for insurance coverage the results of the test must have a direct impact on clinical decision-making (39-41)	• Payment for genetic tests is dependent on the insurance plan that is chosen by the individual, and most medically necessary genetic tests are covered after co-pays and deductibles (39-41)
• Cigna	• Coverage of genetic tests varies by condition and plan (42) • Newborn screening for genetic disorders is covered in accordance with state mandates (42) • Susceptibility tests such as the BRCA1/2 breast cancer genetic test are covered if individuals meet specific criteria regarding personal medical history or family history (42) • General population screening is not covered (42)	• Tests outside of prenatal screening require recommendations for testing from certified providers and must be delivered by certified providers (42) • Individuals must meet indication and/or disease-specific criteria for requesting the genetic test (42) • To be eligible for insurance coverage the results of the test must have a direct impact on clinical decision-making (42)	• Payment for genetic tests is dependent on the insurance plan that is chosen by the individual, and most medically necessary genetic tests are covered after co-pays and deductibles.
• United Healthcare	• Coverage varies widely by test and by state (43) • Screening services, like predictive and pre-symptomatic genetic tests and services, that are used to detect an undiagnosed disease or disease predisposition, are not covered (43)	• Individuals must meet set disease and test-specific criteria (43)	• Coverage for genetic tests is available with co-pays and deductibles paid for by the individual (43)

What does the evidence say about the processes or criteria for determining whether and when clinical genetic tests should be publicly available, and how this has been implemented in comparator jurisdictions?

We found one systematic review,(44) three non-systematic review,(45-47) four primary studies,(48-51) and 11 frameworks (52-63) that address the question above by proposing a range of criteria and types of evidence that should be used to make decisions on what genetic tests to fund and under what conditions.

Findings from reviews and primary studies

In searching the literature, we identified eight documents (one systematic review, three non-systematic reviews, and four primary studies) that answered the question above. These documents focus broadly on: the principles that could be used to underpin decision-making; the criteria that should be taken into account; and the challenges and facilitators of effective evaluation and decision-making in allocating resources to clinical genetic tests.

One of the non-systematic reviews classified normative principles for allocating resources into four categories of value-based decisions that could guide choices about what genetic tests to fund:

- needs-based allocation;
- maximizing total benefits;
- treating people equally; and
- rewarding social usefulness.(45)

One primary study based on semi-structured interviews with genetic health service providers and one non-systematic literature review focused on defining criteria that should be taken into account when making decisions about publicly-funding genetic tests, including:

- evidential basis;
- cost-effectiveness;
- access to appropriate equipment;
- availability of preventive strategies following the test;
- equity in access to new technologies; and
- length of wait times for the test.(46; 48)

Similarly, another more recent study conducted interviews with those involved in making funding decisions for genetic testing in Canada and found the clinical utility of the test was rated as being the most important criteria in decision-making. Participants in the study highlighted that public coverage of genetic testing should prioritize tests that confirm a clinical diagnosis or provide prognostic information.(49)

In relation to cost considerations of genetic tests, one older medium-quality systematic review and one non-systematic literature review identified features of high-quality economic evaluations of clinical genetic tests, including:

- a well-defined question specifying a viewpoint, the time period, relevant costs and consequences, and the alternatives to be compared;
- consideration has been given to how costs may differ in the short term, long term and across populations;
- a comprehensive description of the competing alternatives, including not only other clinical genetic tests but also more generally what other alternatives exist for achieving population health objectives, has been developed;
- the effectiveness of technologies or services being compared is established;
- the importance and relevant costs and consequences for each alternative are identified by using a range of perspectives;

- costs and consequences were valued appropriately;
- an incremental analysis of costs and consequences of alternatives was performed;
- allowances were made for uncertainty and variability of estimated costs and consequences; and
- the economic evaluation includes consideration for possible issues to patients including ethical, social and legal implications.(44; 47)

More generally, one primary study examined the challenges and facilitators of making coverage decisions for genetic tests based on findings from a facilitated workshop with senior level decision-makers. The study identified the following six challenges:

- unclear standards of what is good enough to merit coverage;
- missing or ambiguous information about the technology and its evaluations;
- timeliness of available information and evaluations of the test;
- differing interpretations of value for money among decision-makers and stakeholders;
- keeping coverage decisions up to date with changes in the technology's' purpose, effects and costs;
- understanding social values of patients.(47; 50)

Another primary study used structural equation modelling to examine the components of the decision-making process and examined 55 coverage decisions of newborn genetic screenings. The study found stakeholder participation and transparency improved the reasonableness of coverage decisions, and transparency in decision-making was associated with improvements in the methodological rigour of the decision-making process.(51)

