Ontario Health

ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES

Genetic Testing for Familial Hypercholesterolemia: Health Technology Assessment

Key Messages

What Is This Health Technology Assessment About?
Familial hypercholesterolemia (FH) is an inherited condition in which affected individuals have very high levels of cholesterol in their blood. They have an increased risk of early onset of cardiovascular disease if they are not properly treated. People with FH can be identified clinically or by undergoing genetic testing. A genetic test for FH involves taking a small sample of DNA from the blood, saliva, or inside of the cheek to examine for the presence of the condition.

This health technology assessment looked at how effective genetic testing is in improving health outcomes and in identifying people with FH among the relatives of people who are confirmed by genetic testing to have the condition. It also looked at the cost-effectiveness and budget impact of publicly funding genetic testing for FH for people who are suspected of having FH or have a clinical diagnosis of FH, and also for their first-, second-, and third-degree relatives (known as cascade screening), as well as the experiences, preferences, and values of people with high cholesterol and or a diagnosis of FH.

What Did This Health Technology Assessment Find?
People who have received a positive result for their genetic test for FH are more likely to take appropriate intervention measures to improve their health than are people who received a clinical judgment only. Also, performing genetic testing on relatives of people who are genetically confirmed with FH can identify more people with the condition.

Compared to clinical evaluation without genetic testing, genetic testing would be cost-effective to confirm FH in individuals who have a clinical diagnosis of FH. Our economic analysis also found that genetic and lipid cascade screening are both cost-effective compared to no cascade screening. However, when compared with each other, genetic cascade screening is less cost-effective than lipid cascade screening. Publicly funding genetic testing for individuals with a clinical diagnosis of FH would have a budget impact of about $64 million (cost of test alone) in the next 5 years. However, if we consider improved health outcomes after genetic diagnosis, our analysis found that there would be a savings of about $141 million over that same time period. Publicly funding a genetic cascade screening program for relatives of people with a genetic diagnosis of FH would cost about an additional $66 million (cost of test alone). If we consider health outcome–related costs, the budget impact would be an additional of $73 million over the next 5 years.

Most people with a positive FH genetic test perceived the screening, diagnosis, and treatment for FH positively. Receiving a genetic diagnosis of the condition may contribute to higher adherence to treatment in an effort to control cholesterol levels. People we spoke with felt that greater awareness and education would allow for more efficient uptake of cascade screening.

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The statements, conclusions, and views expressed in this report do not necessarily represent the views of those we consulted.

A Note About Terminology

As a government agency, Ontario Health can play an active role in ensuring that people of all identities and expressions recognize themselves in what they read and hear from us. We recognize that gender identities are individual. Thus, in this health technology assessment, we use gender-inclusive pronouns and terms as much as possible. However, when citing published literature that uses the terms "male" and "female," we also use these terms for consistency with the cited studies.

Citation

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Abstract

Background

Familial hypercholesterolemia (FH) is an inherited disorder characterized by abnormally elevated low-density lipoprotein (LDL) cholesterol serum levels from birth, which increases the risk of premature atherosclerotic cardiovascular disease. Genetic testing is a type of a medical test that looks for changes in genes or chromosome structure to discover genetic differences, anomalies, or mutations that may prove pathological. It is regarded as the gold standard for screening and diagnosing FH. We conducted a health technology assessment on genetic testing for people with FH and their relatives (i.e., cascade screening). The assessment included an evaluation of clinical utility (the ability of a test to improve health outcomes), the diagnostic yield (ability of a test to identify people with FH), cost-effectiveness, the budget impact of publicly funding genetic testing for FH, and patient preferences and values.

Methods

We performed a systematic literature search of the clinical evidence. For evaluation of clinical utility, we assessed the risk of bias of each included study using the ROBINS-I tool and the quality of the body of evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria.

We performed a systematic economic literature search and conducted a cost-effectiveness and cost–utility analysis with a lifetime horizon from a public payer perspective. We assessed the cost-effectiveness of using genetic testing both for confirming a FH clinical diagnosis and for cascade screening in relatives of genetically confirmed cases. We evaluated the cost effectiveness of cascade screening strategies with genetic testing, sequential testing, and lipid testing approaches. We also analyzed the budget impact of publicly funding genetic testing in Ontario.

Results

We included 11 studies in the clinical evidence review. Overall, our review found that genetic testing to diagnose FH improves several health outcomes (GRADE: Moderate) compared with clinical evaluation without a genetic test. We also found that genetic cascade screening leads to a high diagnostic yield of FH.

According to our primary economic evaluation, genetic testing is a dominant strategy (more effective and less costly) compared with no genetic testing for individuals with a FH clinical diagnosis. It reduced the number of FH diagnoses, led to fewer cardiovascular events, and improved QALYs. For first-degree relatives of genetically confirmed cases, all cascade screening strategies (genetic testing, sequential testing, and lipid testing) were cost-effective when compared with no cascade screening in a pairwise fashion. The ICERs of cascade screening with genetic, sequential, and lipid testing compared with no cascade screening were $58,390, $50,220, and $45,754 per QALY gained, respectively. When comparing all screening strategies together, cascade screening with lipid testing was the most cost-effective strategy. At commonly used willingness-to-pay values of $50,000 and $100,000 per QALY gained, the probability of lipid cascade screening being cost-effective was 53.5% and 71.5%, respectively.

The annual budget impact of publicly funding genetic testing for individuals with a clinical FH diagnosis in Ontario ranged from a cost saving of $2 million in year 1 to $64 million in year 5, for a total of $141 million saved over the next 5 years, assuming the cost of genetic testing remains at $490 per person. If only testing-related costs were considered, the budget impact was estimated to be an additional cost of $7 million in year 1, increasing to $20 million in year 5, for a total cost of $64 million over the next 5 years. For relatives of genetically confirmed cases, publicly funding genetic cascade screening would lead to an additional cost of $5 million in year 1, increasing to $27 million in year 5,

for a total cost of $73 million over the next 5 years. If only testing-related costs were considered, the budget impact was estimated to be an additional of $66 million.

Conclusions

Genetic testing for FH has a higher clinical utility than clinical evaluation without a genetic test. It also results in a high diagnostic yield of FH through cascade screening. For individuals with a clinical diagnosis of FH, genetic testing would be a cost-saving and more effective diagnostic strategy. For relatives of index cases confirmed through genetic testing, genetic and lipid cascade screening are both cost-effective compared with no screening, but genetic cascade screening is less cost-effective than lipid cascade screening. We estimated that publicly funding genetic testing for individuals with a clinical diagnosis of FH in Ontario would save $141 million, and publicly funding genetic testing in a cascade screening program for relatives would cost an additional $73 million over the next five years.

Most people with a positive genetic test perceived the screening, diagnosis, and treatment for FH more positively. The discovery of the condition can lead people to adhere to relevant treatments in an effort to control their cholesterol levels. People we spoke with felt that greater awareness and education would allow for more efficient uptake of cascade screening.

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Objective

This health technology assessment evaluates the clinical utility of genetic testing for familial hypercholesterolemia (FH), and the diagnostic yield of genetic cascade screening for first-, second-, and third-degree relatives of an index case whose FH diagnosis was confirmed using a genetic test. It also evaluates the cost-effectiveness and budget impact of publicly funding genetic testing for FH and genetic cascade screening, and the experiences, preferences, and values of people with high cholesterol and/or a diagnosis of FH.

Background

Health Condition

Lipids, such as cholesterol and triglycerides, are insoluble in water and must bind to lipoproteins so that they can circulate throughout the body in the extracellular water (water that is outside of cells, including in the blood). Low-density lipoprotein (LDL) is one of the five major groups of lipoprotein particles that transport lipid molecules.[1] When the body has too much LDL cholesterol (LDL-C), plaque can build up inside the arteries, causing them to narrow over time. This process is called atherosclerosis and can result in angina, heart attack, ischemic stroke, or peripheral artery disease.[1]

Familial hypercholesterolemia, also known as familial hyperlipoproteinemia type 2A or Fredrickson type 2A hyperlipidemia, is an inherited disorder characterized by abnormally elevated serum levels of LDL-C, which increases the risk of premature atherosclerotic cardiovascular disease. This is evidenced by the Copenhagen General Population Study,[2] where the risk of a cardiovascular disease in people with FH was high compared with people without FH. If left untreated, FH can lead to premature atherosclerosis, cardiovascular disease, and premature death.[3] Genes that are related to monogenic etiology in FH include *LDLR*, *APOB*, *PCSK9*, *STAP1*, *APOE*, *LDLRAP1*, *LIPA*, *ABCG5*, and *ABCG8*.[4] Most cases of FH are caused by autosomal-dominant pathogenic variants (defective alleles located in non-sex chromosomes that mask the effects of other alleles of the same gene) in the LDL-receptor (LDLR) gene. The main function of the LDL receptor (encoded by the LDLR gene) is to remove LDL-C from blood circulation and deliver it into the cell, where it can be used for various cell functions.[3] Defects in the genes that code for proteins involved in cholesterol metabolism or LDL-receptor function and processing, such as apolipoprotein B (*APOB*) and proprotein convertase subtilisin/kexin type 9 (*PCSK9*), can also lead to FH, although these mechanisms occur much less frequently.[3] Most people with FH have the heterozygous form of FH; that is, they carry a pathogenic gene variant in one of the two alleles.[3] Rarely, individuals will have a homozygous form of FH (i.e., both of their alleles harbour the same pathogenic gene variant).[3] Other rare genotypes for FH are compound heterozygosity (i.e., the presence of a different pathogenic variant in each allele) and double heterozygosity (i.e., the presence of pathogenic variants in two alleles of two different genes).3 These rare genotypes generally result in a much more severe disease expression than that caused by a single heterozygous variant.3 Although more rarely, FH can also be caused by recessive or dominant variants in several other genes involved in cholesterol metabolism.[3]

Clinical Need and Target Population

About 1 in 250 Canadians have the heterozygous form of FH.[5,6] Familial hypercholesterolemia is more common in certain populations due to founder effects (the loss of genetic variation that occurs when a new population is established by a small percentage of individuals from a larger population).[7] In certain areas of Quebec, the prevalence is as high as 1 in 80. Familial hypercholesterolemia affects approximately 1 in 100 Lebanese and Afrikaners, and 1 in 67 South African Ashkenazi Jews.[5,6] Familial hypercholesterolemia is underdiagnosed and undertreated in Canada and worldwide.[5,6]

Current Diagnosis and Treatment Options

Most FH diagnostic criteria involve examination of elevated cholesterol, which is a prerequisite for assessing other criteria such as the presence of tendon xanthomas, or identification of a personal or family history of premature cardiovascular disease and a positive genetic test. The Canadian

Cardiovascular Society has issued a guideline for diagnosing FH in Canada (Figure 1).[6] Other commonly used criteria for diagnosing FH in Canada and worldwide include the Simon Broome Register, Dutch Lipid Clinics Network, and the American Heart Association.[8] The Canadian Cardiovascular Society currently recommends a goal of LDL-C < 2.0 mmol/L or non–high density lipoprotein < 2.6 mmol/L in people with FH who have established atherosclerotic cardiovascular disease. Cascade screening of relatives of affected individuals (lipid screening of first-degree relatives of individuals with FH and consideration of genetic testing) is considered the most cost-effective and practical strategy to improve identification of people with FH and has been implemented in many countries as the basis for developing FH registries.[6]

Treatment for FH includes lifestyle management (e.g., exercise and correction of sedentary behaviours, weight control, blood pressure control, diabetes management, and smoking cessation) and cholesterol-lowering drugs (e.g., statins, ezetimibe, *PCSK9* inhibitors).[6] *PCSK9* inhibitors are a novel treatment for FH and are recommended for people who are at high risk for a cardiovascular problem and cannot control their blood cholesterol with statins or other conventional cholesterol-lowering drugs.[9] *PCSK9* inhibitors work by targeting the protein *PCSK9*, which regulates the levels of LDL receptor.[9]

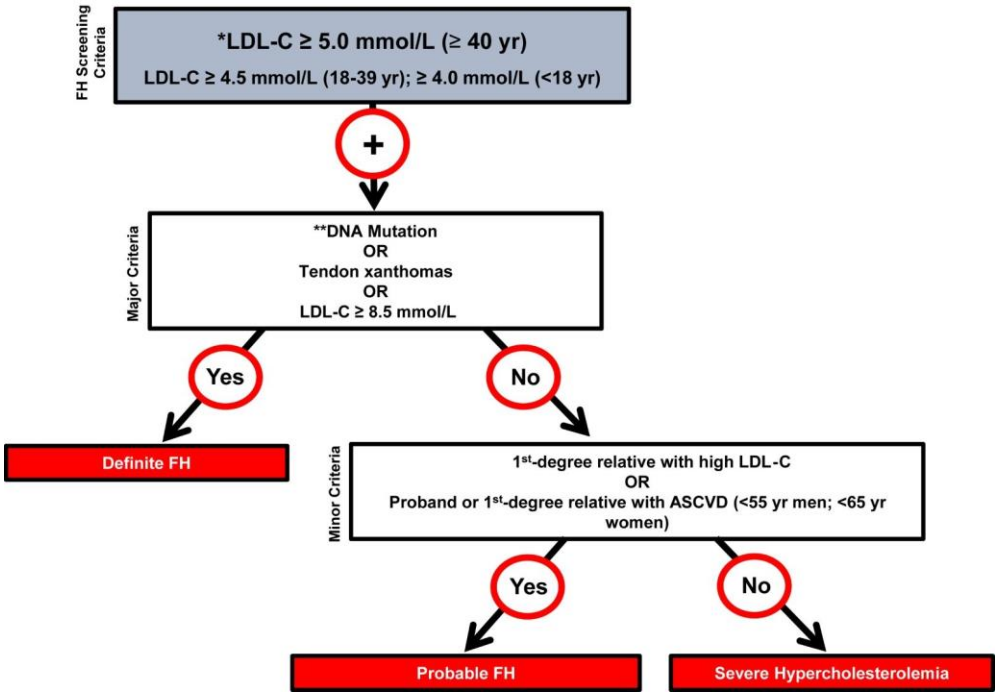

Figure 1: Canadian Definition for the Clinical Diagnosis of Familial Hypercholesterolemia

*Secondary causes of high LDL-C should be ruled out (severe or untreated hypothyroidism, nephrotic syndrome, hepatic disease [biliary cirrhosis], and medication especially antiretroviral agents).

**Causal DNA mutation refers to the presence of a known FH-causing variant in the LDLR, APOB, or PCSK9 gene on the basis of presence of the variant in ClinVar (ncbi.nlm.nih.gov/clinvar), the Human Gene Mutation Database (hgmd.cf.ac.uk/ac/index.php), or Western Database of Lipid Variants (ncbi.nlm.nih.gov/PubMed/23623477) databases, in the proband or a first-degree relative.

Source: Reproduced with permission from Brunham et al.[6]

Health Technology Under Review

Genetic testing refers to several techniques used to determine the genotype of an individual.[10] Methods for genetic testing for FH may include (1) genotyping of previously known DNA variants (e.g., by using DNA microarrays or TaqMan genotyping), or (2) scanning for both previously known and newly discovered DNA variants by examining all nucleotides within a single gene, a panel of selected genes, or the entire exome or genome (e.g., Sanger or capillary electrophoresis sequencing, next-generation gene sequencing [NGS]).[8,10] Sequencing panels targeted to known FH gene variants (targeted NGS) provide comprehensive results and are more commonly used than exome sequencing or genome sequencing.[8] Clinical exome sequencing is not used for isolated FH (i.e., FH without any other medical concerns that could make it more likely to be syndromic). Various sample types can be used for genetic testing, including whole blood, saliva, or buccal swabs.[8] Although FH genetic testing usually involves DNA sequencing, deletions and duplications of genes (del–dups) can be hard to detect using traditional DNA sequencing methods.[8] For example, approximately 10% of causative variants in FH are del–dups or large copy number variants, which can be missed by DNA sequencing methods. Targeted NGS methods have an advantage over traditional sequencing methods in that they are better at detecting these variants.[11] However, there are non-sequencing techniques such as the Multiplex Ligation-dependent Probe Amplification (MLPA) assay that can detect variants at the molecular level.[12]

Regulatory Information

There is a laboratory-validated targeted NGS panel (LipidSeq) developed and used by the lipid genetics clinic at London Health Sciences Centre in Ontario.[13] LipidSeq targets 69 genes and 185 single-nucleotide polymorphisms that are associated with dyslipidemias and metabolic disorders, including those that are known to cause FH.[14] LipidSeq does not require Health Canada approval because it is a laboratory-developed genetic test.

Ontario Context

Diagnosis of Familial Hypercholesterolemia

In Ontario, the diagnosis of FH is mostly based on clinical criteria (Drs. Stasia Hadjiyannakis, Elaine Goh, Mina Madan, Nita Chahal, and Robert Hegele, telephone communications, October 2020). Although the Canadian Cardiovascular Society has developed a simplified definition for diagnosing FH,[6] the Simon Broome Register and Dutch Lipid Clinic Network criteria remain widely used in Ontario. In certain situations, a genetic test can be requested by a cardiologist to confirm FH (Drs. Stasia Hadjiyannakis and June Carroll, telephone communications, October to November 2020).

Genetic Testing for Familial Hypercholesterolemia

The Ontario Ministry of Health is funding genetic testing for FH as an out-of-country service (Drs. Robert Hegele and Elaine Goh, telephone communication, October 2020) for qualified patients[15,16] (see Appendix 4). The samples are usually sent to Invitae for analysis (Dr. Elaine Goh, telephone communication, October 2020). Invitae uses a targeted NGS panel to detect variants in the genes *LDLR*, *APOB*, *PCSK9*, and *LDLRAP1*.[17]

A genetic testing service is also available at one lipid genetics clinic in Ontario (Dr. Robert Hegele, telephone communication, October 2020). Since 2013, the lipid genetics clinic has received requests from physicians across Canada to analyze genetic samples using the LipidSeq panel (Dr. Robert Hegele, email communication, January 2021). Costs for testing are covered under research grants (Dr. Robert Hegele, email communication, January 2021). However, since 2020, the clinic has reduced the number of tests due to lack of adequate funding. As of this writing, the clinic has provided testing to over 1,000 Ontarians and submitted a licensing application for this test to the Ministry of Health.

PCSK9 inhibitors (drugs that are usually prescribed to individuals with FH who are unable to control their blood cholesterol using conventional medications) are funded by the Ministry of Health under Limited Use Benefits (Appendix 4).[15,16]

Canadian and International Context

An FH registry was initiated in Canada in 2014 to increase awareness and access to standard-of-care therapies.[18] Over 200 clinicians and scientists in 19 academic centers across Canada are involved in collecting data for this registry.[18] As of 2018, the registry had 3,184 patients, of whom 3,108 were heterozygous FH, 14 were homozygous FH, and 63 had other lipoprotein disorders (*ABCA1*, *SMPD1*, *APOAI*, and *LCAT* pathogenic variants).[18] Countries such as Spain, Wales, and the Netherlands have successfully implemented nationwide FH registries, while Australia, the Czech Republic, Ireland, New Zealand, Norway, the Slovak Republic, Slovenia, and Brazil have established regional programs.[19]

In Quebec, FH genetic testing is available locally for LDLR and covered by provincial health insurance. Referral is usually done by family physicians or pediatricians following lipid profile test results. We were unable to obtain the funding status for other Canadian provinces and territories.

Expert Consultation

We engaged with experts in the specialty areas of primary care, genetics, endocrinology, cardiology, and general medicine to help inform our understanding of aspects of the health technology and our methodologies and to contextualize the evidence.