Findings from analytical and evaluative frameworks

In addition to the literature above, we identified 11 theoretical frameworks to guide the evaluation of clinical genetic tests. Of the frameworks found, the oldest example was developed by Wilson and Junger and includes the following three criteria:

- that the condition should be an important health problem;
- there should be a test that is suitable to detect the disease at an early or latent phase; and
- there needs to be an accepted treatment for the condition once detected.(64)

Since its development, other frameworks (including those presented below) have built off of this work by tying qualitative or quantitative measures to each criterion. While frameworks differ in the exact criteria that they have identified, the frameworks generally agree on the need to determine the analytical validity, clinical validity or clinical utility of a test as well as the ethical, social and legal implications of genetic testing.(63)

These four elements underpin the most frequently cited framework - the ACCE (an acronym that stands for its four components: analytical validity, clinical validity, clinical utility, and ethical, social and legal implications) – which is the basis for three other frameworks that are included in Table 3 and Table 4 (U.K. Genetic Testing Network, Andalusian Agency for Health Technology Assessment Framework, and the European Network Framework for Public Health Genomics).(52)

All of the frameworks draw on randomized control trials (RCTs) as the primary evidence base for evaluating genetic tests.(52) The frameworks specify that, where possible, the RCTs should provide direct evidence (i.e., a clear link between the evidence and an outcome without an intervening inference) between the test and both laboratory and clinical outcomes. In recognizing the limitations of evidence in this area, some of the frameworks suggest that where high-quality indirect evidence (i.e., where a link between the evidence and an outcome require an inference) exists, this could be used in its place. Interestingly, one framework, the European Network Framework for Public Health Genomics, calls on the use of a Constructive Technology Assessment (CTA) as an evidence base from which to evaluate the impact of genetic tests.(55) A CTA

examines the social challenges surrounding the adoption and use of technology and can take the form of dialogue workshops, consensus conferences, public debates, scenario workshops, or citizen reports.(55)

The first step in the process of applying each of the frameworks is to identify the relevant clinical scenario, the test of interest, and the population of interest.(65) In establishing this, common measures included in the frameworks were:

- pattern of inheritance of a disease;
- mutation spectrum including prevalence of the mutation;
- whether there are other tests currently available; and
- how the test can be used (i.e., diagnosis, treatment, prognosis).(65)

Other common criteria for evaluation are defined in Table 2.

Table 2: Common criteria used across frameworks for evaluating genetic tests (adapted from the Canadian Agency for Drugs and Technologies in Health)(66)

Criteria	Definition	Examples of measurements/considerations included in the 10 frameworks
Analytical validity	The accuracy with which a laboratory test is capable of identifying a genetic variant	• Precision • Reliability (reproducibility) • Sensitivity • Specificity • How measures compare to existing diagnostic methods in a laboratory setting
Clinical validity	The accuracy with which a test predicts a certain clinical outcome	• Diagnostic specificity • Diagnostic sensitivity • Positive predictive value • Negative predictive value • Likelihood ratio • Clinical relevance • How it compares to other diagnostic methods
Clinical utility	The probability that performing a test will have an effect in terms of health, considering both the effects of positive and negative results	• Internal validity • External validity • Anticipated benefit and risk of using the test • How it will add to the treatment of the patient • How it will change the patient's health outcomes • Whether it affords an advantage over existing methods • Consequences of false positive and false negatives
Ethical, social and legal implications	Examination of the possible consequences of genomic research in the use of genetic information, integration of new genetic technologies, issues surrounding the design and conduct of genetic research, and the education of healthcare professionals, policymakers and students about genetics and genomic research	• Stigmatization and discrimination from test results • Consent and ownership of data • Safeguards to protect information • Repercussions on family members • Opportunity cost of choosing to fund this test • Licensing of the technology • Reporting requirements
Economic considerations	Direct and indirect costs of choosing to develop, fund and publicly provide select genetic tests	• Cost-effectiveness • Cost-utility • Opportunity cost • Replacement costs of existing technology • Labour cost of development • Cost of professional services, healthcare follow-ups, and expertise

Two primary limitations for the application of these frameworks were also identified. First, each has different scopes of genetic tests or health technologies for which they can be used. Specifically, many of these frameworks have particular scopes that may limit their use for evaluating certain genetic tests. Of the 11 frameworks identified, the Frybeck-Thornbury hierarchy and the USPSTF are used for healthcare technologies more generally, and therefore may have some criteria that are not specific to the outcomes of genetic testing, for example assessing morbidity and mortality.(65) Further, other frameworks such as ACCE and Genetic testing Evidence Tracking Tool (GETT) have been developed to be used for single gene tests and may be difficult to extend to multi-gene panels.(65) Second, most of the frameworks do not provide guidance on how value judgments (e.g., how to weigh the criteria in each framework) should be made. Instead, these frameworks assist decision-makers to identify where there is a lack of evidence in evaluating the genetic test and compare these findings against existing alternatives.