PROSPERO Registration

This health technology assessment has been registered in PROSPERO, the international prospective register of systematic reviews (CRD42021245147), available at crd.york.ac.uk/PROSPERO.

Clinical Evidence

Research Questions

1. What is the clinical utility of genetic testing compared with clinical diagnosis without FH genetic testing for individuals with a possible, probable, or confirmed case of familial hypercholesterolemia (FH) as defined by the study?
2. Does genetic cascade screening result in a high diagnostic yield of FH among first-, second-, or third-degree relatives of an index case with FH confirmed through genetic testing?

Methods

Clinical Literature Search

We performed a clinical literature search on February 11, 2021, to retrieve studies published from database inception until the search date. We used the Ovid interface in the following databases: MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, the Health Technology Assessment Database, and the National Health Service Economic Evaluation Database (NHSEED).

A medical librarian developed the search strategies using controlled vocabulary (e.g., Medical Subject Headings) and relevant keywords designed to capture the population and intervention. We created database auto-alerts in MEDLINE and Embase, and monitored them for the duration of the assessment period. We also performed a targeted grey literature search of health technology assessment agency websites as well as clinical trial and systematic review registries. See Appendix 1 for our literature search strategies, including all search terms.

Eligibility Criteria

STUDIES

Inclusion Criteria

- English-language full-text publications
- Studies published from database inception until February 11, 2021
- Cohort studies including before–after studies (for the first research question), randomized-controlled studies (for the first research question), descriptive/prevalence studies (for the second research question), health technology assessments, systematic reviews/meta-analyses (for both research questions)

Exclusion Criteria

- Animal and in vitro studies
- Non-systematic reviews, narrative reviews, abstracts, editorials, letters, case reports, and commentaries

FIRST RESEARCH QUESTION

Participants

- People with a possible, probable, or confirmed clinical diagnosis of FH (as defined by the studies)

Intervention

- Any FH genetic test (i.e., genotyping, Sanger sequencing, targeted next-generation sequencing, exome sequencing, or genome sequencing)

Comparator

- Clinical evaluation without genetic testing (the use of any diagnosis scoring system where a genetic test was not involved to confirm FH. This may include biochemical testing)

Outcome Measures

- Treatment adherence
- Treatment change
- Lifestyle change
- Quality of life
- Atherosclerotic cardiovascular disease (i.e., acute coronary syndromes, a history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, ischemic stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin)
- LDL-C control
- Mortality

SECOND RESEARCH QUESTION

Participants

- First, second-, or third-degree relatives of an index case with FH confirmed through genetic testing

Genetic Test

- Any genetic test for FH (i.e., genotyping, Sanger sequencing, targeted next-generation sequencing, exome sequencing, or genome sequencing)

Outcome Measure

- A positive genetic test for FH

Literature Screening

Two reviewers used Covidence systematic review management software[20] to perform a screening of titles, abstracts, and full text of studies that appear eligible for the review, according to the inclusion criteria. At each stage, the primary reviewer screened all articles and a secondary reviewer screened a random sample of the same articles, according to the method of Nevis et al.[21] Disagreements were resolved through a consensus by the same reviewers.

Reference lists were examined by the primary reviewer for any additional relevant studies not identified through the search. Citation flow and reasons for exclusion for full text articles were reported according to the PRISMA statement.[22]

Data Extraction

We extracted relevant data on study characteristics and risk-of-bias items using a data form to collect information on the following:

- Source (e.g., citation information, study type)
- Methods (e.g., study design, study duration and years, reporting of missing data, reporting of outcomes, whether the study compared two or more groups)
- Outcomes (e.g., outcomes measured, number of participants for each outcome, number of participants missing for each outcome, outcome definition and source of information, unit of measurement, upper and lower confidence limits, time points at which the outcomes were assessed)

The primary reviewer extracted data and the secondary reviewer verified data extraction.

Statistical Analysis

Since no study reported the precision of point estimates, we derived confidence intervals using available information within studies. To find the clinical utility (first research question), we computed conservative (non-optimal) confidence intervals because there was no sufficient information provided in studies, to allow us to derive optimal intervals. To find the diagnostic yield of for genetic

cascade screening (second research question), we computed confidence intervals using the Clopper-Pearson method.[23] We did not conduct a meta-analysis because of heterogeneity in both outcomes and the scope of genetic cascade screening. For statistical analysis, we used SAS version 9.4[24] and R version 4.11.[25]

Critical Appraisal of Evidence

CLINICAL UTILITY

We assessed the risk of bias of included studies using the ROBINS-I tool.[26] This tool obviates the need for the prior assumption that non-randomized studies start at a high risk of bias. We evaluated the quality of the body of evidence for each outcome according to the *Grading of Recommendations Assessment, Development, and Evaluation* (GRADE) *Handbook*.[27] The body of evidence was assessed based on the following considerations: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The overall rating reflects our certainty in the evidence.

GENETIC CASCADE SCREENING

We did not use any domain-based bias assessment tool because, to our knowledge, none have been developed for incidence and prevalence studies. However, we noted that underestimation of the yield (the proportion of relatives of index cases who can be identified through genetic cascade screening as having FH), which was the only potential serious bias, was unlikely to impact the conclusion of this report given that the observed yield in the included studies was high.

Results

Clinical Literature Search

The search of the clinical literature yielded 5,003 citations published from database inception until February 11, 2021, after removing duplicates. Of these, 4,117 were for the clinical utility research question and 879 were for the genetic cascade screening research question. The agreement between the two reviewers during the studies screening process was 99.6% (4984 out of 5003 citations). The disagreement was resolved by reviewers through consensus. In total, we identified 11 studies that met our inclusion criteria, including two[28,29] that met the criteria for both research questions. See Appendix 3 for a list of selected studies excluded after full-text review. Figure 2 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the clinical literature search.

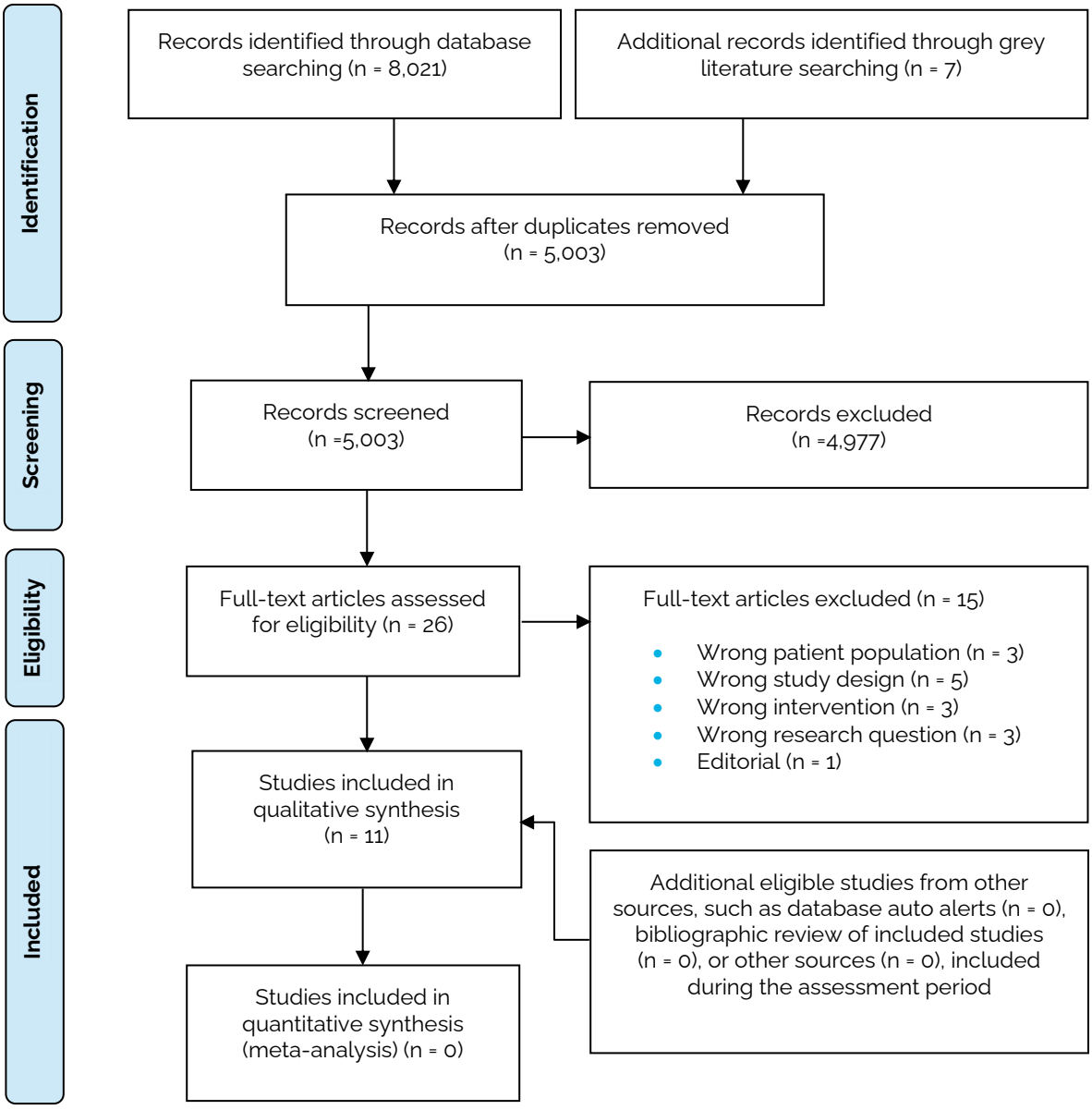

Figure 2: PRISMA Flow Diagram—Clinical Search Strategy

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.
Source: Adapted from Page et al.[22]

Risk of Bias in the Included Studies

We determined the risk of bias for four non-randomized studies using the ROBINS-I tool.[26] For one study,[30] we determined the risk of bias to be serious for the two outcomes measuring LDL-C control (LDL-C, reaching LDL-C target after using cholesterol-lowering drugs) and one outcome measuring treatment adherence (using cholesterol-lowering drugs). For another study,[28] we determined the risk of bias to be serious for LDL-C but low for the remaining outcomes (Table A1). For the remaining two studies,[31,32] we determined the risk of bias to be low for all outcomes.

Characteristics of Included Studies

All 11 included studies received ethics approval. Of these, two were eligible for the clinical utility research question, seven for the diagnostic yield of genetic cascade screening research question, and two for both research questions (Table 1). The outcomes reported for the clinical utility research question included those measuring treatment change (increasing statin dose, adding ezetimibe to existing LDL-C lowering therapy, initiating statin treatment, initiating ezetimibe therapy, remaining untreated with cholesterol-lowering drugs, and changing treatment regimen), use of cholesterol-lowering drugs, LDL-C control (LDL-C level, reaching LDL-C target after using cholesterol-lowering drugs), and total cholesterol control (total cholesterol level) (Tables 2 and 3, below).

Table 1: Characteristics of Included Studies

Author, year, country	Study design	Type of genetic test	Age	Sex[a]	Index cases with genetically confirmed FH, n	Relatives testing positive with pathogenic variant, n (%)	Relatives testing negative with pathogenic variant, n (%)
Studies evaluating the clinical utility of FH genetic testing							
Bell et al, 2015, Australia[28]	Before–after	Sanger sequencing	Mean: 35.6 ± 19.2 to 37.6 ± 19.6	Females 51.1% to 51.6%	100	188 (51.4)	178 (48.6)
Jones et al, 2018, Netherlands[32]	Before–after	GS and ES	Median: 66	Females 65%	23	NA	NA
Huijgen et al, 2010, Netherlands[29]	Before–after	ES	Mean: 42 ± 12	Females 54%	781	1,328 (31.4)*	2,900 (68.6)
D'Erasmo et al, 2020, Italy[33]	Before–after	Not provided	Mean 43.1 ± 15.4	Females 51.0%	252	NA	NA
Studies evaluating the yield of FH genetic cascade screening							
Bell et al, 2015, Australia[28]	Prevalence	Sanger sequencing	Mean: 35.6 ± 19.2 to 37.6 ± 19.6	Females 51.1% to 51.6%	100	188 (51.4)	178 (48.6)
Huijgen et al, 2010, Netherlands[29]	Prevalence	ES	Not provided	Not provided	781	1,328 (31.4)[b]	2,900 (68.6)
Muir et al, 2010, New Zealand[34]	Prevalence	Not provided	Not provided	Not provided	76	159 (45.0)	194 (55.0)
Setia et al, 2018, India[35]	Prevalence	Sanger sequencing	Children: Mean: 9.9 ± 4.8 Adults: Mean: 33.7 ± 13.7	Females 39.1%	31	88 (66.1)	45 (33.9)
Amor-Salamanca et al, 2017, Spain[36]	Prevalence	Targeted NGS	Mean: 54.0 ± 6.7	Females 12.6%	9[c]	6 (50.0)	6 (50.0)
De Paiva Silvino et al, 2020, Brazil[37]	Prevalence	Targeted NGS	Mean: 34.0 ± 33.0	Females 58.0%	19	72 (67.3)	35 (32.7)

Author, year, country	Study design	Type of genetic test	Age	Sex[a]	Index cases with genetically confirmed FH, n	Relatives testing positive with pathogenic variant, n (%)	Relatives testing negative with pathogenic variant, n (%)
Jannes et al, 2015, Brazil[38]	Prevalence	Sanger sequencing and MLPA	Mean: 43.3 ± 17.9 to 44.6 ± 17.1	Females 54.4% to 59.8%	125	234 (59.4)	160 (40.6)
Leren et al, 2004, Norway[39]	Prevalence	Sanger sequencing	Mean: 37.6 ± 20.6 to 38.1 ± 19.8	Females 56.3% to 60.2%	188	407 (47.9)[d]	444 (52.1)
Wu et al, 2017, China[40]	Prevalence	ES	Mean: 11.4 ± 7.7 to 41.5 ± 17.7	Females 47.1%	47[e]	133 (93.0)	10 (7)

Abbreviations: ES, exome sequencing; FH, familial hypercholesterolemia; GS, genome sequencing; MLPA, multiplex ligation-dependent probe amplification; NA, not applicable; NGS, next generation sequencing.
[a]See A Note About Terminology in Acknowledgments regarding use of sex descriptors.
[b]n = 991 for first-, second-, and third-degree relatives only.
[c]Only seven index cases were eligible for cascade screening.
[d]n = 146 for affected relatives who reported the effect of genetic testing.
[e]39 were homozygous/compound heterozygous and eight were heterozygous.

Findings of Included Studies

CLINICAL UTILITY

Most studies evaluating the clinical utility of genetic testing were restricted to index cases, with the exception of Bell et al,[28] where the focus was on the relatives of index cases identified through genetic cascade screening.

All studies had their point estimates in favour of the utility of genetic testing (Tables 2 and 3), but the certainty in evidence varied across outcomes (Table A2). The GRADE certainty in evidence was moderate for four outcomes measuring treatment change (increased statin dose, initiating statin treatment, adding ezetimibe to existing LDL-C lowering therapy, and untreated with cholesterol-lowering drugs), one outcome measuring LDL-C control (LDL-C level), and one outcome measuring total cholesterol control (total cholesterol level). Evidence was downgraded to moderate due to indirectness.

The GRADE certainty was low for one outcome measuring treatment change (changing treatment regimen), one outcome measuring the use of cholesterol-lowering drugs, and one outcome measuring LDL-C control (reaching LDL-C target after using cholesterol-lowering drugs). Evidence was downgraded to low due to risk of bias and indirectness.

The GRADE certainty was very low for one outcome measuring treatment change (initiating ezetimibe therapy), downgraded due to indirectness and imprecision.

There were no studies that evaluated the outcomes measuring lifestyle change, atherosclerotic cardiovascular disease, quality of life, or mortality.

Table 2: Clinical Utility of FH Genetic Testing Versus Clinical Evaluation Without Genetic Testing (Risk Differences)

Author, year, country	Outcome	Study size, n	n (%) with outcome at baseline	n (%) with outcome after genetic testing	Risk difference in % (95% CI)[a]
Treatment change					
Bell et al, 2015 Australia[28,b]	Increased statin dose	73	0 (0.0)	22 (30.1)	30.1 (13.5–45.5)
Bell et al, 2015 Australia[28,b]	Adding ezetimibe to existing LDL-C lowering therapy	73	0 (0.0)	16 (21.9)	21.9 (5.1–37.8)
Bell et al, 2015 Australia[28,b]	Initiating statin treatment	73	0 (0.0)	46 (63.0)	63.0 (48.5–74.9)
Bell et al, 2015 Australia[28,32,b]	Initiating ezetimibe treatment	73	0 (0.0)	11 (15.1)	15.1 (−1.8 to 31.3)
Jones et al, 2018 Netherlands[32]	Changing treatment regimen	23	0 (0.0)	9 (39.1)	39.1 (8.5–64.5)
D'Erasmo et al, 2020 Italy[33]	Remain untreated with cholesterol-lowering drugs[c]	252	104 (41.3)	22 (8.7)	−32.5 (−40.8 to −23.9)
Use of cholesterol-lowering drugs					
Huijgen et al, 2010 Netherlands[29]	Cholesterol-lowering drug treatment	781	397 (50.83)	636 (81.4)	30.6 (25.8–35.3)
LDL-C control					
Huijgen et al, 2010 Netherlands[29]	Reached LDL-C target after using cholesterol-lowering drugs	297[d]	0 (0.0)	65 (21.9)	21.9 (13.8–29.8)

Abbreviations: CI, confidence interval; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol.
[a]CIs were computed by the authors of this health technology assessment. The computed CIs are conservative as they do not account for repeated measurements.
[b]This assessment was only done to FH-positive relatives with follow-up data. For all other studies, the assessment was done on index cases.
[c]Follow-up was initiated both before and after genetic testing. In both periods, baseline and end-of-follow-up measurements were taken to evaluate how many people remain untreated with cholesterol-lowering drugs.
[d]These participants reported their LDL-C level at the end of follow-up.

Table 3: Clinical Utility of FH Genetic Testing Versus Clinical Evaluation Without Genetic Testing (Mean Differences)

Author, year, country	Type of outcome	Study size, n	Mean (±SD) at baseline	Mean (±SD) after genetic testing	Mean difference (95% CI)[a]
Total cholesterol control					
Bell et al, 2015 Australia[28,b]	Total cholesterol, mmol/L	73	6.6 (1.0)	5.4 (1.0)	−1.2 (−1.5 to −0.9)
LDL-C control					
Bell et al, 2015 Australia[28,b]	LDL-C, mmol/L	73	4.5 (1.0)	3.4 (1.0)	−1.1 (−1.4 to −0.8)
Huijgen et al, 2010 Netherlands[29]	LDL-C, mmol/L	781	4.1 (1.3)	3.2 (1.1)	−0.9 (−1.0 to −0.8)

Abbreviations: CI, confidence interval; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation.
[a]CIs were computed by the authors of this health technology assessment. The CIs are conservative as they do not account for repeated measurements.
[b]This assessment was limited to FH-positive relatives with follow-up data.

DIAGNOSTIC YIELD

Studies for genetic cascade screening reported the yield that ranged from 31.4% (95% confidence interval [CI], 30.0%–32.8%) to 93.0% (95% CI, 87.5%–96.7%) (Figure 3 and Table 4). For most studies, relatives were contacted directly by study staff, who initiated contact after a consent from the index case (Table 4). In these studies, the mean number of new cases identified per index case ranged from 1 to 3. Only one study applied the indirect contact approach.[39] In this study, the mean number was 2.