The tables below provide an overview of the frameworks (both analytical and evaluative) found in the literature, their scope (e.g., for what types of tests they can be used), where they are (or have been used) and the criteria that they identify. The frameworks have been divided into two tables based on whether they present an analytical (Table 3) or evaluative framework (Table 4). A scoping review conducted by the Department of Health and Human Service's Agency for Healthcare Research and Quality (AHRQ) distinguished these two types of frameworks by noting that analytical frameworks provide key questions for those evaluating tests to consider (e.g., ACCE).(54) This is in contrast to evaluation frameworks that instead focus on the types of evidence necessary for evaluating the test, and provide conceptual guidance on principles that should underpin an evaluation (e.g., McMaster University Evaluation Framework).(54) While the analytical and evaluative frameworks provide separate approaches to taking stock of the evidence that exists for a particular genetic test, both the McMaster Evaluative Framework and the Frybeck-Thornbury framework have some aspects that combine the two approaches. These frameworks, along with the other nine that were found, have been summarized in Table 3 and 4 below.

Table 3. Analytical frameworks for evaluating the use and public funding of genetic tests

Framework	Process	Criteria
U.S. Preventative Services Task Force *Jurisdiction:* U.S. *Scope:* All preventive services (e.g., screening, counselling, and preventative medications) (61)	• An independent, volunteer panel of national experts in prevention and evidence-based medicine is struck to assess the availability of direct and indirect evidence on a test based on available randomized control trials • Based on the noted benefits and harms (i.e., magnitude of benefit) combined with the certainty of the evidence (ranging from low to high), provide a letter grade between A and I • Letter grades are associated with a recommendation that determines whether or not the genetic test should be provided or funded	• Available RCTs on the genetic test are examined to determine: o health benefits and harms; o ethical, legal and societal issues; and o economic impact. • Once the evidence base has been summarized, the following questions are used to determine the quality of the evidence (referred to as the level of certainty in the framework that can vary along a continuum from low to high). o Do the studies have the appropriate research design to answer the key questions? o To what extent are the existing studies of high quality (e.g., internal validity)? o To what extent are the results of the studies generalizable to the general population (e.g., external validity)? o How many studies have been conducted that directly (or indirectly) address the question? o How large are the studies? o How consistent are the results of the studies? o Are there additional factors that assist in drawing conclusion?
ACCE Evaluation Framework *Jurisdiction:* U.S./ U.K. (adapted) *Scope:* Emerging genetic tests (53)	• Collecting, evaluating, interpreting and reporting on direct evidence (RCTs) for genetic tests based on 44 questions across the five criteria of: disorder/settings; analytical validity; clinical validity; clinical utility; and ethical, legal, societal implications • The ACCE was intended to identify gaps in knowledge on the evidence of certain tests in efforts to provide and to push forward a research agenda	• Disorder/settings (e.g., defining clinical disorder; clinical setting in which test will be performed; DNA tests associated with the disorder; stand-alone test or a series of tests) • Analytic validity (e.g., qualitative or quantitative; sensitivity of test; specificity of test; internal validity) • Clinical validity (e.g., sensitivity in clinical settings; specificity in clinical settings; prevalence of the disorder; external validity) • Clinical utility (e.g., natural history of the disorder; impact of test on patient care; diagnostic tests currently available; action or measurable benefit following test) • Ethical, legal, societal implications (e.g., stigmatization and discrimination of testing or diagnosis; legal issues regarding consent and ownership of data; safeguards currently in place)
The Evaluation of Genomic Application in Practice and Prevention Framework (EGAPP) *Jurisdiction:* U.S. *Scope:* prioritizes pharmacogenomics tests and genetic tests	• An independent panel of 16 multidisciplinary members undertakes a topic selection (e.g., genetic test or condition) • Once selected, an analytical framework is used that provides key questions on how to frame the evidence review and a clinical scenario • A systematic review of the evidence is then undertaken including reviewing the level of certainty (adapted from USPTF	• Is there direct evidence that using the test leads to clinically meaningful improvement in outcomes or in medical or personal decision-making? • The following questions outline an indirect-evidence pathway to demonstrate clinical utility when good-quality direct evidence is unavailable. o How valid and reliable are available tests? o How well will the tests predict outcomes? o What actions should be based on results? o What benefits and harms are associated with the clinical use of the tests? o How should the medical community, public health and policymakers respond?

that can be used to diagnose common conditions (56)	framework)	
UK Genetic Testing Network *Jurisdiction:* U.K. *Scope:* Genetic tests for rare single gene disorders (60)	• Submission of a gene dossier for evaluation by the Genetic Test Evaluation Working Group, which consists of professionals from clinical genetics, clinical laboratory genetics and public health, as well as commissioning and patient groups • Testing criteria are submitted along with the gene dossier that define the appropriateness of the genetic test referral • Applications are then evaluated according to 19 key criteria (nine of which evaluate the test while an additional nine evaluate its impact on healthcare outcomes)	• Evaluation criteria (based on findings from RCTs) o Seriousness of the condition o Prevalence of the condition o The purpose of the test (e.g., diagnosis, treatment, prognosis and management, presymptomatic testing, and risk assessment) o The technical details of the test o The context in which the test is to be used (e.g., defined population groups) o The characteristics of the test (e.g., clinical sensitivity, specificity and predictive value) o The clinical utility of the test (e.g., how it adds to patient management and the availability of alternative diagnostic procedures) o Ethical, legal and social implications o Price of the test • Prioritizes healthcare outcomes o Alerts significant clinical comorbidities o Reduces mortality o Avoids diagnostic procedures, tests or multiple hospital appointments o Confirms targeted therapy or management o Earlier diagnosis allowing commencement of earlier treatment o Avoids irreversible harm o Enables access to educational and social support o At-risk family members who test negative for a familial mutation can be discharged from follow-up o At-risk family members who test positive have appropriate follow-up o Avoids incorrect management
Andalusian Agency for Health Technology Assessment Framework *Jurisdiction:* Andalusia, Spain *Scope:* genetic tests requiring DNA or RNA (52)	• Modified criteria from the ACCE based on three phases of transitioning the development of genetic tests into clinical practice: 1) phase of research into the performance of the genetic test; 2) phase of clinical research into the result of genetic tests; and 3) phase of research into the impact on health services and onto the population receiving the test • The framework is dependent on the use of high-quality clinical trials (e.g., RCTs) to assess the analytical validity, clinical validity and clinical utility of the genetic tests	• Define the clinical condition where the genetic test will be used (Phase 1) • Phase 1: Assess existing scientific literature for analytical validity, including: o reliability of the test; and o sensitivity, specificity and predictive values • Phase 2: Assess existing scientific literature for clinical validity, including: o external validity o internal validity; and o clinical relevance • Phase 2: Assess existing scientific literature for clinical utility, including: o whether the test affords some advantage over existing methods; and o whether the test shows a benefit for monitoring the defined condition • Phase 3: Assess the social repercussions and ethical implications (e.g., potential to use the information to discriminate against patients; eugenics; repercussions on family members) • Phase 3: Estimate the economic and organizational impact, including:

		○ costs associated with the genetic test itself; ○ genetic counselling services; and ○ care and treatment for those requiring follow-up after the test
The Genetic Evidence Testing Tool (analytical framework) *Jurisdiction:* Not specified *Scope:* Used for any molecular genetic test (59)	• Once a specific disease is chosen, a list of 72 defined items and questions grouped into 10 categories and 26 sub-categories structure the identification evidence to determine whether there is a sufficient body of knowledge to make prioritization and funding decisions on the available tests • There is no specified way of moving through the 72 questions	• Overview of the disease: Epidemiology and genetics ○ Disease prevalence ○ Disease outcomes ○ Clinical management and treatment ○ Costs associated with disease ○ Pattern of inheritance ○ Genetic heterogeneity ○ Mutation prevalence ○ Mutation penetrance ○ Neomutation rate • Diagnostic tools ○ Approaches other than molecular ▪ Methods ▪ Analytical validity ▪ Clinical validity ▪ Infrastructure and costs ○ Molecular approaches ▪ Methods ▪ Analytical validity ▪ Clinical validity ▪ Infrastructure and costs ▪ Interpretation ▪ Consensus or best practice guidelines • Quality-improvement program ○ Internal ○ External • Clinical utility ○ Objectives • Screening or diagnostic strategies • Impacts on the health system ○ Foreseeable needs for testing ○ Costs ○ Test accessibility ○ Availability and accessibility of professional services, healthcare and follow-up, expertise and training • Psychological and social aspects of the analysis • Ethical and legal aspects of the analysis

		• Synthesis • Research priorities • References

Table 4. Evaluative frameworks for evaluating the use and public funding of genetic tests

Framework	Process	Criteria

McMaster University Evaluation Framework (evaluative framework)
 	