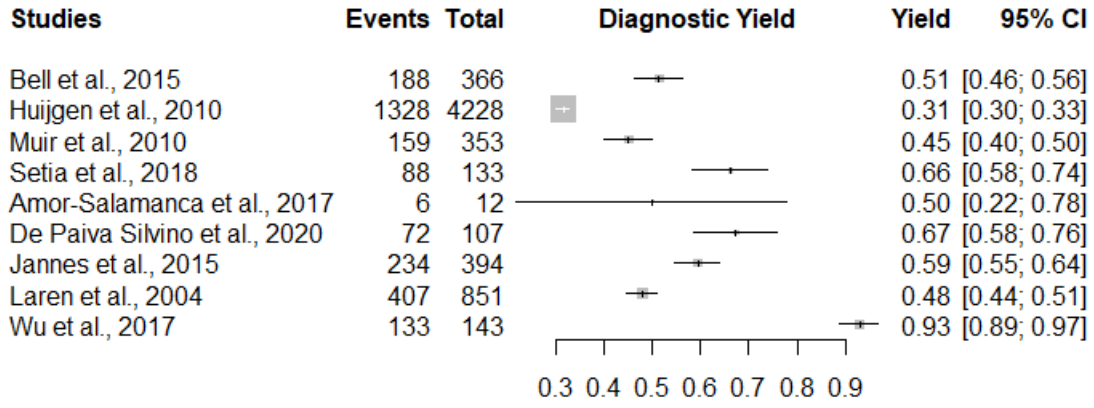

Figure 3: Diagnostic Yield of Genetic Cascade Screening

Abbreviation: CI, confidence interval.
Note: the yield is presented in decimal form rather than as a percentage.

Table 4: Diagnostic Yield of Genetic Cascade Screening

Author, year, country	Index cases, n	Initial contact method for relatives[a]	Degree of relatedness of the index case to the relatives	Mean new cases per index case	Total number of relatives	Number of FH-positive relatives	Diagnostic yield, % (95% CI)[b]
Bell et al, 2015 Australia[28]	100	Direct	Not specified	2	366	188	51.4 (46.1–56.6)
Huijgen et al, 2010 Netherlands[29]	781	Unknown	1st, 2nd, 3rd degrees and above	2	4,228	1,328	31.4 (30.0–32.8)
Muir et al, 2010 New Zealand[34]	76	Direct	1st degree	2	353	159	45.0 (39.8–50.4)
Setia et al, 2018 India[35]	31	Direct	1st and 2nd degree	3	133	88	66.1 (57.5–74.1)
Amor-Salamanca et al, 2017 Spain[36]	9	Unknown	1st degree	2	12	6	50.0 (21.1–78.9)
De Paiva Silvino et al, 2020 Brazil[37]	19	Unknown	1st and 2nd degree	4	107	72	67.3 (58.2–76.4)
Jannes et al, 2015 Brazil[38]	125	Direct	1st degree	2	394	234	59.4 (54.4–64.3)
Leren et al, 2004 Norway[39]	188	Indirect	1st degree	2	851	407	47.9 (44.4–51.2)
Wu et al, 2017 China[40]	47	Direct	1st and 2nd degree	3	143	133	93.0 (87.5–96.7)

Abbreviations: CI, confidence interval; FH, familial hypercholesterolemia.
[a]"Direct" means relatives were contacted directly by study staff, who initiated contact after a consent from the index case. "Indirect" means relatives were contacted indirectly by staff through index cases.
[b]CIs were computed by the authors of this health technology assessment using the Clopper-Pearson method.

Ongoing Studies

We are aware of the following ongoing studies registered on clinicaltrials.gov that have potential relevance that may affect this review (identifiers: NCT04419090, NCT04526457, NCT04656028, NCT04148001, NCT04370899, and NCT03198897).

Discussion

Our clinical review found that FH genetic testing can improve several health outcomes and help with identification of new cases through genetic cascade screening. Although our assessment of the diagnostic yield of cascade screening was restricted to genetic tests, we are aware of several studies not meeting our eligibility criteria that evaluated the yield of cascade screening using clinical criteria such as the Simon Broom Registry or the Dutch Lipid Clinic Network.[41-44] The yield in these studies was comparable to some of the included studies in our review and ranged from 30% to 61%. However, we could not appraise the quality of evidence from these studies because any assessment of a test other than a genetic test was beyond the scope of this review. There is documented

evidence on the importance of engaging primary care physicians in FH screening programs, but that also was outside the scope of this review.[45,46]

For most of the included studies, evaluation of clinical utility was restricted to index cases. In the only study where the assessment was done on relatives of index cases identified through genetic cascade screening,[28] the findings supported the clinical utility of genetic testing. In that study, the authors recruited relatives through direct contact by a trained nurse, but it is unclear how much, if any, of the observed clinical utility was due to the effectiveness of the direct contact approach. There is documented evidence[47,48] that, for more distant relatives (second- or third-degree), direct contact is more effective than indirect contact. The direct approach is thought to be more effective in these cases because of the greater challenges faced by the index case, who may have difficulty contacting more distant relatives.[43,49] There could be ethical implications with the direct approach, although strong evidence is still lacking.[37]

The Australian Medical Services Advisory Committee (MSAC) has recommended genetic testing for heritable mutations associated with FH in qualified individuals, and targeted cascade screening in first- and second-degree relatives of index cases with a confirmed genetic diagnosis. Their public summary document on which the recommendation is based has concluded that genetic testing for FH and associated interventions has non-inferior safety and uncertain incremental effectiveness.[50] Our assessment on clinical utility rated most outcomes as having moderate certainty in evidence. We also noted that the yield in genetic cascade screening may have been underestimated in some studies because they did not include second- or third-degree relatives, but this was unlikely to alter our conclusion given the high yield observed in virtually all studies. The MSAC summary document did not provide citations, so we are unable to determine if the studies assessed in their report meet our eligibility criteria.

Strengths and Limitations

We note two major limitations. First, there was the unavailability of multiple studies evaluating the same outcome, which prevented us from assessing consistency of results across different settings on several outcomes. However, even though none of the included studies were completed in Canada, they were conducted in countries with universal health care systems similar to Canada, although varying in their particulars from public and government-funded to private universal coverage. Second, we did not identify studies evaluating the clinical utility of genetic testing on the outcomes measuring lifestyle change, atherosclerotic cardiovascular disease, quality of life, or mortality. All the identified outcomes in this review were proxy rather than direct measures for atherosclerotic cardiovascular disease, one of the ultimate outcomes a genetic test is trying to prevent. However, there is published evidence linking FH pathogenic variants with higher incidence of atherosclerotic cardiovascular diseases.[51] There is also one study linking treatment for FH and the reduction in cardiovascular events.[2]

Conclusions

Our review found that genetic testing can improve four outcomes measuring treatment change (increased statin dose, initiating statin treatment, adding ezetimibe to existing LDL-C lowering therapy, and remain untreated with cholesterol-lowering drugs), one outcome measuring LDL-C control (LDL-C level), and one outcome measuring total cholesterol control (total cholesterol level) (GRADE: Moderate). Additionally, it may improve one outcome measuring treatment change (changing treatment regimen), one outcome measuring the use of cholesterol-lowering drugs, and one outcome measuring LDL-C control (reaching LDL-C target after using cholesterol-lowering drugs) (GRADE: Low). We are uncertain about the evidence on the clinical utility of genetic testing on one outcome measuring treatment change (initiating ezetimibe therapy) due to indirectness and imprecision (GRADE: Very low). There were no studies that evaluated the clinical utility of genetic testing on the outcomes measuring lifestyle change, atherosclerotic cardiovascular disease, quality of life, or mortality. We also found that genetic cascade screening can result in high diagnostic yield of FH, allowing for earlier diagnosis and treatment.

Economic Evidence

Research Questions

We aimed to answer the following research questions on the use of genetic testing for familial hypercholesterolemia (FH):

1. What is the cost-effectiveness of genetic testing compared with clinical evaluation without genetic testing for individuals with a possible, probable, or confirmed clinical diagnosis of FH?
2. What is the cost-effectiveness of genetic cascade screening compared with no genetic cascade screening for identification of FH in first-, second-, or third-degree relatives of an index case with FH confirmed through genetic testing?

Methods

Economic Literature Search

We performed an economic literature search on February 16, 2021, to retrieve studies published from database inception until the search date. To retrieve relevant studies, we developed a search using the clinical search strategy with an economic and costing filter applied.

We created database auto-alerts in MEDLINE and Embase and monitored them for the duration of the assessment period. We also performed a targeted grey literature search of health technology assessment agency websites, systematic review registries, and the Tufts Cost-Effectiveness Analysis Registry. See the Clinical Literature Search section, above, for further details on methods used. See Appendix 1 for our literature search strategies, including all search terms.

Eligibility Criteria

We screened potentially relevant records according to the following eligibility criteria.

STUDIES

Inclusion Criteria

- English-language full-text publications
- Studies published from database inception until February 16, 2021
- Cost–benefit analyses, cost-effectiveness analyses, cost-minimization analyses, or cost–utility analyses

Exclusion Criteria

- Narrative reviews, editorials, case reports, commentaries, and abstracts

PARTICIPANTS

- First research question: individuals with a possible, probable, or confirmed clinical diagnosis of FH
- Second research question: first-, second-, or third-degree relatives of an index case with FH

INTERVENTIONS

- Any genetic test for FH (i.e., genotyping, Sanger sequencing, targeted next generation sequencing, exome sequencing, or genome sequencing)

COMPARATORS

- First research question: clinical evaluation without genetic testing
- Second research question: cascade screening without genetic testing or no cascade screening

OUTCOME MEASURES

- Costs
- Health outcomes (e.g., quality-adjusted life-years, number of FH diagnoses, number of cardiovascular events)
- Incremental costs
- Incremental effectiveness
- Incremental cost-effectiveness ratios

Literature Screening

A single reviewer conducted an initial screening of titles and abstracts using Covidence[20] and then obtained the full texts of studies that appeared eligible for review according to the inclusion criteria. The same reviewer then examined the full-text articles and selected studies eligible for inclusion. The reviewer also examined reference lists and consulted content experts for any additional relevant studies not identified through the search.

Data Extraction

We extracted relevant data on study characteristics and outcomes to collect information about the following:

- Source (e.g., citation information, study type)
- Methods (e.g., study design, analytic technique, perspective, time horizon, population, intervention[s], comparator[s])
- Outcomes (e.g., health outcomes, costs, incremental cost-effectiveness ratios)

Study Applicability and Limitations

We determined the usefulness of each identified study for decision-making by applying a modified quality appraisal checklist for economic evaluations originally developed by the National Institute for Health and Care Excellence (NICE) in the United Kingdom to inform the development of NICE's clinical guidelines.[52] We modified the wording of the questions to remove references to guidelines and to make it specific to Ontario. Next, we separated the checklist into two sections. In the first section, we assessed the applicability of each study to the research question (directly, partially, or not applicable). In the second section, we assessed the limitations (minor, potentially serious, or very serious) of the studies.

Results

Economic Literature Search

The database search of the economic literature yielded 338 citations published from database inception until February 16, 2021. We identified five additional studies from other sources, for a total of 233 after removing duplicates. In total, we identified 14 studies that met our inclusion criteria. Figure 4 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the economic literature search.

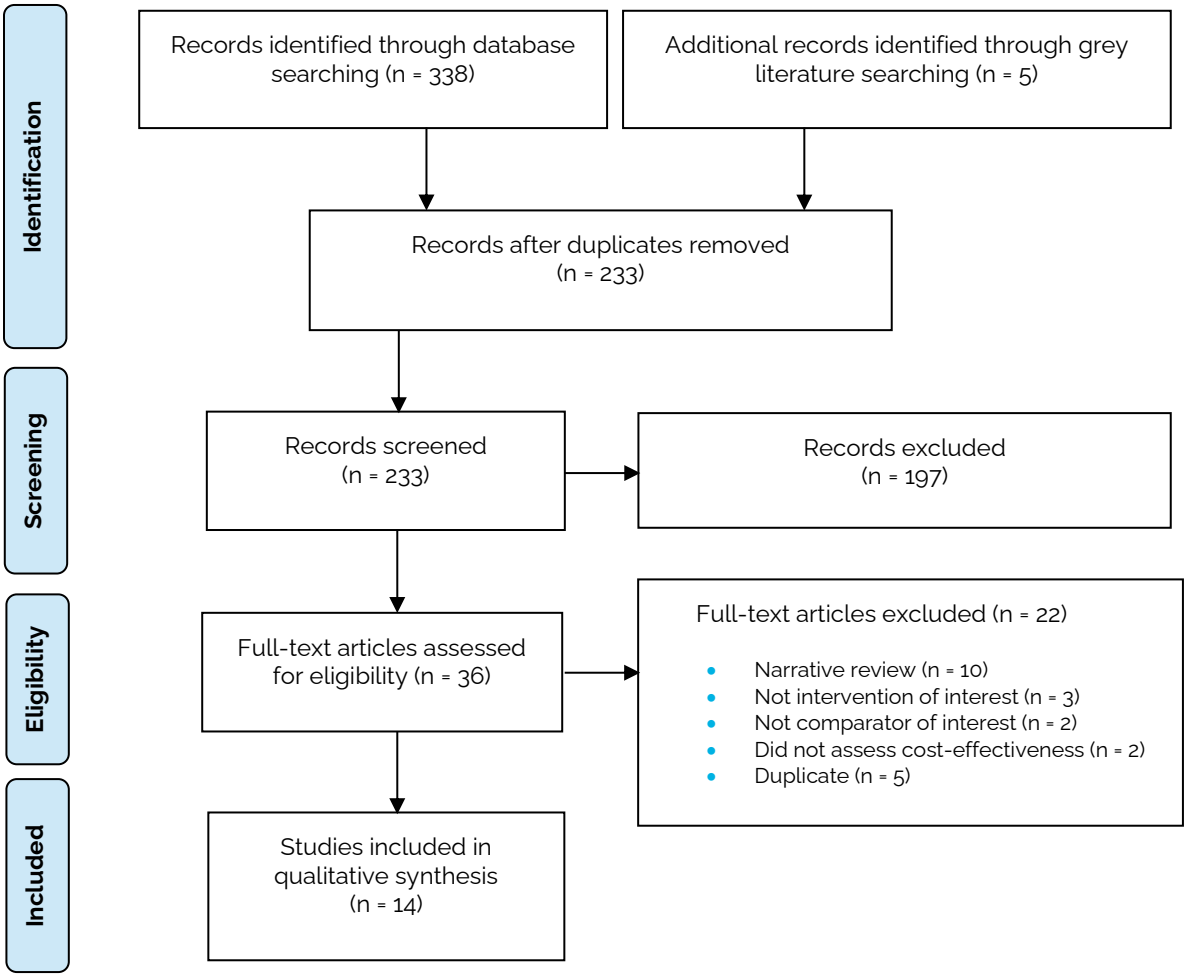

Figure 4: PRISMA Flow Diagram—Economic Search Strategy

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.
Source: Adapted from Page et al.[22]

Overview of Included Economic Studies

We included a total of 14 studies.[53-66] The studies were conducted in Australia, Europe, and the United States. No study was conducted using a Canadian perspective. All included studies used a model-based analysis approach. Ten studies were cost–utility analyses, and four were cost-effectiveness analyses. All studies evaluated cascade screening in relatives of index cases. Two studies included both index cases and relatives of index cases,[58,65] but only one of these two studies reported the cost and effectiveness outcomes separately for the genetic testing of index cases with clinical diagnosis.[65] Table 5 summarizes the results of the included studies.

Genetic Testing for Individuals with a Clinical Diagnosis of FH

Only one study reported the cost and effectiveness outcomes of using genetic testing to confirm the clinical diagnosis of FH.[65] This study compared two genetic testing panels (FH20 and LIPOchip) and comprehensive genomic analysis versus clinical diagnosis without genetic testing. In this analysis, the clinical diagnosis was based on the Simon Broome criteria (including both confirmed and possible FH). The target population was index cases 50 years of age or older, and the outcomes were observed over a lifetime horizon. The comprehensive genomic analysis approach was assumed to

have 100% sensitivity and specificity. In contrast, the lipid testing was highly sensitive (sensitivity = 0.90), but not specific (specificity = 0.29).

For a hypothetical cohort of 1,000 individuals with possible or confirmed FH based on the Simon Broome criteria, the comprehensive genomic analysis was less costly and less effective than the lipid testing strategy (cost saved, £2,150 GBP per person; QALY loss, 0.02 per person). No probabilistic sensitivity analysis was conducted.

The incremental cost-effectiveness ratios (ICERs) of comprehensive genomic analysis versus lipid testing were also estimated across different age subgroups. However, there was great uncertainty regarding the ICER estimates of different age subgroups. The authors suggested that this was due to small or negligible quality-adjusted life-year (QALY) differences (QALY losses after comprehensive genomic analysis were estimated as 0.02, 0.05, 0.01, and 0.00 for index cases who were 15, 35, 65, and 75 years old, respectively).[65]

Genetic Cascade Screening

All included studies evaluated the cost-effectiveness of cascade genetic testing (Table 5).

STUDY POPULATION AND TIME HORIZON

Two studies were in children, aged 10[53] and between 1 and 2 years old.[62] Seven studies were in adults.[54-56,60,61,63,67] Five studies included both children and adults.[58,59,64-66] One study of cascade screening focused on first-degree relatives only,[61] another on both first- and second-degree relatives.[54] Only one study, by Sharma and colleagues,[65] evaluated the cost-effectiveness of using genetic cascade screening for first-, second-, and third-degree relatives. Notably, two studies assessed the cost-effectiveness of FH genetic testing for both diagnosis of index cases and cascade screening of relatives,[58,65] and one estimated the ICER based on differences in total costs and QALYs of both index cases and relatives between strategies.[65] All but two studies applied a 10-year time horizon.[54,59]

CASCADE SCREENING AND OTHER CASE IDENTIFICATION STRATEGIES ASSESSED IN THE INCLUDED STUDIES

Most studies evaluating genetic cascade screening strategies included a genetic approach that offered genetic testing regardless of lipid testing results.[53-56,58-61,63,65-67] One study took a sequential approach that gave genetic testing only to those with abnormal lipid testing results.[62] Genetic cascade screening was compared to no cascade screening[53,54,56,58-60,62,66,67] or lipid cascade screening.[55,61-63,65] There were also various screening or case identification strategies that included genetic testing in their pathway. These screening strategies differed according to the certainty of index case diagnosis. For example, Nherera and colleagues[63] compared various cascade screening strategies with genetic testing or with lipid testing only for relatives of people with confirmed or possible FH index cases according to the Simon Broome criteria. Additionally, genetic screening was used in settings other than family-based screening, such as for people in primary or secondary care (ex., after myocardial infarction, acute coronary syndrome, or stroke).[56,61,64]

For all analyses, those who were diagnosed as having FH were offered lipid-lowering therapy.

COST-EFFECTIVENESS OF GENETIC CASCADE SCREENING

Most studies suggested that genetic cascade screening was either cost-effective compared with no cascade screening (ICER: $3,565 AUD per QALY in Australia [2019],[54] £5806 GBP per QALY in the United Kingdom [2014–2015],[58] or €29,608 EUR per QALY in Spain [2016][59]) or dominant across different contexts.[53] Nevertheless, caution is needed to interpret the results because some other analyses suggested that genetic cascade screening may not be cost-effective. For example, Marang-van de Mheen and colleagues[60] concluded that the ICER for genetic cascade screening and treatment for all individuals with a FH mutation was estimated to be €31,260 EUR per life year gained when compared to no screening.