Jurisdiction: Ontario
 	
Scope: New predictive genetic tests (62)
	• Specifies three domains for decision-makers to consider (i.e., evaluation criteria, acceptable cutoffs and conditions on coverage) as well as a set of questions for evaluating the effectiveness, efficiency, normative issues and technologic assembly
	• Framework should be worked through in order
		• Evaluation criteria
		  ○ Effectiveness and efficiency questions
		  ▪ Does the technology work?
		  ▪ Is it cost effective?
		  ○ Normative questions
		  ▪ Do individuals want it?
		  ▪ Does the community want it on behalf of individuals?
		  ▪ Is it equitable to cover this technology at the expense of other things?
		  ▪ Is the technology otherwise ethical?
		  ○ Assembly questions
		  ▪ What is the technology and what is it for?
		  ▪ How is it situated?
		  ▪ Who has developed the technology and who is it for?
		• Acceptable cutoffs
		  ○ What process will be used to define the cutoffs for funding the test? This could include:
		  ▪ the application of a consistent abstract principle (e.g., acceptable cost per life-year gained)
		  ▪ existing precedents from similar tests
		  ▪ comparison of evaluation criteria to those of other technologies already covered
		• Conditions on coverage
		  ○ Clarification of the purpose of the test
		  ○ Improved research protocols
		  ○ Set periodic re-evaluation of evidence
		  ○ Enhanced interventions into personal, family and societal effects
		  ○ Published clinical-practice protocols and guidelines
		  ○ Ethics protocols
		  ○ Legal regulation
		  ○ Priority setting

Fryback-Thornbury Hierarchic Model of Efficacy	• Describes six levels of efficacy for diagnostic tests in a hierarchy of evidence
	• RCTs are used to determine
		• Technical efficiency
		  ○ In the laboratory setting, does the test measure what it intends to measure?
		• Diagnostic accuracy efficacy
		  ○ What are the medical characteristics of the test?

(evaluative framework) *Jurisdiction:* U.S. *Scope:* All diagnostic tests (58)	answers to each of the questions in each level • The intention of the framework is to determine the continuum of efficacy for each diagnostic test	○ Does the test result distinguish patients with or without the target disorder? • Diagnostic thinking efficacy ○ Does the medical test help clinicians come to a diagnosis? ○ Does the test change the clinician's estimate of the probability of a specific disease? • Therapeutic efficacy ○ Does the medical test aid in planning treatment? ○ Does the medical test change or cancel planned treatments? • Patient outcome efficacy ○ Do patients benefit from the use of the test? ○ Do patients who undergo this test fare better than similar patients who are not tested? • Societal efficacy ○ What is the cost-benefit or cost-effectiveness of the test?
Evaluation framework for genomic test development *Jurisdiction:* All clinical genetic tests *Scope:* Not reported (63)	• Specifies six phases in the development of genetic tests as well as a specific criteria that can be used to identify knowledge gaps in the literature at each phase for the relevant decision-makers • This framework is meant for diverse stakeholders across the entire lifespan of the technology, including genetic test developers to evaluate initial performance, and policymakers to determine funding priorities	• Marker identification and assay development (e.g., establish association between biomarkers and outcomes of interest; develop assay based on identified biomarkers) • Initial test performance and assay refinement (e.g., diagnostic accuracy; association with development outcome; association with drug metabolism or pathophysiological response in a broader population) • Test validation and generalizability (e.g., diagnostic accuracy in a broader population; association with development of outcome in a broader population; association with drug metabolism or pathophysiological response in a broader population) • Clinical test performance and health impacts (e.g., effects on outcomes in patients or their relatives; effects on management of risk level or patient outcomes, clinical outcomes in those with and without treatment selection or treatment response guided by the test) • Comparison with existing tests (e.g., diagnostic efficacy or accuracy compared to existing tests; reclassification compared to existing risk scores or prediction models; treatment selection or response compared to existing tests) • Population impacts (e.g., implication of effects on family/community/society; large-scale implementation feasibility; ethical, social or legal issues)
EuroGenTest framework for prioritizing clinical genetic-testing services *Jurisdiction:* Not specified *Scope:* All clinical genetic tests (3)	• Specifies three broad criteria, with seven sub-criteria that should be used to compare evidence across clinical genetic tests and prioritize tests for funding • No quantitative ranking has been completed for how to weigh the criteria in the framework, and could be completed through a consensus process across stakeholders involved in the evaluation	• Medical benefit ○ Clinical benefit for tested individual ○ Non-clinical benefit for the tested individual ○ Benefit for family members ○ Likelihood of developing the disease ○ Time window in which individual can benefit from the test • Health need ○ Severity of the disease ○ Progression of the disease • Costs