When compared to lipid screening with or without a program to improve treatment adherence following diagnosis, one study suggested that genetic cascade screening was not cost-effective.[55] Similar results were observed from other studies when genetic cascade screening was compared to lipid cascade screening.[61,62]

There were other screening or case identification strategies with genetic testing in their pathway. The cost-effectiveness of genetic cascade screening when compared to these strategies was unclear. When considering both costs and QALYs for index cases and their relatives, Sharma and colleagues[65] estimated that the ICER was £1,030 GBP per QALY gained for the comprehensive genomic analysis versus the lipid approach. Another study in the United Kingdom suggested that a combination strategy of genetic cascade screening for relatives of confirmed FH index cases with causative mutation and lipid cascade screening for relatives of confirmed or possible FH cases without causative mutation was the most cost-effective option compared with other cascade screening strategies (i.e., genetic or lipid cascade screening for all relatives of FH index cases).[63] Crosland and colleagues[56] compared cascade screening with other approaches, including case identification, with either Simon Broome or the Dutch Lipid Collaborative Network (DLCN) criteria in the primary or secondary care setting, and concluded that primary care case identification with the Simon Broome criteria was the most cost-effective strategy.

Therefore, it is challenging to reach a conclusion regarding the cost-effectiveness of genetic cascade screening. The variability in the ICER results was partly explained by the choice of comparison (genetic cascade screening was compared to no cascade screening or lipid cascade screening). However, other available screening or case identification options with genetic testing in their pathways added further uncertainty on the optimal use of genetic testing.

Table 5: Results of Economic Literature Review—Summary

Author, year, country	Analytic technique, study design, perspective, time horizon	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
Ademi et al, 2020[53] Australia	Cost–utility analysis Markov model Publicly funded health care system Lifetime horizon with a cycle length of 1 y	1,000 hypothetical 10-y-old children suspected of having heterozygous FH, based on the presence of the condition in a primary family member	Screened and genetically confirmed for the condition, followed by statin treatment of affected individuals No screening	Total QALYs (for 568 patients) • Screening: 10,348 • No screening: 9,510 Incremental QALY: 1.07/person Discount rate: 5%	Currency, year: AUD, 2019 Total costs (for 568 patients): • Screening: $13,558,855 • No screening: $14,202,908 Incremental cost: $1,134/person Discount rate: 5%	ICER: screening strategy dominant[a] PSA results: the probabilities of screening strategy being cost saving and cost-effective were 51.2% and 48.8%, respectively
Ademi et al, 2014[54] Australia	Cost–utility analysis Markov model Publicly funded health care system 10-y horizon with a cycle length of 1 y	Relatives (1st- and 2nd-degree relatives) of probands with FH	Cascade screening based on genetic testing, supplemented with the measurement of plasma low-density lipoprotein cholesterol concentration, and treatment with statins No screening	Total QALYs (mean per person) • Screening: 7.81 • No screening: 7.52 • Incremental QALY: 0.29 Discount rate: 3%	Currency, year: AUD, 2013 Total costs (mean per person): • Screening: $2,920 • No screening: $1,352 • Incremental cost: $1,567 Discount rate: 3%	ICER: $3,565 per QALY PSA results: The 2.5th and 97.5th percentiles for ICER were between $2,004 and $5,228 per QALY gained
Chen et al, 2014[55] United States	Cost–utility analysis Decision tree and Markov model Societal perspective Lifetime time horizon with a cycle length of 1 y	Caucasian male adults with a family history of FH and high-risk baseline cholesterol levels of 46 mg/dL HDL-C, 224 mg/dL LDL-C, and 305 mg/dL total cholesterol	Genetic screening, lipid screening with statin adherence program vs. lipid screening	Total QALYs (mean per person) • Genetic screening: 18.29 • Lipid screening with adherence program: 18.77 • Lipid screening (reference): 18.28	Currency, year: USD, 2013 Total costs (mean per person): • Genetic screening: $15,594 • Lipid screening with adherence	ICER: $519,813 per QALY for genetic screening and $12,223 per QALY for lipid screening and adherence program PSA results: the probabilities of being cost-effective were 99%

Author, year, country	Analytic technique, study design, perspective, time horizon	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
				• Incremental QALY: 0.01 for genetic screening and 0.39 for lipid screening and adherence program Discount rate: 3%	program: $16,385 • Lipid screening (reference): $10,396 • Incremental costs: $5,198 for genetic screening, and $5,989 for lipid screening and adherence program Discount rate: 3%	for lipid screening with adherence program and 55% for the genetic screening, at a willingness-to-pay value of $50,000 per QALY
Crosland et al, 2018[56] United Kingdom	Cost–utility analysis Decision tree and Markov model National health service perspective Lifetime time horizon with a cycle length of 1 y	Males and females between ages 40 and 70 who were broadly representative of the population within these age bands	• No cascade screening and no case identification • Cascade screening • Primary care case identification: o No cascade screening from new index cases o Clinical assessment with DLCN criteria o Clinical assessment with SB criteria • Secondary care case identification: o Clinical assessment	Total QALYs (mean per person) No cascade screening and no case identification: • 11.4079 Cascade screening: • 11.41755 Primary care case identification: • No cascade screening from new index cases: 11.45383 • Clinical assessment with DLCN criteria: 11.46325 • Clinical assessment with	Currency, year: GBP, 2015–2016 Total costs (mean per person): No cascade screening and no case identification: • £6,797 Cascade screening: • £6,843 Primary care case identification: • No cascade screening from new index cases: £6,852 • Clinical assessment with DLCN criteria: £6,882	ICER[b] Cascade screening: • Extended dominated[c] Primary care case identification • No cascade screening from new index cases: £1,186 per QALY • Clinical assessment with DLCN criteria: £3,254 per QALY • Clinical assessment with SB criteria: £13,365 per QALY

Author, year, country	Analytic technique, study design, perspective, time horizon	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
			with DLCN criteria o Clinical assessment with SB criteria • Primary and secondary care case identification: o Clinical assessment with DLCN criteria o Clinical assessment with SB criteria	SB criteria: 11.46357 Secondary care case identification: • Clinical assessment with DLCN criteria: 11.41991 • Clinical assessment with SB criteria: 11.41999 Primary and secondary care case identification: • Clinical assessment with DLCN criteria: 11.4657 • Clinical assessment with SB criteria: 11.46601 Discount rate: 3.5%	• Clinical assessment with SB criteria: £6887 Secondary care case identification: • Clinical assessment with DLCN criteria: £6982 • Clinical assessment with SB criteria: £7004 Primary and secondary care case identification: • Clinical assessment with DLCN criteria: £7021 • Clinical assessment with SB criteria: £7048 Discount rate: 3.5%	Secondary care case identification: • Clinical assessment with DLCN criteria: dominated[a] • Clinical assessment with SB criteria: dominated[a] Primary and secondary care case identification: • Clinical assessment with DLCN criteria: £63514 per QALY • Clinical assessment with SB criteria: £82,388 per QALY PSA results: Strategy 3 had a 57% probability of being the most cost-effective option at a willingness-to-pay value of £20,000 per QALY gained, and was the most cost-effective

Author, year, country	Analytic technique, study design, perspective, time horizon	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
						strategy for values of £17,000 to £30,000 per QALY gained
Kerr et al, 2017[58] United Kingdom	Cost–utility analysis Markov model National health service perspective Lifetime time horizon with a cycle length of 1 y	People with a clinical diagnosis of possible or confirmed FH (index cases) and relatives of monogenic index cases	A cascade screening pathway with three steps: DNA testing of relatives of monogenic index cases, treatment with high-intensity statins and, in some cases, ezetimibe for monogenic relatives No DNA tests, no cascade screening, and no treatment of relatives	Lifetime QALY gained by age group (mean per person) • 20–34: 0.56 • 35–44: 0.46 • 45–54: 0.48 • 55–64: 0.36 • 65–74: 0.31 • 75+: 0.21 • Cohort: 0.48 Discount rate: 3.5%	Currency, year: GBP, 2014–2015 Lifetime cost increase by age group (mean per person) • 20–34: £2,722 • 35–44: £2,943 • 45–54: £2,789 • 55–64: £2,732 • 65–74: £2,495 • 75+: £2,285 • Cohort: £2,781 Discount rate: 3.5%	ICER by age groups (per QALY) • 20–34: £4,489 • 35–44: £6,369 • 45–54: £5,770 • 55–64: £7,587 • 65–74: £8,056 • 75+: £11,072 • The whole cohort: £5,806 No PSA results reported
Lazaro et al, 2017[59] Spain	Cost–utility analysis Decision tree National health system and societal perspectives 10-y time horizon with a cycle length of 1 y	FH patients identified by total cholesterol measurement and the relatives of index cases (adult relatives with TC > 250 mg/dL and for children aged > 3 y with TC > 220 mg/dL)	Strategy with three steps: (1) following the index case detection strategy for adults with TC > 300 mg/dL in primary care; (2) cascade screening for adult relatives with TC > 250 mg/dL and for children aged > 3 y with TC > 220 mg/dL; (3) lipid lowering therapy for all patients with hypercholesterolemia or FH	QALY (for 9,000 individuals) • Cascade screening: 62,175 • No intervention: 61,408 Incremental QALY for 9,000 individuals: 767 Discount rate: 3%	Currency, year: EUR, 2016 Total costs (for 9,000 individuals) • Cascade screening: €59,995,147 from a national health system perspective; €84,526,762 from a societal perspective • No intervention: €37,299,078 from a national health	ICER From a national health system perspective: €29,608 per QALY From a societal perspective: cascade screening was dominant[a] No PSA results reported

Author, year, country	Analytic technique, study design, perspective, time horizon	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
			No intervention		system perspective; €87,348,705 from a societal perspective • Incremental costs for 9,000 individuals: €22,696,068 from a national health system perspective; €−2,821,943 from a societal perspective Discount rate: 3%	
Marang-van de Mheen et al, 2002[60] Netherlands	Cost-effectiveness analysis Model-based approach Unclear perspective, including both direct and indirect medical costs Lifetime horizon	Individuals screened for an LDL receptor gene mutation in the period 1994–1997, ≥16 y	DNA-based screening followed by treatment versus no screening	Total years of life gained in reference to no screening (mean per person) • All individuals with a FH mutation treated: 1.14 • All individuals with a FH mutation and a cholesterol level above the 95th percentile of the general population treated: 1.32 • All individuals with a FH mutation and fulfilling the treatment criteria in the national consensus	Currency, year: EUR, 2002 Total costs (mean per person) • All individuals with a FH mutation treated: €35,637 • All individuals with a FH mutation and a cholesterol level above the 95th percentile of the general population treated: €39,582 • All individuals with a FH mutation and fulfilling the	Costs per year of life gained • All individuals with a FH mutation treated: €31,260 • All individuals with a FH mutation and a cholesterol level above the 95th percentile of the general population treated: €29,918 • All individuals with a FH mutation and fulfilling the

Author, year, country	Analytic technique, study design, perspective, time horizon	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
				guideline treated: 1.36 • Same as 1, but only if untreated at screening: 1.21 • Same as 2, but only if untreated at screening: 1.34 • Same as 3, but only if untreated at screening: 1.53 No discount	treatment criteria in the national consensus guideline treated: €34,911 • Same as 1, but only if untreated at screening: €38,847 • Same as 2, but only if untreated at screening: €41,435 • Same as 3, but only if untreated at screening: €42,387 No discount	treatment criteria in the national consensus guideline: €25,613 • Same as 1, but only if untreated at screening: €32,164 • Same as 2, but only if untreated at screening: €30,843 • Same as 3, but only if untreated at screening: €27,770 No PSA results reported
Marks et al, 2000[61] United Kingdom	Cost-effectiveness analysis Combination of decision analysis and life table analysis Unclear perspective, including both direct and indirect medical costs Lifetime horizon	First degree relatives of people with diagnosed familial hypercholesterolemia	Clinical and genetic screening strategies with universal screening, opportunistic screening in primary care, screening of people admitted to hospital with premature myocardial infarction, or tracing relatives of affected patients	Life year gain discounted Clinical screening strategy • Universal screening (aged 16 y): 5.2 • Universal screening (aged 16–54 y): 3.5 • Opportunistic screening in primary care (aged 16–54 y): 3.7	Currency, year: GBP, unclear currency year Costs not separately reported Discount rate: 6%	Costs per life year gained Clinical screening strategy • Universal screening (aged 16 y): £2,777 • Universal screening (aged 16–54 y): £13,029 • Opportunistic screening in primary care

Author, year, country	Analytic technique, study design, perspective, time horizon	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
				• Opportunistic screening of people admitted with premature myocardial infarction (aged 16–54 y): 0.8 • Family tracing (aged 16–54 y): 3.5 Genetic screening strategy • Universal screening (aged 16 y): 5.2 • Universal screening (aged 16–54 y): 3.5 • Opportunistic screening in primary care (aged 16–54 y): 3.7 • Opportunistic screening of people admitted with premature myocardial infarction (aged 16–54 y): 0.8 • Family tracing (aged 16–54 y): 3.5 Discount rate: 1%		(aged 16–54 y): £11,310 • Opportunistic screening of people admitted with premature myocardial infarction (aged 16–54 y): £9,281 • Family tracing (aged 16–54 y): £3,097 Genetic screening strategy • Universal screening (aged 16 y): £14,842 • Universal screening (aged 16–54 y): £78,060 • Opportunistic screening in primary care (aged 16–54 y): £70,009 • Opportunistic screening of people admitted with premature myocardial infarction (aged 16–54 y): £21,106 • Family tracing (aged 16–54 y): £4,914

Author, year, country	Analytic technique, study design, perspective, time horizon	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
						PSA results not reported
McKay et al, 2018[62] United Kingdom	Cost-utility analysis Decision tree and Markov model National Health Service Lifetime horizon, cycle length unclear	1–2-y-old children exposed to universal screening	1. No universal screening (allows for any ongoing cluster testing) 2. Cholesterol screening 3. Sequential genetic testing: cholesterol screening (i.e., genetic testing followed by cholesterol screening among mutation-positive individuals) 4. Sequential cholesterol screening: genetic testing (i.e. cholesterol screening followed by genetic testing among cholesterol-positive individuals) 5. Parallel cholesterol screening-genetic testing (i.e., cholesterol screening coincident with genetic testing)	Total QALYs per 10,000 screened • No screening: 992.2 • Cholesterol-only screening: 1,009.1 • Sequential cholesterol-genetic screening: 1,010.7 • Sequential cholesterol-genetic screening plus reverse cascade screening: 1,027.5 • Sequential genetic-cholesterol screening: 1,000.7 • Sequential genetic-cholesterol screening plus reverse cascade screening: 1,022.2 • Parallel cholesterol-genetic screening: 1,011.5 • Parallel cholesterol-genetic screening plus reverse	Currency, year: GBP, 2017 Total costs per 10,000 screened • No screening: £225,983 • Cholesterol-only screening: £561,071 • Sequential cholesterol-genetic screening: £640,288 • Sequential cholesterol-genetic screening plus reverse cascade screening: £672,362 • Sequential genetic-cholesterol screening: £2,745,892 • Sequential genetic-cholesterol screening plus reverse cascade screening: £2,786,918	ICER by age group, per QALY • No screening: reference • Cholesterol-only screening: £19,298 • Sequential cholesterol-genetic screening: £21,872 • Sequential cholesterol-genetic screening plus reverse cascade screening: £12,480 • Sequential genetic-cholesterol screening: £283,799 • Sequential genetic-cholesterol screening plus reverse cascade screening: £84,240 • Parallel cholesterol-genetic

Author, year, country	Analytic technique, study design, perspective, time horizon	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
			6–8. Comparators 3–5, respectively, plus reverse cascade screening	cascade screening: 1,033.0 Discount rate: 3.5%	• Parallel cholesterol-genetic screening: £2,823,343 • Parallel cholesterol-genetic screening plus reverse cascade screening: £2,864,370 Discount rate: 3.5%	screening: £131,635 Parallel cholesterol-genetic screening plus reverse cascade screening: £63,957 PSA results: the probability of being cost-effective was 96.8% at a willingness-to-pay value of £20,000 per QALY gained for sequential genetic-cholesterol screening plus reverse cascade screening strategy
Nherera et al, 2011[63] United Kingdom	Cost–utility analysis Decision tree and Markov model National Health Service Lifetime horizon with a cycle length of 1 y	People suspected of having FH; ≥50 y for index cases and ≥30 y for relatives	Screening with 1. Cholesterol method 2. DNA method 3. DNA + DFH. In addition to comparator 2, cholesterol method was used for those relatives of confirmed FH index cases 4. DNA + DFH + PFH: In addition to comparator 2, cholesterol method was used for those relatives	Total QALYs (mean per person) • DNA: 24.12 • DNA + DFH: 24.28 • DNA + DFH + PFH: 25.18 • Cholesterol: 10.89 Discount rate: 3.5%	Currency, year: GBP, 2010–2011 Total costs (mean per person) • DNA: £50,918 • DNA + DFH: £52,670 • DNA + DFH + PFH: £54,799 • Cholesterol: £44,576 Discount rate: 3.5%	ICER • £479 for DNA method compared with cholesterol method • £3,666 for DNA + DFH + PFH method compared with DNA method DNA + DFH method was dominated by DNA and DNA + DFH + PFH methods PSA results: the probability of the

Author, year, country	Analytic technique, study design, perspective, time horizon	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
			of confirmed and possible FH index cases			DNA + DFH + PFH approach being cost-effective was 100%, at a willingness-to-pay value of £20,000 per QALY gained
Oliva et al, 2009[67] Spain	Cost-effectiveness analysis Model-based approach National health system (single payer) Lifetime horizon	Relatives of index cases in the national genetic testing program	Genetic screening and statin treatment No screening	Life-years (mean per person) • Screened: 56.7 • Not screened: 55.4 • Life-years gained: 1.3 Discount rate: 3%	Currency, year: EUR, 2005 Total costs (mean per person) • Screened: €8,891 • Not screened: €4,298 • Incremental: €4,593 Discount rate: 3%	Incremental cost per life-year gained: €3,423 PSA results: the probability of screening strategy being cost effective was over 95% at a willingness-to-pay value of €7,400 per QALY gained
Pelczarska et al, 2018[64] Poland	Cost–utility analysis Markov model Public payer perspective Lifetime horizon with a cycle length of 1 y	Three populations: people getting first job, 6-y-old children, people after the first onset of acute coronary syndrome or stroke	Universal screening using clinical or genetic diagnosis for people getting their first job Universal screening of 6-y-old children, based on genetic diagnosis Opportunistic screening of people after the first onset of acute coronary syndrome or stroke using only clinical or genetic criteria (for all or limited to people with disease before	Total incremental QALY per 100,000 probands Universal screening for people with first job: • Clinical testing: 1,450 • Genetic testing: 1,528 Universal screening for 6-y-old children: • Genetic diagnosis: 1,371 Opportunistic screening of people after the first onset of acute coronary	Currency, year: PLN (1 PLN = 0.2292 EUR), currency year unclear Total incremental costs of diagnosis and treatment per 100,000 probands Universal screening for people with first job • Clinical testing: zł 3,341,131 • Genetic testing: zł 5,293,109 Universal screening for 6-y-old children	ICER: PLN per QALY gained Universal screening for people with first job • Clinical testing: zł 2,304 • Genetic testing: zł 3,465 Universal screening for 6-y-old children • Genetic diagnosis: zł 4,555 Opportunistic screening of people after the first onset of acute coronary