Public Health Genomics European Network framework for public heath genomics
 	
Jurisdiction: Not specified
 	
Scope: Public health genetic testing (55)
	• Framework combines the use of health-technology assessments, health-needs assessments and health-impact assessments with the continuum of translational research
	• Continuum of translational research includes four phases that are necessary to translate genomic discoveries into healthcare and disease prevention, and each of these phases are mapped onto an assessment and should be completed in order
		• Phase 1: Determine whether new discoveries in the genomics field have useful applications for clinical and public health practice
		  ○ Undertake observational research and clinical trials using evaluation criteria set out in the ACCE (above)
		• Phase 2: Assess the value of a genetic test and translate this into guidelines
		  ○ Undertake a health-technology assessment that comprises:
		  ▪ critical analysis of the analytical and clinical validity of the test;
		  ▪ assessment of the utility;
		  ▪ determining the acceptability of the test and feasibility of its implementation for diagnostic and screening strategies;
		  ▪ undertaking an organizational analysis of the technology's interaction with healthcare delivery and services
		• Phase 3: Integrate evidence-based guidelines into health practice
		  ○ Undertake a health-needs assessment to identify how the genetic test can best be used in practice, which includes:
		  ▪ identifying a population of interest;
		  ▪ determining the aspects of health functioning and conditions that might have a significant impact on their health;
		  ▪ collecting information to describe the health problems and any identified inequalities in health and access to services; and
		  ▪ using this information to determine priorities for the most effective development or use of the genetic-testing technology.
		• Phase 4: Evaluate the health outcomes of a genomic application in practice on a population level
		  ○ Undertake a health-impact assessment to anticipate the impact of introducing genetic testing technologies, including:
		  ▪ identify the policies that will be affected by the introduction of the test;
		  ▪ identify the direct and indirect health effects to be considered;
		  ▪ assess the risks and benefits to the populations which may be affected (includes ethicial, legal and social implications, as well as those outside of the health field);
		  ▪ present the results to decision-makers; and
		  ▪ monitor and evaluate the consequences of implementation.

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APPENDICES

The following tables provide detailed information about the systematic reviews and primary studies identified in the rapid synthesis. The ensuing information was extracted from the following sources:

- systematic reviews - the focus of the review, key findings, last year the literature was searched, the proportion of studies conducted in Canada; and
- primary studies - the focus of the study, methods used, study sample, jurisdiction studied, key features of the intervention and the study findings (based on the outcomes reported in the study).

For the appendix table providing details about the systematic reviews, the fourth column presents a rating of the overall quality of each review. The quality of each review has been assessed using AMSTAR (A MeaSurement Tool to Assess Reviews), which rates overall quality on a scale of 0 to 11, where 11/11 represents a review of the highest quality. It is important to note that the AMSTAR tool was developed to assess reviews focused on clinical interventions, so not all criteria apply to systematic reviews pertaining to delivery, financial or governance arrangements within health systems. Where the denominator is not 11, an aspect of the tool was considered not relevant by the raters. In comparing ratings, it is therefore important to keep both parts of the score (i.e., the numerator and denominator) in mind. For example, a review that scores 8/8 is generally of comparable quality to a review scoring 11/11; both ratings are considered "high scores." A high score signals that readers of the review can have a high level of confidence in its findings. A low score, on the other hand, does not mean that the review should be discarded, merely that less confidence can be placed in its findings and that the review needs to be examined closely to identify its limitations. (Lewin S, Oxman AD, Lavis JN, Fretheim A. SUPPORT Tools for evidence-informed health Policymaking (STP): 8. Deciding how much confidence to place in a systematic review. *Health Research Policy and Systems* 2009; 7 (Suppl1):S8).

All of the information provided in the appendix tables was taken into account by the authors in describing the findings in the rapid synthesis.

Appendix 1: Summary of reviews on examining the public provision and funding of genetic tests