Author, year, country	Analytic technique, study design, perspective, time horizon	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
			age 55 in men and 65 in women) No intervention	syndrome or stroke using only clinical criteria: • People with disease before age 55 in men and 65 in women: 3,774 • All: 712 Opportunistic screening of people after the first onset of acute coronary syndrome or stroke using only genetic criteria • People with disease before age 55 in men and 65 in women: 4,329 • All: 817 Discount rate: 3.5%	• Genetic diagnosis: 6,244,489 PLN Opportunistic screening of people after the first onset of acute coronary syndrome or stroke using only clinical criteria • People with disease before age 55 in men and 65 in women: zł 1,774,110 • All: zł 3,595,867 Opportunistic screening of people after the first onset of acute coronary syndrome or stroke using only genetic criteria • People with disease before age 55 in men and 65 in women: zł 14,784,743 • All: zł 17,464,619 Discount rate: 5%	syndrome or stroke using only clinical criteria • People with disease before age 55 in men and 65 in women: zł 470 • All: zł 5,048 Opportunistic screening of people after the first onset of acute coronary syndrome or stroke using only genetic criteria • People with disease before age 55 in men and 65 in women: zł 3,415 • All: zł 21,375 No PSA results reported

Author, year, country	Analytic technique, study design, perspective, time horizon	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
Sharma et al, 2012[65] United Kingdom	Cost–utility analysis Decision tree and Markov model National Health Service Lifetime horizon	Adults with heterozygous FH, focusing on index cases with a clinical diagnosis of FH based on the Simon Broome criteria (either confirmed or possible FH)	Elucigene FH20 Elucigene FH20_MLPA LIPOchip CGA LDL-C	Total QALYs (for 1,000 individuals) Index cases • CGA: 13,056 • LDL-C: 13,079 Index cases and relatives • CGA: 39,231 • LDL-C: 34,744 Discount rate: 3.5%	Currency, year: GBP, 2010–2011 Total costs (for 1,000 individuals) Index cases: • CGA: £15,528,212 • LDL-C: £17,678,183 Index cases and relatives • CGA: £48,501,362 • LDL-C: £43,880,789 Discount rate: 3.5%	ICER for index cases only: CGA was less costly (savings of £2,150 per person) and less effective (QALY −0.02 per person) compared to lipid testing ICER for both index cases and relatives: £1,030 per QALY gained PSA results: CGA had a 100% probability of cost-effectiveness at a willingness-to-pay value of £20,000 per QALY gained
Wonderling et al, 2004[66] Netherlands	Cost-effectiveness analysis Life table analysis Unclear perspective, including treatment and screening costs Lifetime horizon	Relatives of index cases in the national genetic testing program	Genetic screening and statin treatment No screening	Life-years gained per new untreated case: 0.9 Discount rate: 4%	Currency, year: USD, 2001 • Total incremental cost per new untreated case: $7,500 Discount rate: 4%	Incremental cost per life-year gained: $8,800 No PSA results reported

Abbreviations: CGA, comprehensive genomic analysis; DFH, definite familial hypercholesterolemia; DLCN, Dutch lipid clinic network; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PFH, possible familial hypercholesterolemia; FH, familial hypercholesterolemia; ICER, incremental cost-effectiveness ratio; mo, month(s); PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; SB, Simon Broome; TC, total cholesterol.

[a]A dominant strategy is less costly and more effective than the strategy being dominated.

[b]Calculated by dividing the difference in costs by the difference in QALYs for each strategy compared with the next best alternative strategy, excluding dominated and extendedly dominated options.

[c]Interventions that are extendedly dominated are ruled out. If the ICER for Strategy A compared to Strategy B is higher than the ICER for Strategy C compared to Strategy B, then Strategy A is considered extended dominant and ruled out.

Applicability and Limitations of the Included Studies

Appendix 5 provides the results of the applicability and quality appraisal checklist for economic evaluations (see Tables A3 and A4). Six studies were deemed partially applicable[53,54,56-58,63] and eight were deemed not applicable to our research question. The concerns related to applicability mainly arise from two sources: narrower study populations and standard care practices that are different for Ontario, including the use of other clinical criteria (e.g., the Simon Broome criteria or the DLCN criteria), the availability of genetic testing, and different screening or case identification approaches.

There was limited evidence regarding the use of genetic testing in individuals with a clinical diagnosis. The costs and effectiveness outcomes were influenced by age, but the impact of age on the cost-effectiveness results was unclear. For cascade screening, the included studies had different target populations. For example, they either focused on a certain age group[53,55,62] or included only first-degree relatives.[61] It is still unclear what the optimal cascade screening strategy is. For example, should genetic cascade screening be reserved for a specific category of family member (e.g., first-degree relatives only)?

Another concern is that the studies in the literature used different diagnostic criteria. For example, six studies used the Simon Broome criteria,[56,58,62-65] while five studies used the DLCN criteria.[56,59,60,64,66] In Ontario, clinicians often use the Canadian definition of FH.[18] As a result, the diagnoses of index cases in the included studies may be inconsistent with the Ontario clinical practice. Other screening or case identification approaches with genetic testing in the pathway may differ from Ontario practice. For example, Nherera et al[63] assessed cascade screening of index cases identified through the Simon Broome criteria. In this study, if the index cases were positive for a pathogenic variant, their relatives were tested and treated, but when the index cases were not positive for a pathogenic variant, the index cases were classified as confirmed or probable FH. Their relatives were offered lipid testing and treated if they were diagnosed too.

Discussion

Our economic evidence review suggested that genetic cascade screening is cost-effective compared to no cascade screening in most scenarios. Genetic cascade screening has the potential to improve health outcomes and help with identification of new cases. It also enables early intervention for individuals at high risk of cardiovascular disease. However, the existing economic evidence is inadequate to answer whether there is additional value for individuals with a clinical diagnosis of FH to receive the genetic testing because of the uncertainty surrounding the results and its limitation in applicability. There is also an evidence gap regarding who are the target populations for cascade screening (e.g., first-, second, or third-degree relatives of genetically confirmed index cases), and what is the optimal strategy to include genetic testing.

The literature suggests that the cost-effectiveness of cascade screening using FH genetic testing might depend on the comparator. One cost–utility analysis from the US setting compared genetic cascade screening to lipid screening and concluded that genetic cascade screening may not be cost effective when it is compared with lipid screening.[55] Therefore, the additional value of genetic testing to lipid testing in cascade screening may be limited. Because genetic testing for FH is not widely available in Ontario, screening with lipid testing for relatives of index cases is the standard of care. It is of interest to understand the cost-effectiveness of genetic cascade screening compared to lipid cascade screening. Meanwhile, the technology behind genetic testing for FH is rapidly evolving. In the last decade, the world has witnessed a significant price reduction for genetic testing and there is recent clinical evidence regarding new medication on familial hypercholesterolemia. But the existing economic evidence provided little information on the impact of cascade screening on the treatment decision and adherence, and how this was connected to the benefit predicted in the cost-effectiveness.

In Ontario, LipidSeq, a targeted sequencing, evaluates monogenic and polygenic factors on 69 genes and 185 single-nucleotide polymorphisms (SNPs).[14] The cost and performance of this genetic testing

panel may differ from the testing in existing evaluations, which may be targeting some rather than all potentially relevant genes (most FH panels focus on three genes: *LDLR, APOB, PSCK9*), or using different testing methodologies (affecting their ability to detect certain types of gene variants).

Furthermore, in Ontario, the clinical practice regarding FH may differ from other provinces and countries. This difference may invalidate the assumptions in most studies evaluating the cost-effectiveness of genetic testing for children.[53,62] All these studies suggested that it may be worthwhile to conduct a cost-effectiveness analysis from an Ontario perspective. To determine the cost-effectiveness of genetic testing in the Ontario setting, we need to consider the clinical practice of FH diagnosis and cascade screening of relatives, as well as the available genetic testing in Ontario. Owing to 1) a lack of evidence on the genetic testing used for individuals with a clinical diagnosis of FH, 2) the limited evidence on genetic cascade screening compared with lipid screening, and 3) the concerns over applicability of these included studies, we plan to conduct a primary economic evaluation relevant to the clinical practice and policy of genetic testing for FH in Ontario.

Strengths and Limitations

Our economic evidence review has several strengths. It is comprehensive and provides an updated evidence summary on the use of genetic testing for FH. A majority of the included studies support the cost-effectiveness of genetic cascade screening compared with no cascade screening. However, because most of the studies were comparing genetic cascade screening versus no screening, this review is limited regarding its generalizability. The evidence is insufficient to answer other important policy questions regarding the use of genetic testing, especially the use of genetic testing based on risk category (i.e., possible, probable, or confirmed FH). Additionally, most of the included studies were not based on the latest evidence regarding diagnosis and management of FH. An updated analysis based on latest evidence is necessary.

Conclusions

Our systematic review of the economic evidence suggested that genetic cascade screening is probably cost-effective compared to no cascade screening. However, we found limited evidence on the cost-effectiveness of genetic testing for confirmatory diagnoses of FH in individuals with a clinical diagnosis (index cases), and the optimum way to use genetic testing in the diagnostic pathway is unclear. To account for the cost-effectiveness of genetic testing in the Ontario setting, it is necessary to conduct a *de novo* analysis that examines the Canadian or Ontario practice and incorporates the context-specific parameters and the latest evidence about the treatment decision, disease progression, and long-term health outcomes.

Primary Economic Evaluation

We identified several published studies that evaluated the cost-effectiveness of genetic cascade screening for relatives of index cases with familial hypercholesterolemia (FH), but none took a Canadian perspective. There was limited evidence on the cost-effectiveness of genetic testing for individuals with a clinical diagnosis of FH. Owing to these limitations, we conducted a primary economic evaluation.

Research Questions

1. For an individual with a clinical diagnosis of FH, what is the cost-effectiveness of genetic testing compared with no FH genetic testing confirmation?
2. For first-, second-, or third-degree relatives of an individual with FH (confirmed through genetic testing), what is the cost-effectiveness of genetic cascade screening compared with no genetic cascade screening for identification of FH?
3. For individuals with a clinical diagnosis of FH and relatives of genetically confirmed FH cases, what is the cost-effectiveness of genetic testing compared with no genetic testing? (This question combines questions 1 and 2, capturing the full diagnostic pathway.)

Methods

The information presented in this report follows the reporting standards set out by the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement.[68]

Type of Analysis

We conducted probabilistic cost–utility analyses as it is the reference case approach recommended by the Canadian Agency for Drugs and Technologies in Health (CADTH) guidelines for economic evaluation.[69]

Outcomes of Interest

The effectiveness outcome of interest is quality-adjusted life-years (QALYs), which considers both the patient's survival and their quality of life (1 QALY represents 1 year of perfect health).[70] A generic outcome measure such as QALYs allows decision-makers to make comparisons across different conditions and interventions.

We also conducted cost-effectiveness analyses with outcomes expressed in natural units. The value of genetic testing for FH is to help identify those people who are potentially at very high risk of cardiovascular disease (CVD) events and provide primary or secondary prevention to lower risks of premature CVD events and death. For health outcomes, we used the following natural units and estimated each outcome separately for index cases and the relatives of genetically confirmed cases:

- Number of FH diagnoses. A FH diagnosis is defined by the presence of pathogenic variants identified through genetic testing, regardless of lipid testing results, or a clinical diagnosis (including possible, probable, or confirmed FH) in the case of no genetic testing
- Average number of CVD events per person. We considered this outcome because a potential benefit of genetic testing is that individuals with a FH diagnosis can receive early intervention to prevent premature CVD events[55]

For costs, we considered both short- and long-term direct medical costs, such as those associated with genetic testing, professional fees, lipid-lowering therapy, and fatal or non-fatal atherosclerotic cardiovascular events (CVD events).

Target Population

For the first research question, our target population includes adults with a clinical diagnosis of FH based on clinical evaluation without genetic testing (e.g., lipid testing, family history, and personal history). The average age of the target population is 43 years (range: 18–60 years).[18] A clinical diagnosis of FH includes possible, probable, or confirmed FH based on the Dutch Lipid Collaborative Network (DLCN) criteria, hereinafter referred to as individuals with at least a clinical diagnosis of possible FH. The DLCN criteria are a validated set of criteria based on the history of premature CVD in the index case's first-degree relatives, their own CVD history, untreated lipid levels, and physical signs such as the presence of tendon xanthomata or arcus cornealis prior to the age of 45. According to the score, the diagnosis based on DLCN criteria could be unlikely, possible, probable, or confirmed. In our reference case, our target population was individuals with at least a clinical diagnosis of possible FH based on DLCN criteria. This is to focus on the benefit of genetic testing, which is to add certainty to the FH diagnosis.

For the second research question, the target population includes the relatives (both children and adults, age range: 5–60 years) of the index cases confirmed with genetic testing. Because of the different baseline risk levels, we separately assessed the cost-effectiveness of cascade screening for first-,
second-, and third-degree relatives with or without genetic testing.

For the third research question, the target population includes both the index cases (to confirm the FH diagnosis by genetic testing) and the relatives (to conduct cascade screening with or without genetic testing to identify additional cases).

In our analysis, the risk profiles of CVD and death events depend on sex and age. We estimated the costs and effectiveness for males and females separately and calculated the average as the estimate for the whole population.

Perspective

We conducted this analysis from the perspective of the Ontario Ministry of Health.

Interventions and Comparators

COMPARATOR

In Ontario, the diagnosis of FH is mostly based on clinical criteria (Drs. Stasia Hadjiyannakis, Elaine Goh, Mina Madan, Nita Chahal, and Robert Hegele, telephone communications, October 2020). As shown in Figure 1, guidelines by the Canadian Cardiovascular Society recommend that the diagnosing of FH be based on lipid testing, physical examination (to determine the presence of conditions associated with FH, such as tendon xanthomas), a personal and family history of cardiovascular diseases and FH, and genetic testing.[71] We assume that usual care for FH diagnoses includes lipid testing, physician examination (to determine the presence of conditions associated with FH, such as tendon xanthomas), and a personal and family history of cardiovascular disease and FH.

INTERVENTION

Genetic testing may help avoid misdiagnoses, missed diagnoses, or inaccurate treatment decisions following incorrect and missed diagnosis, as well as improve treatment adherence. In this health technology assessment, we assumed LipidSeq (a next-generation sequencing test available in Ontario) was used for genetic testing of FH in our population of interest.[14]

Table 6 summarizes the interventions and comparators evaluated in the economic model. The first research question compares genetic testing with clinical evaluation without genetic testing (see Tables 6 and 7).

- Genetic testing: all individuals with a clinical diagnosis of FH through lipid testing continue with genetic testing for pathogenic variants
- Clinical evaluation without genetic testing: cholesterol levels, including LDL-C, were measured through lipid testing

For the second research question, we compared three cascade screening strategies (two with genetic testing) with no cascade screening (see Tables 6 and 7).

- Cascade screening with sequential testing: screen with lipid testing first for all first-, second-, and third-degree relatives, followed by genetic testing for those with elevated LDL-C levels. Relatives could be diagnosed as with FH (phenotype +/genotype +) or without FH (phenotype +/genotype –, phenotype –/genotype unknown)
- Cascade screening with genetic testing only: genetic testing (as well as lipid testing as part of usual care) for all first-, second-, and third-degree relatives. Based on the test result, relatives could be diagnosed as with FH (phenotype +/genotype +, phenotype –/genotype +), without FH (phenotype –/genotype –), or with an alternative diagnosis (phenotype +/genotype –)
- Cascade screening with lipid testing only: only lipid testing is used to screen relatives. First-, second-, and third-degree relatives could be diagnosed as with FH (phenotype +/genotype unknown) or without FH (phenotype –/genotype unknown)
- No cascade screening: do nothing. The diagnosis is unknown (phenotype unknown/genotype unknown) for the relatives, and no treatment regimen is adopted

We further compared different diagnostic pathways, which are combinations of the strategies in the two previous research questions; for example, diagnosis of index cases with genetic testing, followed by cascade screening with sequential testing (see Tables 6 and 7).

Table 6: Testing Strategies Evaluated in the Model

Intervention	Comparator	Population
Confirmatory diagnosis in index cases		
Genetic testing	Clinical evaluation without genetic testing (FH clinical diagnosis based on lipid testing only)	Individuals with a possible, probable, or confirmed clinical diagnosis of FH
Cascade screening in relatives		
Sequential testing: lipid testing for everyone followed by genetic testing for those with elevated LDL-C levels Genetic testing: genetic testing regardless of LDL-C levels	Lipid testing only No cascade screening	First-, second-, or third-degree relatives of an index case with FH confirmed through genetic testing
Diagnostic pathway of FH		
Genetic testing for individuals with a FH clinical diagnosis and cascade screening for relatives with sequential testing Genetic testing for individuals with a FH clinical diagnosis and cascade screening for relatives with genetic testing Genetic testing for individuals with a FH clinical diagnosis and cascade screening for relatives with lipid testing only Genetic testing for index cases and no cascade screening Clinical evaluation without genetic testing for individuals with a FH clinical diagnosis and cascade screening for relatives with sequential testing Clinical evaluation without genetic testing for individuals with a FH clinical diagnosis and cascade screening with genetic testing	Clinical evaluation without genetic testing for individuals with a FH clinical diagnosis and cascade screening with lipid testing only Clinical evaluation without genetic testing for individuals with a FH clinical diagnosis, no cascade screening	Individuals with a possible, probable, or confirmed clinical diagnosis of FH and first-, second-, or third-degree relatives of an index case with FH confirmed through genetic testing

Abbreviations: FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol.

We assumed individuals would receive different subsequent management based on their diagnostic results. For the first research question, we assumed that all individuals who have a clinical diagnosis are offered lipid-lowering therapy. For the second research question, only relatives who are diagnosed with FH and with elevated LDL-C (Table 7) will be offered lipid-lowering therapy. The first-line treatment is statins. In a scenario analysis, we explored the impact on cost-effectiveness if patients are offered *PCSK9* inhibitors, a new treatment with higher effectiveness and cost that recently became available in Canada.[72]

Table 7: Diagnostic Results and Subsequent Management in the Model

Clinical diagnosis[a]	Genetic testing	Diagnosis	Lipid-lowering therapy	Research questions[b]
Phenotype +	Genotype +	Genetically confirmed FH	Yes[c]	1, 2, and 3[d]
Phenotype –	Genotype +	Genetically confirmed FH	No, monitor LDL-C	2 and 3
Phenotype +	Genotype –	Alternative diagnosis, such as severe hypercholesterolemia or no hypercholesterolemia	Yes, treat LDL-C[e]	1, 2, and 3[d]
Phenotype –	Genotype –	No FH	No	2 and 3
Phenotype +	Genotype unknown	A clinical diagnosis of FH	Yes[c]	1, 2, and 3[d]
Phenotype –	Genotype unknown	No FH	No	2 and 3
Phenotype unknown	Genotype unknown	Unknown diagnosis[f]	No	2 and 3

Abbreviations: FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol.
[a] Clinical diagnosis is based on lipid testing as well as personal and family history. Personal and family history are part of usual care and will be offered to individuals receiving genetic testing.
[b]The first research question compares genetic testing strategy with no genetic testing strategy; the second research question compares three cascade screening strategies (two with genetic testing) with no cascade screening; the third research question compares different diagnostic pathways, which are combinations of the strategies in the two previous research questions; for example, diagnosis of index cases with genetic testing followed by cascade screening with sequential testing.
[c]Lipid-lowering therapy starts for adults diagnosed with FH.
[d]Because the target population is individuals with possible, probable, or confirmed clinical diagnosis of FH, these individuals have already received lipid testing. Those without a clinical diagnosis or where no clinical evaluation was conducted are not considered in strategy 1.
[e]For individuals with phenotype +/genotype – results, alternative diagnosis may be considered, but high cholesterol needs to be treated.
[f]The diagnosis is unknown because no testing, either lipid or genetic, was provided.