Type of review	Focus of review	Key findings	Year of last search/ publication date	AMSTAR (quality) rating	Proportion of studies that were conducted in Canada
Non-systematic literature review	Assess ethical and economic criteria to prioritize genetic services in a fair and reasonable manner (45)	The study classified principles for allocating healthcare resources into four categories: need-based allocation; maximizing total benefits; treating people equally; and promoting and rewarding social usefulness. The study discussed normative frameworks for healthcare funding systems that account for these categories and their application to the use of available genetic tests. Needs-based allocation When resources are scarce, the degree of an individual's need for medical intervention is an important criterion for allocation. The study described a 'health-related need,' which constitutes a gap between actual and desirable health states and is independent of whether there is anything that can be done to mitigate the gap, as well as a 'intervention need,' which requires that an intervention is available for which there is scientific evidence that can reduce the gap between the actual and desirable health state. The author noted that generally, the strength of evidence supporting the ability of a medical technology to ameliorate intervention needs is likely to be an important criterion in decision-making about medical technology. Additionally, the Department of Health of New South Wales distinguishes genetic tests of high or low priority based on their expected benefit. For example, diagnostic testing is considered high priority 'when confirmation of a clinical diagnosis will lead to changes in management of an affected person.' Maximizing total benefits Benefit maximization relates to the question of how many resources should be allocated to different health and intervention needs, and to what extent higher needs justify higher resource spending. The study described two major health economic schools of thoughts that provide different viewpoints for answering this question: welfare economics and extra-welfare economics. Welfare economics views patients as autonomous citizens and consumers whose welfare is to be maximized, whereas the extra-welfare economics perspective includes benefit measures other than individual welfare. Treating people equally Equity is a widely acknowledged criterion for fair prioritization of resources. For example, the expected benefit and cost-effectiveness of genetic tests may depend on specific characteristics of the target group, such as gender or ethnicity. However, stratifying patients by these criteria can raise legal and ethical concerns, and create undesirable inequities. Promoting and rewarding social usefulness The final category of principles for allocating limited resources is the promotion and reward of social usefulness. This can involve prioritizing resources to specific individuals to facilitate future usefulness, such as giving healthcare staff priority in the allocation of scarce influenza vaccine. It can also mean prioritizing specific individuals who have promoted important values	Not reported in detail	N/A	Not reported in detail

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		or have undergone specific sacrifices, such as allocating healthcare resources to those who have made healthy lifestyle choices. However, this category may raise several ethical concerns.			
Systematic literature review	Economic considerations for health insurance coverage of emerging genetic tests (62)	The systematic review undertook an analysis to inform a policy regarding the public insurance coverage of new genetic predictive tests in Ontario. The review identified four important areas of analysis for structuring a strong economic evaluation: asking an answerable questions; identifying costs and consequences; identifying alternatives; and determining a viewpoint <u>Asking an answerable question</u> Asking a well-defined answerable question, which includes a viewpoint, the relevant costs and consequences, and any alternatives that will be included in the comparison. <u>Identifying costs and consequences</u> Costs for an economic evaluation include both direct costs as well as indirect costs (e.g., labour costs for research and development of a genetic test). The review found that the cost of a genetic test may be affected by several dynamics including markets for laboratory services, provider behaviour and patient behaviour. In terms of the consequences of a genetic test, the review found that these come largely from assessing the clinical effectiveness of the genetic test. <u>Identifying alternatives</u> The review highlights that the conventional alternative is the status quo, or already-covered practices that serve the same clinical purposes. The clinical perspective for identifying alternatives should be whether a new genetic test is the best tool addressing the needs of genetically at-risk individuals and their families. The review however, also proposes that a population-health perspective should be used, in which case the test becomes whether allocating resources to the test represents better value than other services that pursue clinically different goals and address the needs of different sub-populations. <u>Determining a viewpoint</u> The final area of analysis is to determine a viewpoint, which includes determining what is relevant economic evidence. The view point for the economic evaluation could include that of an individual, a community, an insurer, a nation or a sub-population. In choosing the viewpoint from which the economic evaluation should be conducted, other important considerations include a timeframe for the evaluation (i.e., short, medium, or long term) and the level of equity in access to the new genetic test across affected individuals.	2002	5/9 (AMSTAR rating provided by McMaster Health Forum)	Not reported in detail

Type of review	Focus of review	Key findings	Year of last search/ publication date	AMSTAR (quality) rating	Proportion of studies that were conducted in Canada
Non-systematic literature review	Considerations in assessing and appraising predictive genetic tests (46)	The exploratory review outlines the major issues to consider for predictive genetic testing that may impact their benefits and harms, and outlines approaches to assessing these in a scientific manner. The review found medical benefits to include potential improvements in health outcomes, risk prediction for individuals and their family members, medical management of genetic conditions, as well as improvements in anxiety and mental and physical functioning. Genetic tests were also found to have harms that can be incurred with certain individuals. The exploratory review noted that harms were most clearly associated with diagnosis of Huntington's disease. Individuals who test positive may experience an immediate increase in health worries. These harms may also extend beyond the health sector to having implications for health and life insurance purchases and the privacy of information. The way that benefits and harms of genetic tests are to be assessed and weighted is likely dependent on whether the genetic test is used in symptomatic individuals or as predictive testing.	2010	N/A	Not reported in detail
Non-systematic literature review	Develop a set of criteria that could assist decision-makers in evaluating the cost effectiveness of genetic testing (47)	A cost-effectiveness genetic test meets key criteria. The genetic test should examine a gene that has a strong established association with a clinically relevant outcome. The variant allele prevalence should be high enough to warrant testing, with prevalence among different racial sub-groups specified. The results of the genetic test should also have a significant impact on the quality of life, mortality, or expensive medical care costs, and reduce the overall event rate as measured by the attributable risk reduction. Lastly, a rapid, reliable, and relatively inexpensive assay should be available. In order to assess these criteria, manufacturers should provide detailed clinical and economic information, and outcomes modelling. The criteria did not address ethical and psychological dilemmas, like impacts on health and life insurance.	Not reported in detail	N/A	Not reported in detail