Time Horizon and Discounting

We used a lifetime horizon in the reference case analysis to account for long-term costs and outcomes for all research questions. We also considered shorter time horizon (5 years) in scenario analyses. In accordance with CADTH guidelines,[69] we applied an annual discount rate of 1.5% to both costs and QALYs incurred after the first year. All costs were expressed in 2021 Canadian dollars.

Main Assumptions

The main assumptions applicable to all research questions were as follows:

- Other interventions related to hypercholesterolemia, including exercise and dietary change, are the same across different testing strategies
- Genetic testing is the gold standard of FH diagnosis, so the sensitivity and specificity of genetic testing are assumed to be 100% (i.e., we did not consider false positive or false negative results)
- The time for returning results is negligible, and there are no costs or disutilities related to waiting for the testing results
- The diagnostic results indirectly influence the outcomes through treatment change (initiation or change of lipid-lowering therapy), which in turn leads to better LDL-C reduction
- The treatment effect is constant over the lifetime and after diagnosis

- For individuals with positive phenotype but negative genetic testing results, alternative diagnoses related to hypercholesterolemia will be considered and treated

The main assumptions applicable only to the first research question were:

- The index case has at least a clinical diagnosis of possible FH based on the DLCN criteria so we can evaluate the additional value of genetic testing for individuals with a FH clinical diagnosis. Because the sensitivity and specificity were assumed to be 100%, false positive results are only applicable to FH cases based on a clinical diagnosis
- Genetic testing has no impact on the patient's adherence to the lipid-lowering therapy in the reference case. We explored the impact of better adherence after genetic testing in a scenario analysis
- Only adults would present as potential index cases and seek a diagnosis of FH. This assumption is based on clinical expert opinion that the majority of index cases are adults (Elaine Goh, MD, personal communication: email, May 10, 2021)

The main assumption applicable only to the second research question was:

- Biological relatives of index cases (adults and children) who were confirmed through genetic testing will be offered cascade screening

The main assumption applicable only to the third research question was:

- All risks among different generations and cost and outcome estimates are independent of each other

Model Structure

We developed a decision-analytic model to evaluate the cost-effectiveness of genetic testing in the diagnosis and cascade screening of FH. The model combines a decision tree and a Markov model. The decision tree estimates the testing costs and diagnostic results (diagnosed with FH, diagnosed without FH, unknown diagnosis, or alternative diagnosis). We used one decision tree to model genetic testing in index patients with a FH clinical diagnosis and another decision tree to model genetic testing in cascade screening of relatives of the index case. The same Markov model was used to simulate the long-term costs and outcomes after the diagnosis, including the occurrence of CVD events and death, as well as QALYs.

DECISION TREE MODELS

First Research Question: Genetic Testing for Index Cases

We aim to assess the cost-effectiveness of genetic testing compared with no genetic testing for individuals with a clinical diagnosis of FH.[71] As shown in Figure 5, all individuals enter the decision tree with a clinical diagnosis of FH. The genotype of those who receive no genetic testing is unknown, and they may have a true positive or false positive diagnosis. The results for those who receive genetic testing could be either positive or negative. People with positive genetic results (FH-relevant pathogenic variants) are considered true positive. People with negative genetic results (no known FH-relevant pathogenic variants) are considered as having other hypercholesterolemia (that will be treated) or no hypercholesterolemia (we assume these people will be treated for 2 years and then discontinue their treatment). The subsequent management received by patients with different diagnostic results are shown in Table 7, above.

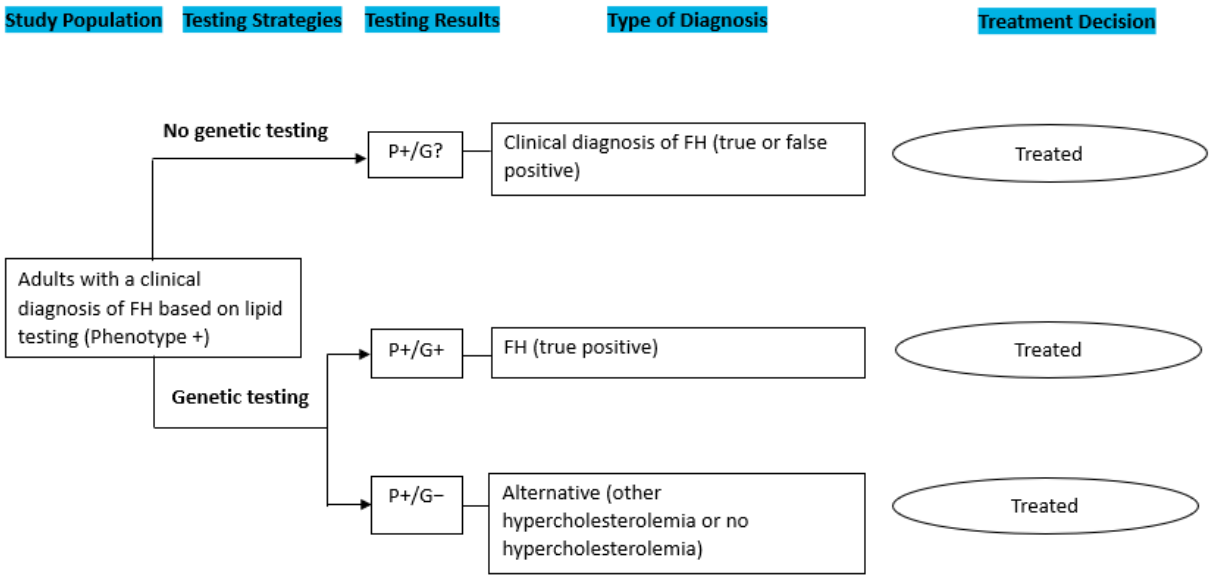

Figure 5: Decision Tree for Genetic Testing of Individuals With Clinical Diagnosis of FH

Abbreviations: FH, familial hypercholesterolemia; G+, genotype positive, genetically confirmed FH diagnosis; G−, genotype negative, without pathogenic variant; G?: genotype unknown; P+, phenotype positive.
Note: boxes represent test results or underlying conditions, including diagnosed with or without FH; ovals represent cohorts in the Markov model.

Second Research Question: Cascade Screening in Relatives of Genetically Confirmed Index Cases
We aim to assess the cost-effectiveness of genetic cascade screening compared with no genetic cascade screening to identify FH in relatives of individuals with a genetically confirmed FH diagnosis. Figure 6 and Table 6 (above) show the genetic cascade screening and control strategies for relatives of an index case with FH. As described in Interventions and Comparators (above), the compared strategies may include screening with a sequential testing algorithm, with genetic testing only, with lipid testing only, or no cascade screening at all.

Depending on the types of cascade screening, the types of diagnosis relatives could receive are:

- With FH, including:
  - True positive results based on clinical diagnosis only (phenotype +/genotype unknown) or confirmed by genetic testing (phenotype +/genotype +, phenotype –/genotype +)
  - False positive results based on lipid testing (phenotype +/genotype unknown)
- Without FH, including true negative and false negative results. Both clinical diagnosis and genetic testing can generate true or false negative results (phenotype –/genotype – or phenotype –/genotype unknown)
- Alternative diagnosis if clinical diagnosis suggests FH but there is no known FH-relevant pathogenic variant (phenotype +/genotype –) (see Table 7 and Figure 6)

If relatives do not receive cascade screening, their diagnosis is unknown, and they are not offered treatment. However, some may have FH (missed diagnosis) or other hypercholesterolemia conditions, or some may not have FH and do not need treatment.

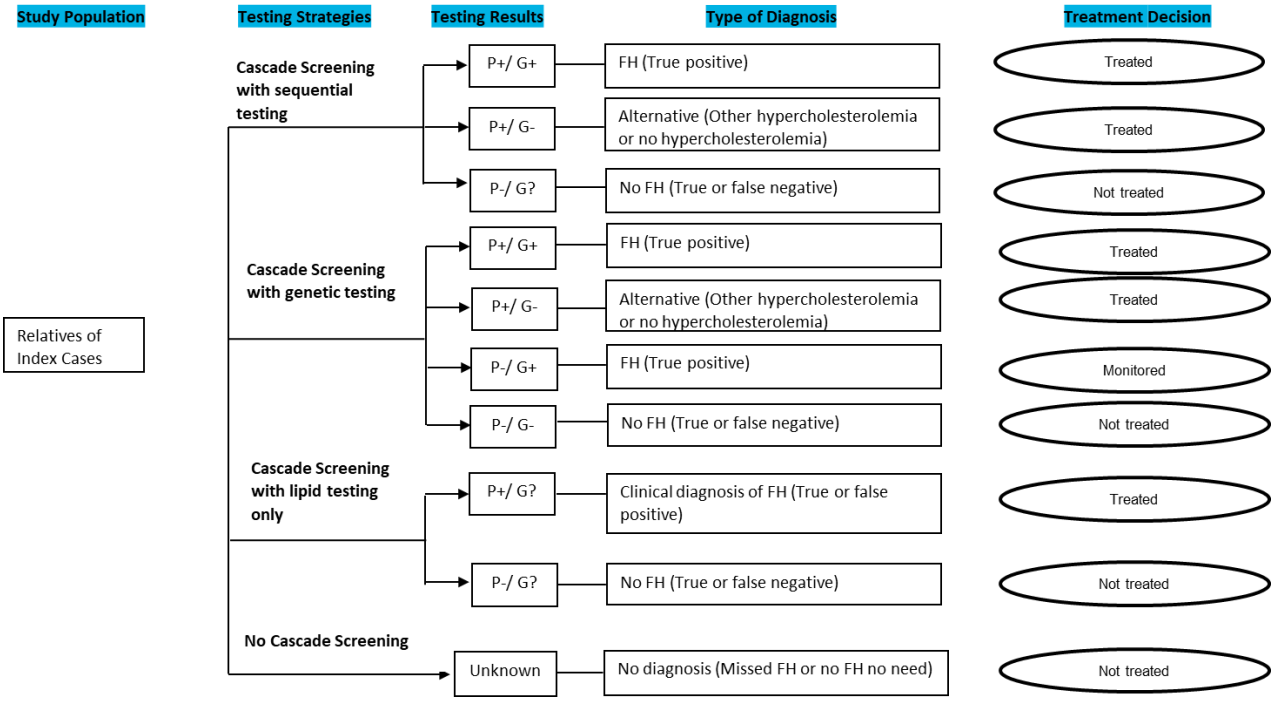

Figure 6: Decision Tree for Cascade Screening of Relatives

Abbreviations: FH, familial hypercholesterolemia; G+, genotype positive, genetically confirmed FH diagnosis; G–, genotype negative, without pathogenic variant; G?: genotype unknown; P+, phenotype positive; P–, phenotype negative.
Note: boxes represent test results or underlying conditions; ovals represent cohorts in Markov model.

Third Research Question: Both Confirmatory Diagnosis and Cascade Screening
We aim to assess the cost-effectiveness of using genetic testing for the whole pathway by combining the decision trees for the two previous research questions (Figures 5 and 6). We assumed the diagnostic pathways would be applied to three individuals from a family, including one index case (individual with a clinical diagnosis of FH, age 43 years) and two first-degree relatives (ages 8

and 28 years). We estimated the average costs and QALYs per family across the diagnostic pathways.

TREATMENT DECISION BASED ON DIAGNOSTIC RESULTS

In our analysis, individuals can be diagnosed as with or without FH; they may also receive an alternative (e.g., severe hypercholesterolemia) or unknown diagnosis. Those who truly have FH may receive a diagnosis that is true positive, false negative, or unknown (i.e., missed opportunity for diagnosis and treatment). Meanwhile, those who truly do not have FH may receive a diagnosis that is false positive, true negative, or unknown (these individuals may not receive treatment for the wrong reasons, but because they do not have FH, they do not need treatment).

Individuals Diagnosed As with FH (Both True and False Positives)

We assume that individuals who are diagnosed with FH and have elevated LDL-C will be offered lipid-lowering therapy (Table 7).

- In the case of no genetic testing, if the diagnosis is established with lipid testing and disease history (phenotype +/genotype unknown), the treatment will start with statins as the first-line therapy
- If the diagnosis is genetically confirmed and there is also elevated LDL-C level (phenotype +/genotype +), we assumed that treatment is the same lipid-lowering therapy as for those having a clinical diagnosis (i.e., statins). In our scenario analysis, we explore the impact of individuals with FH receiving *PCSK9* inhibitors in addition to statins
- If the diagnosis is based on genetic testing alone, without elevated LDL-C (phenotype –/genotype +), we assume these individuals will not start lipid-lowering therapy before the LDL-C is elevated. They will receive lipid testing every 2 years[58]
- Individuals receiving statin treatment need monitoring. The statin monitoring incurs additional costs but no additional disutility because it does not require a change in the health state

Those who receive a true positive diagnosis are correctly diagnosed and treated. Those who receive a false positive diagnosis receive unnecessary treatment. Because the presence of genetic mutation is considered the gold standard, false positive results are only applicable to people who receive a clinical diagnosis. We assume that these individuals will discontinue treatment after 2 years.

Individuals Diagnosed As Without FH (Both True and False Negative)

Individuals diagnosed as not having FH, either excluded by both lipid and genetic testing, or by clinical diagnosis after lipid testing and disease history, will stay with no treatment.

People who receive a true negative diagnosis do not need treatment. People who receive a false negative diagnosis miss necessary treatment and have higher lifetime medical costs due to cardiovascular complications from their untreated condition.

Individuals With Alternative Diagnoses

For all research questions, alternative diagnoses could be considered for individuals who have a clinical diagnosis of FH, but genetic testing does not confirm the presence of known pathogenic variants (phenotype +/genotype –) (see Table 7, above). These individuals will still be offered lipid-lowering therapy to treat high LDL-C levels.[58]

Individuals With an Unknown Diagnosis (Missed Diagnosis or Unknown Diagnosis but No Treatment Needed)

Relatives of genetically confirmed FH cases who receive neither clinical evaluation with lipid testing nor genetic testing are of unknown diagnosis (see Table 7, above). They would not receive any treatment. Therefore, if they have FH or any other hypercholesterolemia conditions, they would miss the opportunity to receive early intervention (missed diagnoses). However, individuals with an

unknown diagnosis who do not have FH will not experience loss in health as they do not need treatment.

MARKOV MODEL

Figure 7 shows the Markov model used to simulate disease progression and death. This model has a lifetime horizon and a cycle length of 1 year. All research questions share the same model structure, but their initial cohorts differ. Depending on the underlying condition, diagnostic results, and treatment decision, the initial cohorts could be:

- True positive FH diagnosis and treated
- False positive FH diagnosis and treated
- Hypercholesterolemia other than FH, but treated for LDL-C
- True negative FH diagnosis and untreated
- False negative FH diagnosis and untreated
- True positive FH and monitored
- Hypercholesterolemia other than FH and untreated

All individuals will enter the Markov model immediately after the diagnosis and treatment decision is determined by the decision tree, and their long-term outcomes will be simulated until death or they reach age 110 years. The Markov model includes four health states: pre-CVD, CVD, post-CVD, and death. For the first research question, we assume that a portion of individuals with a diagnosis of FH start from a CVD event.[18] These individuals will have begun lipid-lowering therapy by the time they enter the model. The remaining individuals for the first research question and all individuals for the second research question start in the pre-CVD health state. We describe the definitions of the modelled health states and transition pathways below.

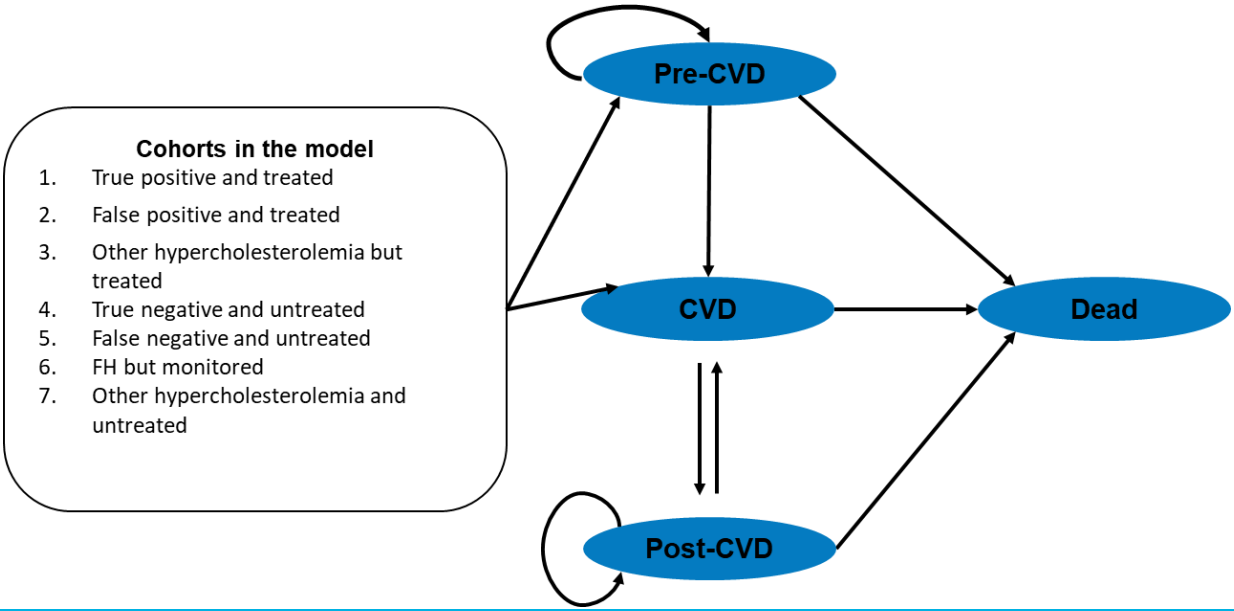

Figure 7: Markov Model Structure

Note: Each oval represents a health state in the Markov model; arrows indicate allowed transitions. Death is the absorbing health state.
Abbreviations: CVD, cardiovascular disease; FH, familial hypercholesterolemia.

Pre-CVD: people who are not experiencing CVD events, regardless of their underlying conditions. The utility and costs related to the pre-CVD health state are equivalent to those of the general population. People in the pre-CVD state may die because of background mortality. They may also stay in the pre-CVD state or enter the CVD state by having an event.

CVD: people within 1 year of their first CVD event. Individuals may enter this health state after an event of acute coronary syndrome, acute myocardial infarction, stable or unstable angina, coronary or arterial revascularization, stroke, transient ischemic attack, or peripheral artery disease. After a CVD event, individuals may die (fatal CVD event) or transition to the post-CVD state.

Post-CVD: people who survived a CVD event for more than 1 year since their last event. Individuals in the post-CVD state may stay in this health state, experience another CVD, or die. Compared with pre-CVD individuals, individuals in this health state have higher health care costs and a lower health-related quality of life, as well as a higher risk of death.

Dead: people have a risk of death determined by their health state and treatment at any cycle. As this model has a lifetime horizon, everyone completes the model by entering the dead health state.

Individuals who have experienced CVD events (are in CVD or post-CVD states) cannot transition back to the pre-CVD state. They can experience up to three CVD events (transition from post-CVD to CVD) in the lifetime horizon.

The diagnostic results and treatment decisions influence the transition between health states in the following ways:

- Individuals with FH (those who have received a true positive or false negative diagnosis) have a higher risk of CVD events than those without FH (those who have received a true negative or false positive diagnosis)
- Lipid-lowering therapy can lower the risk of CVD events but has no impact on the fatality of CVD events that do occur

Clinical Outcomes and Utility Parameters

We used four types of input parameters to populate the model: variables that model the probability of FH diagnosis, variables that model the natural history of CVD events, variables that modify the natural history of CVD events with lipid-lowering therapy, and variables that capture health state utilities (i.e., health-related quality of life).

PROBABILITIES OF FH DIAGNOSIS AND TREATMENT

We identified the model parameters from our clinical evidence review, expert consultations, current clinical guidelines on the diagnosis of FH, and other literature.

Probability of FH Diagnosis

We used the prevalence of FH in the target population (the pretest probability) along with the sensitivity and specificity to predict FH diagnoses. We based our estimate of the prevalence of FH in individuals suspected of having FH in a large clinical database in Canada with 5,987 individuals. The analysis carried out using this database suggested that the sensitivity, specificity, positive predictive value (PPV), and negative predictive values of the current Canadian definition for FH (including both clinical diagnosis and genetic testing) were 99.7%, 98.9%, 95.3%, and 99.9%, respectively, when compared with the Simon Broome Criteria; and 100%, 98.8%, 94.5%, and 100%, respectively, when compared with DLCN criteria.[71] We calculated the PPV as follows: PPV = (sensitivity × prevalence) / ([sensitivity × prevalence] + [1 – specificity] × [1 – prevalence]). We thus calculated that the prevalence of FH in this large Canadian database was between 17.1% (using DLCN as the reference testing) and 18.3% (using the Simon Broome Criteria as the reference testing) based on the sensitivity, specificity,

and PPV. In our reference case, we used 18% as the prevalence of FH in people suspected of having FH.

We assumed that physicians (primary care physicians or specialists) would use the Canadian definition for FH, in the absence of genetic testing, to make a clinical diagnosis. We used the prevalence of FH in individuals suspected of FH and the sensitivity and specificity of the Canadian definition for FH without genetic testing to estimate the number of individuals with a clinical diagnosis of FH for the index cases.

For cascade screening, following the Mendelian inheritance pattern, if an index case is genetically confirmed to be carrying a pathogenic variant for FH, the probabilities of their first-, second-, third-degree relatives carrying the same pathogenic variant are assumed to be 50%, 25%, and 12.5% , respectively.[3]

Diagnostic Accuracy

We used the sensitivity and specificity for at least a clinical diagnosis of possible FH according to the DLCN clinical criteria as the diagnostic accuracy for a clinical diagnosis of FH in Canada (Table 8) in our reference case, because the Canadian definition for FH is highly consistent with the DLCN criteria. For relatives of genetically confirmed cases, we assumed the clinical diagnosis having sensitivity and specificity for a probable diagnosis according to the DLCN criteria. This is because, according to the Canadian definition for FH, first-degree relatives with pathogenic variants can increase the certainty of their relatives' FH diagnosis.[71]

Because genetic testing is considered the gold standard, we assumed a sensitivity and specificity equal to 1.

Probabilities of Treatment

For all research questions, we assumed that people who are diagnosed with FH after entering the model will be offered lipid-lowering therapy.[18] We assumed all index cases would be on lipid-lowering therapy (i.e., statins) when they enter the model in our reference case.[18]

We considered the impact of different lipid-lowering therapies in scenario analyses, including better adherence to statin treatment, add-on therapy of ezetimibe, or *PCSK9* inhibitors (e.g., evolocumab), according to the clinical evidence review results.[3] In these scenario analyses, we assumed that 59% of individuals with at least a clinical diagnosis of possible FH would receive treatment and that genetic testing could improve adherence to lipid-lowering therapy. Our clinical evidence review suggested that genetic testing diagnoses could decrease the proportion of patients who remain untreated with lipid-lowering therapy by 32.5% (see Table 2, above). Therefore, we assumed that adherence to lipid-lowering therapy would be improved by 32.5% (absolute increase) as a result of genetic testing.

Table 8: Diagnostic Accuracy and Treatment Decision Inputs Used in the Economic Model

Model Parameter	Mean (95% CI)	Distribution	Reference
Prevalence of FH			
People suspected of having FH	0.18	Beta	Ruel et al, 2018[71]
Proportion of CVD among people with a clinical diagnosis of FH	0.166	Beta	Brunham et al, 2018[18]
1st-degree relatives[a]	0.5	Fixed[b]	Defesche et al, 2017,[3] assumption[c]
2nd-degree relatives[a]	0.25	Fixed[b]	Defesche et al, 2017,[3] assumption[c]
3rd-degree relatives[a]	0.125	Fixed[b]	Defesche et al, 2017,[3] assumption[c]
General population	0.004	Fixed[b]	Beheshti et al, 2020[73]
Average number of relatives per index case			
1st-degree relatives	2	Fixed[b]	Assumption
2nd-degree relatives	2	Fixed[b]	Assumption
3rd-degree relatives	1	Fixed[b]	Assumption
Diagnostic accuracy			
Sensitivity of at least a clinical diagnosis of possible FH [d]	0.967 (0.939–0.983)	Beta	NICE, 2017[74]
Specificity of at least a clinical diagnosis of possible FH[d]	0.125 (0.057–0.253)	Beta	NICE, 2017[74]
Sensitivity of genetic testing	1	Fixed[b]	Assumption
Specificity of genetic testing	1	Fixed[b]	Assumption
Treatment decision			
Proportion of people receiving lipid lowering therapy[e]			
• Individuals diagnosed with FH:			
P+/G? or P+/G+	1	Fixed[b]	Assumption
P−/G+	0[f]	Fixed[b]	Assumption
• Individuals diagnosed without FH (P−/G? or P−/G−)	0	Fixed[b]	Assumption
• Individuals with alternative diagnosis (P+/G−)	0.7	Beta	Ko et al, 2020[75]
• Individuals with unknown diagnosis (P?/G?)	0	Fixed[b]	Assumption
Adherence to lipid-lowering therapy	0.59[g]	Beta	Brunham et al, 2018[18]
Impact on adherence for individuals with genetically	0.325 (0.239–0.408)[g]	Beta	Assumption based on clinical evidence

Model Parameter	Mean (95% CI)	Distribution	Reference
confirmed FH (absolute increase)			review (scenario analysis only)
Probability of add-on therapy	0.219 (0.051–0.378)[g]	Beta	Clinical evidence review

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; DLCN, the Dutch Lipid Collaborative Network; FH, familial hypercholesterolemia.

[a]The estimates of prevalence apply to both adult and minor relatives.

[b]Values for these variables are fixed and are not considered in the probabilistic sensitivity analysis.

[c]We assume that the inheritance of FH follows the Mendelian inheritance pattern, and only consider heterozygous FH due to very low prevalence of homozygous FH.

[d]The estimates of sensitivity and specificity are for the clinical diagnosis without genetic testing results. We assumed the sensitivity and specificity of at least a clinical diagnosis of possible FH by DLCN criteria represented the sensitivity and specificity of the clinical diagnosis.

[e]P+/G+, phenotype positive and genotype positive; P+/G−, phenotype positive and genotype negative; P+/G?, phenotype positive and genotype unclear; P−/G+, phenotype negative and genotype positive; P−/G−, phenotype negative and genotype negative; P−/G?, phenotype negative and genotype unclear; P?/G?, no phenotype or genotype results, unclear diagnosis.

[f]These individuals will be monitored on a biannual basis through lipid testing.

[g]Only considered in scenario analysis.

Natural History

We identified the model parameters from expert consultations, current clinical guidelines on the diagnosis of FH, and other literature.

Transition probabilities between health states in the Markov model depend on the risk of CVD events and death. For the general population not diagnosed with FH, the risk of CVD events (including fatal CVD events) was calculated according to the incidence rates for ischemic heart disease and stroke from the Canadian Chronic Disease Surveillance System,[76] and incidence rate for intermittent claudication reported in the literature.[77] A Danish national registry reported odds ratios of CVD events for people with possible FH, and with probable or confirmed FH, compared to the general population. According to this report, the odds ratios for people with possible but untreated FH were estimated to be 4.1 for males and 5.4 for females and, for people with possible and treated FH, 19.6 for males and 11.0 for females.[2] The odds ratios were 13.9 and 12.4 for untreated males and females, respectively, with a probable or confirmed FH and 12.6 and 8.7 for treated males and females, respectively, with a probable or confirmed FH case.[2] The odds ratios of CVD were estimated to be 3.4 and 5.0 for males and females, respectively, with CVD history versus those without.[2]

The mortality risks of the general population are populated from the Canadian lifetable by sex and age.[78] We assumed that the probability of death for individuals who experience a new CVD event stays constant, regardless of underlying conditions or treatment. Smolderen et al[79] reported that the probability of death in the first year after a CVD event was estimated to be 11.1%.

After a nonfatal CVD event, the risk of mortality would increase. We estimated the weighted average mortality risks of stroke, heart disease, and peripheral artery diseases (weighted by the probabilities of these events) as the probability of a person transitioning from post-CVD to death.

Risk of CVD and mortality risks are age- and sex-dependent (Table 9). We estimated these probabilities for each sex and age group. As an example, Table A5 shows the age- and sex-dependent probabilities and incidence rates for a 43-year-old female.

Table 9: Natural History Inputs Used in the Economic Model

Model parameter	Mean (95% CI)	Distribution	Reference
Probability of CVD event			
General population (diagnosed without FH)	Weighted average based on probabilities converted from incidence rates for ischemic heart disease, stroke in the CCDSS, and incidence rate of peripheral artery disease from literature by age and sex[a,b]	Beta	PHAC, 2019;[76] Murabito et al, 1997[77]
Odds ratio of CVD for individuals diagnosed with possible FH who are untreated	4.1 (3.5–4.8) for male 5.4 (4.7–6.2) for female[c]	Log-normal	Benn et al, 2012[2]
Odds ratio of CVD for individuals diagnosed with possible FH who are treated	19.6 (16–25) for male 11.0 (8.9–13.6) for female[c]	Log-normal	Benn et al, 2012[2]
Odds ratio of CVD for individuals diagnosed with probable or confirmed FH who are untreated	13.9 (9.0–21.5) for male 12.4 (8.6–17.8) for female[c]	Log-normal	Benn et al, 2012[2]
Odds ratio of CVD for individuals diagnosed with probable or confirmed FH who are treated	12.6 (8.2–19.3) for male; 8.7 (5.9–12.9) for female[c]	Log-normal	Benn et al, 2012[2]
Odds ratio of CVD for individuals with clinical FH but without gene mutations, both sexes	6.0 (5.2–6.9) [c]	Log-normal	Khera et al, 2016[80]
Odds ratio of CVD for individuals with CVD history compared with those without	3.4 for male 5.0 for female[c]	Log-normal	Briffa et al., 2010[81]
Probability of death			
From pre-CVD to death	Canada lifetable by age and sex[a]	Fixed[d]	Statistics Canada, 2020[78]
From CVD to death	11.1%	Beta	Smolderen et al, 2010[79]
From post-CVD to death	Weighted average according to the mortality risk of stroke, heart disease, and peripheral artery diseases, estimated by age and sex[a]	Fixed[d]	Bronnum-Hansen et al, 2001;[82] Crimmins et al, 2008;[83] Vaartjes et al, 2009[84]

Abbreviations: CCDSS, Canadian Chronic Disease Surveillance System; CI, confidence interval; CVD, cardiovascular diseases; FH, familial hypercholesterolemia; OR, odds ratio; RR, relative risk.

[a]Variable is age and sex dependent.

[b]We assumed that risks from ischemic heart disease, stroke, and peripheral artery disease have captured the risk of acute coronary syndromes, acute myocardial infarction, stable or unstable angina, coronary or arterial revascularization, stroke, transient ischemic attack, and peripheral artery disease.

[c]Ors were converted to RRs using the formula $RR = OR/([1 - P_{ref}]+[P_{ref} \times OR])$, in which P_{ref} indicates prevalence of the outcome in the reference group.

[d]Values are fixed and not considered in the probabilistic sensitivity analysis.

IMPACT OF LIPID-LOWERING THERAPY ON NATURAL HISTORY

Lipid-lowering therapy will reduce the risks of CVD. According to the Danish registry,[2] for people with a probable or confirmed FH diagnosis, treatment was associated with lower risk of CVD events (Table 9). However, for people with a possible FH diagnosis, being on treatment was not associated with lower CVD risk. The researchers theorized that this might be the result of individuals with possible FH receiving less intensive cholesterol management strategies or not adhering to the treatment.

HEALTH STATE UTILITIES

A health state utility represents a person's preference for a certain health state or outcome, such as not moving from a pre-CVD state to a CVD state or successfully moving from a CVD state to a post-CVD state. In this analysis, we measured utilities on a scale ranging from 0 (death) to 1 (full health). We obtained health state utility parameters from the literature, including previous model-based economic evaluations identified from the economic evidence review. The age- and sex-dependent Health Utility Index (HUI) values from the general Canadian population was first converted to EQ-5D utilities[85] as the baseline utility values for pre-CVD health state. We further applied proportional utility loss according to reported disutility values for CVD and post-CVD to the age- and sex-dependent baseline utilities.[86]

The disutility associated with CVD events (including stroke) was estimated from a study that measured EQ-5D index scores for chronic conditions from a representative US sample (Table 10). The health state utility was based on preference scores reported for acute myocardial infarction, angina, and stroke.[55] The disutility due to post-CVD was estimated to be 0.18.

Table 10: Utilities to be Used in the Economic Model

Health state	Utility or disutility (95% CI)	Distribution	Reference
Pre-CVD	0.863 (0.861 to 0.865)[a]	Beta	Guertin et al, 2018[85]
CVD	−0.32 (−0.29 to −0.35)[b]	Beta	Chen et al, 2015[55]
Post-CVD	−0.18[b]	Beta[c]	Pelczarska et al, 2018[64]

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HUI, Health Utility Index.

[a]Mean value from the Canada norm using HUI,[85] which we converted to EQ-5D utility values using the formula EQ5D utility = (0.7202142 × HUI3) − (0.0420107 × HUI3^2) + 0.2491915.[87] In our analysis, we adjusted the utility values by age and sex. Utility for a health state is typically measured on an interval scale, with death set at 0 and perfect health set at 1.

[b]Negative values indicate disutility. Disutility represents a decrease in utility (i.e., a decrease in preference for a particular health outcome), typically resulting from a particular health condition (e.g., a symptom or complication).

[c]Assuming standard error as 20% of the mean value.

Cost Parameters

We considered the following categories for cost estimation: diagnosis, including associated clinical visits and diagnostic testing (i.e., lipid testing, genetic testing, and other testing), lipid-lowering therapy, and CVD treatment.

Table 11 summarizes the costs related to the clinical visit and other health care professional services, which is based on the Ministry of Health Schedule of Benefits.[88] We assumed half of the clinical referrals will be made directly through general physicians, with 25% through cardiologists and 25% through endocrinologists. Once the referral has been received, genetic counsellors and medical geneticists would meet with the patient. People will be seen by a genetic counsellor only if they have pathogenic variants for FH.

Table 11: Clinical Visit Costs Used in the Economic Model[a]

Variable	Unit cost ($)	Quantity	Reference
Pre-test			
Family physician	84.45	1	A005, MOH Schedule of Benefits[88]
Cardiologist	157.00	0.25	A605, MOH Schedule of Benefits[88]
Endocrinologist	162.65	0.25	A155, MOH Schedule of Benefits[88]
Medical geneticist	38.20	1	Expert opinion; K223, MOH Schedule of Benefits[88]
Genetic counsellor	359[b]	1	Elaine Goh, MD (personal communication: email, May 10, 2021)
Post-test			
Family physician (for FH-related pathogenic variants)	84.45	0.5	A005, MOH Schedule of Benefits[88]
Cardiologist	157.00	0.25	A605, MOH Schedule of Benefits[88]
Endocrinologist	162.65	0.25	A155, MOH Schedule of Benefits[88]
Genetic counsellor (for FH-related pathogenic variants)	359[b]	1	Elaine Goh, MD (personal communication: email, May 10, 2021)

Abbreviation: FH, familial hypercholesterolemia.
[a]Values are fixed except for genetic counsellor, which is not considered in the probabilistic sensitivity analysis.
[b]Gamma distribution was assumed in the probabilistic sensitivity analysis, assuming standard error as 20% of the mean value.

Resources and costs related to diagnostic and laboratory work may include the following tests: lipid, liver, thyroid, and renal function (Table 12). Echocardiography and stress testing are also needed for the diagnosis of CVD events for people presenting to their physician for the diagnosis of FH.[18] We extracted the cost information for the testing from the Ministry of Health Schedule of Benefits for Laboratory Services.[89] For genetic testing, the cost per test was estimated to be $490 (Robert Hegele, MD, email communication, May 25, 2021).

Table 12: Diagnostic and Laboratory Costs Used in the Economic Model[a]

Variable	Unit cost	Quantity	Reference
Non-genetic testing			
Lipid profiling[b]	49.02	1	MOH Schedule of Benefits for Laboratory Services[89]
Liver function[c]	37.01	1	
Thyroid function[d]	18.89	1	
Renal function[e]	22.78	1	
Echocardiography	212.8	0.5[f]	G570 and G571, MOH Schedule of Benefits: Physician Services[88]
Stress testing	242.55	0.5[f]	G582 and G583, MOH Schedule of Benefits: Physician Services[88]
Genetic testing			
LipidSeq (total)	490.00[g]	1	Robert Hegele, MD (personal communication: email, May 25, 2021)
Cost of sample handling (including shipping, processing, and storage)	70.07	1	Ontario Health (Quality), 2020[90]

[a]Values are fixed and not considered in the probabilistic sensitivity analysis.
[b]Lipid testing includes low-density lipoprotein (L153, L154), high-density lipoprotein (L117), triglycerides (L243), total cholesterol (L055), and total lipid (L151).
[c]Liver function testing includes alanine transaminase (L223), aspartate transaminase (L222), alkaline phosphatase (L191, L192), albumin (L004, L005), and total protein, bilirubin (L029, L030, L031), Gamma-glutamyl transferase (L107), L-lactate dehydrogenase (L146, L147), and prothrombin time (L445).
[d]Thyroid function testing includes thyroid stimulating hormone (L341), triiodothyronine (L336, L607), thyroxine (L338, L339), and thyroglobulin(L609).
[e]Renal function testing includes albumin and total protein (accounted for in the liver function testing), blood urea nitrogen (L251), urea clearance (L250), uric acid (L252), urinalysis (L253), creatinine (L067), creatinine clearance (L068), cystatin C (L069), and complete blood count (L393).
[f]Assuming 50% of individuals with a FH diagnosis will receive echocardiography or stress testing for confirmation.
[g]Gamma distribution was assigned in probabilistic sensitivity analysis, assuming standard error to the mean cost of 20%.

We applied an annual treatment cost of $1,463 for people diagnosed with FH, based on a Canadian report on annual costs of lipid-lowering therapy (Table 13).[91] We assumed that this cost estimate was for the total costs of statins, treatment monitoring, and treatment of adverse events. We considered the costs of ezetimibe and *PCSK9* inhibitors in our scenario analysis. For each item, we estimated the cost as the product of unit cost and its quantity.