Appendix 2: Summary of primary studies on examining the public provision and funding of genetic tests

Focus of study	Methods	Publication date	Sample description	Jurisdiction(s) studied	Key features of the intervention(s)	Key findings
Explore Canadian genetic health providers' perspectives on factors and criteria that influence resource allocation decisions for publicly funded predictive testing in Canada (48)	Semi-structured telephone or email interviews that included 13 questions	2009	The data was collected from a sample of 16 senior lab directors and clinicians at publicly funded Canadian predictive genetic testing facilities. Participants were from British Columbia, Alberta, Manitoba, Ontario, Quebec and Nova Scotia.	Canada	No direct intervention was implemented	The surveyed lab directors and clinicians indicated that predictive genetic tests were funded provincially by one of two predominant funding models. These included that either 1) the genetic testing comes out of the hospital budget, or 2) that predictive genetic tests are funded through the laboratory budget, which in turn is provided through local regional health agencies. In either model, those surveyed (e.g., lab directors and clinicians) played a significant role in determining how these funds were allocated across tests and services. Overall, the study found that largely local and ad hoc decision-making processes are being made in relation to resource allocations for predictive genetic tests.
Determine what funding systems have been developed across Canada and identify the criteria used to evaluate referred-out genetic testing (49)	Semi-structured interviews where participants were asked to describe the system in their respective jurisdictions for funding referred-out genetic testing and their decision-making criteria	2014	Data was collected from a purposive sample of 14 key individuals involved in approving funding for referred-out genetic testing in each Canadian province and territory.	Canada	No direct intervention was implemented	A referred-out genetic test is when samples are sent to laboratories outside of the jurisdiction where the patient lives. The study found that nine of 14 jurisdictions (64%) involve a genetic specialist in the funding decision-making processes. The remaining five jurisdictions that do not involve a genetic specialist do not have genetic services within their jurisdiction. Participants were asked to rate the importance of specific criteria in their decision for funding genetic tests on a scale of 1-5, with 5 being very important. Indication for testing was rated as the most important with an average score of 4.7. This supports the importance of clinical utility in the prioritization of resources for genetic testing. Participants from all jurisdictions indicated that testing that alters treatment is usually or always approved. Additionally, more than half of jurisdictions were reported to approve testing that will confirm a clinical diagnosis, provide prognostic information, or prevent additional testing.
Develop a decision-making framework for the coverage of new health technologies (50)	Through a facilitated workshop, senior-level Canadian decision-makers	2011	16 senior-level Canadian healthcare decision-makers	Canada		Six main issues with current processes were identified: timeliness; methodological considerations; interpretations of 'value for money'; explication of social values; stakeholder engagement; and accountability for reasonableness.

Focus of study	Methods	Publication date	Sample description	Jurisdiction(s) studied	Key features of the intervention(s)	Key findings
	discussed the strengths and weaknesses of international examples of technology funding decision-making processes. These findings were used to construct a technology decision-making framework.					The new framework guides the process of creating and maintaining the list of insured services. The first stage of the framework identifies and defines the decision problem. Key questions at this stage address the type of funding decision, the options available, the key players involved, and the timeline. The second stage of the framework deals with the decision-making process itself. Social value judgments, types of relevant information inputs and sources available, the criteria to be considered, and the mechanisms for appeals are determined. Finally, the last stage, the implementation of the decision, asks about the approaches to communicate recommendations or decisions to various stakeholder groups, the mechanisms to manage appeals to decisions, and the post-decision activities needed, like monitoring of technology. The framework addresses both the principles of procedural justice as well as outcome factors like cost-effectiveness. The framework is designed to be flexible enough for individual decision-making circumstances and contexts. However, its applicability to non-cancer technology decision-making processes is not clear.
Decision-making in coverage for newborn-screening programs (51)	Partial least squares path modelling was used to assess 55 coverage decisions on the extension of newborn-screening programs	2012	A data set of 55 coverage decisions made on newborn-screening technologies	European Union	Decision-making on the public coverage of newborn screening	The study found that the influence from the degree of stakeholder participation on reasonableness is about twice that of the degree of transparency. The degree of transparency of the decision-making was found to significantly influence the level of methodological standards for evidence assessment. The model used in the study supports the presence of three influences for decisions on newborn-screening technology in Europe: the influence of stakeholder participation on the degree of making reasonable coverage decisions; and the effect of stakeholder participation and transparency on the degree of scientific rigour of assessment.

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