For individuals who do not have FH and have not experienced a CVD event, we assumed the health state costs would be 0. However, for those who are diagnosed with FH but have not experienced a CVD event, we applied the treatment-related costs due to lipid-lowering therapy (including treatment of adverse events and monitoring of treatment). To avoid double counting, the health state costs for these individuals with FH but without CVD would be 0. The costs of CVD events in the first and in subsequent years (post-CVD events) were estimated from published data based on adult patients with high-risk cardiovascular diseases between fiscal year 2012 and fiscal year 2016, from the Alberta health databases.[92]

Table 13: Treatment or Health State–Related Costs Used in the Economic Model

Variable	Annual cost ($), mean (95% CI)	Distribution	Reference
Lipid-lowering therapy	1,463.17 (1,419.38–1,505.67)	Gamma	Tran et al, 2021[91]
Evolocumab (PCSK9 inhibitor)	9,214.22	Gamma[a]	Alberta College of Family Physicians, 2018[92]
Ezetimibe	233.60	Gamma[a]	
Health state costs			
Pre-CVD	0	Fixed	Assumption
CVD	47,193.61 (46,042.14–48,346.37)	Gamma	Tran et al, 2021[91]
Post-CVD	9,555.67 (9,068.81–10,041.25)	Gamma	

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; PCSK9, proprotein convertase subtilisin/kexin type 9.
[a]Gamma distribution was assigned after probabilistic sensitivity analysis, assuming standard error to the mean cost of 20%.

Internal Validation

Formal internal validation was conducted by a secondary health economist. This included testing the mathematical logic of the model and checking for errors and accuracy of parameter inputs and equations.

Analysis

We conducted a reference case and sensitivity analyses. We adhered to CADTH guidelines[69] when appropriate. The reference case represents the analysis with the most likely set of input parameters and model assumptions.

For the reference case analysis, we ran 5,000 simulations (probabilistic analysis) to simultaneously capture the uncertainty in all parameters that are expected to vary. We set distributions for variables within the model. We used the beta distribution for variables of probabilities and utilities, gamma distribution for costs, and log-normal distribution for risk ratios and hazard ratios. For all research questions, we calculated the total direct medical costs, numbers of people with a FH diagnosis (either clinical diagnosis or genetic test), deaths, and QALYs with 95% credible intervals for each intervention assessed, separately, for male and female. Then we calculated the mean values for male and female as the estimates for the reference case. For the third research question (diagnostic pathway), we calculated the total direct costs and QALYs for the different cascade screening strategies used for one index case plus two first-degree relatives (who we assumed to be one child and one adult).

We assessed variability and uncertainty in the model using probabilistic analyses. The results of the probabilistic analysis are presented on a cost-effectiveness plane or cost-effectiveness acceptability curve. We present uncertainty quantitatively as the probability that an intervention is cost-effective at various willingness-to-pay values. For the first research question (index cases), we also present uncertainty qualitatively, in one of five categories defined by the Ontario Decision Framework[93]: highly likely to be cost-effective (80%–100% probability of being cost-effective), moderately likely to be cost-effective (60%–79% probability), uncertain if cost-effective (40%–59% probability), moderately likely to not be cost-effective (20%–39% probability), or highly likely to not be cost-effective (0%–19% probability).

SCENARIO ANALYSES AND SENSITIVITY ANALYSES

Table 14 outlines the scenario analyses. By varying input parameters and model assumptions and running 1,000 simulations of the model, these scenario analyses explore how the results are affected. We conducted the following scenario analyses:

Scenario related to all research questions:

- **Scenario 1:** a shorter time horizon of 5 years

Scenarios related to the first research question (index cases):

- **Scenario 2:** improved adherence. Our reference case assumed that there is no impact on adherence, and in this scenario analysis, we used evidence from the clinical evidence review to further explore the impact of improved adherence after a genetically confirmed diagnosis
- **Scenario 3:** add-on therapy. Our reference case assumed that there is no add-on therapy. In this scenario analysis, we used evidence from the clinical evidence review to further explore the cost-effectiveness of add-on treatment after a genetically confirmed diagnosis, using either ezetimibe or evolocumab
- **Scenario 4:** all individuals suspected of having FH as the target population, based on clinical signs and/or family history, regardless of LDL testing results. Our scenario analysis examined the cost-effectiveness of providing genetic testing to all individuals suspected of having FH. The prevalence of FH in this scenario is lower than in the reference case
- **Scenario 5:** individuals with a DLCN probable clinical diagnosis of FH as the target population. Our scenario analysis examined the cost-effectiveness of providing genetic testing to individuals whose clinical diagnosis is more certain than a possible clinical diagnosis

Table 14: Summary of Scenario Analyses

Scenario	Parameters/assumptions in reference case	Parameters/assumptions in scenario analysis
All research questions		
Shorter time horizon	Lifetime horizon	5-y time horizon
First research question		
Inclusion of all individuals suspected of FH	The target population is people with a FH diagnosis only	All people suspected of FH as the target population; assume no individual will be declined genetic testing according to the clinical diagnosis; different prevalence of FH in the target population from the reference case
Probable or likely clinical diagnosis	The target population is people with a possible, probable, or confirmed clinical diagnosis only	The target population is people with a probable clinical diagnosis or only people with a clinical likely diagnosis
Improved adherence	Assumes genetic testing has no impact on adherence	Assumes improved adherence after a genetically confirmed diagnosis
Add-on therapy	Lipid-lowering therapy with statins	Assumes a proportion of people diagnosed with FH will receive add-on therapy of ezetimibe or evolocumab

Abbreviation: FH, familial hypercholesterolemia.

In addition to the above scenario analyses, we also conducted one-way sensitivity analyses to assess the impact of parameter uncertainty. We considered the following parameters:

- Age: CVD risk is age dependent. We conducted our analyses and presented results stratified by age (5–12, 13–22, 23–32, 33–42, 43–52, and 53–62 years), using median age to represent the risks of the groups. With this sensitivity analysis, we also considered the cost-effectiveness when children are the index cases with a clinical diagnosis (in the reference case, the index cases are adults)
- Cost of genetic testing: we explored the impact of genetic testing on the cost-effectiveness. This scenario also evaluated the cost-effectiveness of out-of-country genetic testing (assuming out-of-country testing has the same impact on outcomes and only differs in cost from the reference case)
- Cost of lipid-lowering therapy

Results

Reference Case Analysis

FIRST RESEARCH QUESTION: GENETIC TESTING FOR CONFIRMATION OF FH CLINICAL DIAGNOSIS

Table 15 summarizes our reference case analysis results for index cases. In individuals with a clinical diagnosis of FH, compared with no genetic testing, genetic testing was associated with cost savings and fewer FH diagnoses, fewer CVD events, and QALY gains during the lifetime horizon. For every 10,000 people suspected of having FH, 8,917 would possibly have FH by clinical diagnosis, of which 1,740 would be genetically confirmed. For each individual with at least a clinical diagnosis of possible FH, the average total costs over the lifetime horizon were estimated to be $168,862. Genetic testing led to a cost saving of $27,194 over a lifetime horizon. The probability of genetic testing being cost saving was 100% at a willingness-to-pay value of $50,000 per QALY gained (Figure A1).

Table 15: Reference Case Analysis Results for Genetic Testing of Index Cases (Per Person)

Strategy	Total costs mean (95% CrI), $	No. FH diagnoses mean (95% CrI)	No. CVD events mean (95% CrI)	QALYs mean (95% CrI)	ICER, $/QALY
No genetic testing	168,862 (163,618–174,254)	0.89 (0.83–0.94)	1.58 (1.46–1.70)	14.61 (14.09–15.10)	
Genetic testing	141,668 (137,311–146,033)	0.17 (0.17–0.18)	1.40 (1.29–1.51)	16.68 (16.27–17.05)	
Incremental	−27,194 (−29,718 to −24,668)	−0.72 (−0.77 to −0.65)	−0.18 (−0.20 to −0.17)	2.06 (1.77 to 2.35)	Dominant[a]

Abbreviations: CrI, credible interval; CVD, cardiovascular disease; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

[a]Dominant indicates genetic testing is less costly and more effective than no genetic testing.

FIRST-, SECOND-, AND THIRD-DEGREE RELATIVES OF PEOPLE WITH GENETICALLY CONFIRMED FAMILIAL HYPERCHOLESTEROLEMIA

Table 16 summarizes the cost-effectiveness of cascade screening with sequential, genetic, and lipid testing for first-, second-, and third-degree relatives. For first-degree relatives, the strategies, ranked by mean total costs from low to high, were no screening, lipid, sequential, and genetic screening strategies ($95,987, $105,024, $105,906, and $107,520 per person, respectively). The incremental probabilities of identifying FH cases in first-degree relatives were 38%, 28%, and 50% for lipid, sequential, and genetic screening strategies, respectively, compared with no cascade screening. Because the combination of abnormal lipid testing results and family history of pathogenic variants relevant to FH can lead to high certainty of FH diagnosis, the QALYs gained across different screening strategies (based on lipid, sequential, or genetic testing) were similar (31.33 QALYs across the screening strategies), compared to no cascade screening (31.13 QALYs). Table 16 presents the ICER results for different cascade screening strategies when they were compared with no cascade screening or with each other. The ICERs of different cascade screening strategies ranged from $45,754 to $58,390 per QALY gained compared to no cascade screening for first-degree relatives. The results suggested that all cascade screening could be considered cost-effective when compared to no cascade screening. However, the sequential ICERs suggested that when compared to each other, the most cost-effective strategy was lipid screening.

Table 16: Reference Case Results for Cascade Screening of Relatives

Strategy[a]	Total costs mean (95% CrI), $	No. FH diagnoses mean (95% CrI)	No. CVD events mean (95% CrI)	QALYs, mean (95% CrI)	ICER, $/QALY	
					Versus no screening	Sequential ICER
First-degree relatives						
No screening	95,987 (90,995–101,311)	0 (0; 0)	1.35 (1.26–1.44)	31.13 (30.63–31.60)	—	—
Lipid screening	105,024 (100,998–109,206)	0.38 (0.34–0.43)	1.35 (1.26–1.44)	31.33 (30.91–31.74)	45,754	—
Sequential screening	105,906 (101,860–10,101)	0.28 (0.25–0.32)	1.35 (1.26–1.44)	31.33 (30.91–31.74)	50,220	Cost increasing
Genetic screening	107,520 (103,561–111,602)	0.50 (0.50–0.50)	1.35 (1.26–1.44)	31.33 (30.91–31.74)	58,390	Cost increasing
Second-degree relatives						
No screening	72,433 (69,418–75,631)	0 (0–0)	1.20 (1.12–1.28)	33.02 (32.73–33.30)	—	—
Lipid screening	77,573 (74,994–80,278)	0.29 (0.25–0.34)	1.20 (1.12–1.28)	33.12 (32.86–33.36)	52,037	—
Sequential screening	78,217 (75,605–80,928)	0.14 (0.12–0.16)	1.20 (1.12–1.28)	33.12 (32.86–33.36)	58,564	Cost increasing
Genetic screening	79,094 (76,526–81,770)	0.25 (0.25–0.25)	1.20 (1.12–1.28)	33.12 (32.86–33.36)	67,442	Cost increasing
Third-degree relatives						
No screening	60,657 (58,547–62,898)	0 (0–0)	1.12 (1.04–1.20)	33.97 (33.77–34.15)	—	—
Lipid screening	63,847 (61,824–65,909)	0.24 (0.20–0.30)	1.12 (1.04–1.20)	34.02 (33.83–34.19)	64,602	—
Sequential screening	64,372 (62,358–66,430)	0.07 (0.06–0.08)	1.12 (1.04–1.20)	34.02 (33.83–34.19)	75,251	Cost increasing
Genetic screening	64,881 (62,870–66,940)	0.13 (0.13–0.13)	1.12 (1.04–1.20)	34.02 (33.83–34.19)	85,545	Cost increasing

Abbreviations: CrI, credible interval; CVD, cardiovascular disease; FH, familial hypercholesterolemia; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.
[a]Treatment strategies are ordered by average total costs, from lowest to highest.

The cost-effectiveness results were similar for second- and third-degree relatives. Although, as the FH risk decreases, the ICERs of the same screening strategies were estimated to be higher; for example, the ICERs of lipid screening compared to no cascade screening were $45,754, $52,037, and $64,602 per QALY gained for first-, second-, and third-degree relatives, respectively.

Figures 8, A1, and A2 show the probabilities of cost-effectiveness for different strategies used for different relative groups across a variety of willingness-to-pay values. For first-degree relatives, no cascade screening was the most cost-effective strategy at a willingness-to-pay value of $0 per QALY gained. Lipid testing is the most cost-effective option at commonly used willingness-to-pay values of $50,000 and $100,000 per QALY gained (with probabilities reaching 53.5% and 71.5%, respectively). Cascade screening strategies using a sequential or genetic approach were not cost-effective compared with lipid cascade screening. The cost-effectiveness acceptability curves for the cascade screening of second- and third-degree relatives revealed a similar trend (Figures A2 and A3).

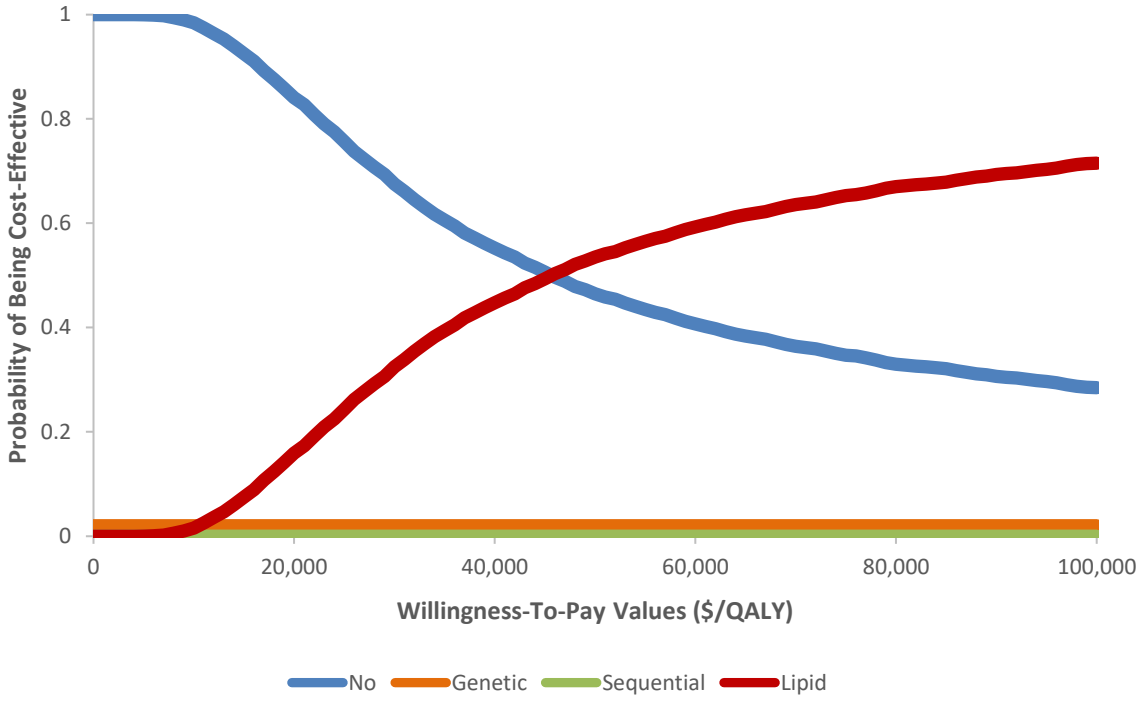

Figure 8: Cost-Effectiveness Acceptability Curve for First-Degree Relatives of Genetically Confirmed Cases

Abbreviation: QALY, quality-adjusted life-year.

Note: the probability of being cost-effective was 0 for cascade screening with genetic testing or with sequential testing; they had same QALY as lipid cascade screening, but were more costly.

GENETIC TESTING FOR BOTH CONFIRMATORY DIAGNOSIS AND CASCADE SCREENING

To assess the cost-effectiveness of the whole diagnostic pathway, we considered the hypothetical scenario of a 43-year-old person with at least a clinical diagnosis of possible FH, and their two first-degree relatives, 8 and 28 years old. We calculated the total costs and outcomes for these three hypothetical people for each diagnostic strategy. Our results suggested that a combination of genetic testing for individuals with a clinical diagnosis of FH and lipid cascade screening for the relatives of genetically confirmed cases appeared to be the most cost-effective strategy.

The reference strategy was no genetic testing for index cases or any cascade screening for their relatives. Of all eight pathways examined, the pathways with genetic testing for index cases were less costly than those without. The pathway starting with genetic testing for index cases but not for their relatives was the least costly option; the pathway with genetic testing for relatives but not for index cases was the most costly. For outcomes, the pathways with genetic testing for index cases led to QALY gains compared to the reference case. In contrast, the pathways without genetic testing for index cases but with cascade screening for relatives led to QALY loss. Thus, the four diagnostic pathways with genetic testing for index cases were dominant.

Of these four diagnostic pathways with genetic testing for index cases, the three pathways with cascade screening for relatives were more costly and more effective compared with the pathway without any cascade screening. The ICER was estimated to be $43,421 per QALY gained for the

pathway with lipid cascade screening. The cascade screening through sequential or genetic approach had very similar effectiveness outcomes to the lipid approach but was more costly (Table 17).

Table 17: Reference Case Analysis Results for Diagnostic Pathways

Strategy[a]	Total costs mean (95% CrI), $	No. FH diagnoses mean (95% CrI)	No. CVD events mean (95% CrI)	QALYs mean (95% CrI)	ICER, $/QALY	
					Versus no screening	Sequential ICER
Clinical-no	283,926 (277,720–290,418)	0.89 (0.83–0.94)	3.76 (3.60–3.93)	76.80 (76.21–77.36)	—	—
Genetic-no	262,141 (256,513–268,084)	0.17 (0.17–0.18)	3.58 (3.43–3.74)	78.38 (77.85–78.89)	Dominant[b]	—
Genetic-lipid	264,845 (259,426–270,688)	0.31 (0.29–0.33)	3.58 (3.43–3.74)	78.45 (77.92–78.93)	Dominant	43,321
Genetic-sequential	264,942 (259,518–270,789)	0.27 (0.26–0.29)	3.58 (3.43–3.74)	78.45 (77.92–78.93)	Dominant	Cost increasing
Genetic-genetic	265,648 (260,187–271,464)	0.35 (0.34–0.36)	3.58 (3.43–3.74)	78.45 (77.92–78.93)	Dominant	Cost increasing
Clinical-lipid	291,565 (285,189–298,231)	1.31 (1.20–1.43)	3.77 (3.61–3.93)	76.49 (75.88–77.05)	Dominated[c]	Dominated[c]
Clinical-sequential	294,510 (288,175–301,201)	1.07 (1.00–1.12)	3.77 (3.61–3.94)	76.39 (75.78–76.98)	Dominated[c]	Dominated[c]
Clinical-genetic	294,787 (288,462–301,470)	1.07 (1.01–1.12)	3.77 (3.61–3.94)	76.39 (75.78–76.98)	Dominated[c]	Cost increasing

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

[a]Treatment strategies are ordered by average total costs, from lowest to highest. In the Strategy column, clinical indicates pathways with only clinical diagnosis for index cases; genetic indicates pathways with genetic testing as the diagnosis for index cases, or cascade screening for relatives; no indicates pathways without a cascade screening program; lipid represents cascade screening using lipid testing; sequential represents the cascade screening strategy with lipid testing as the first testing and genetic testing only for those with abnormal low density lipoprotein.

[b]Dominant indicates strategy is less costly and more effective than the comparator strategy.

[c]Dominated indicates strategy is more costly and less effective than the comparator strategy.

Figure 9 shows the cost-effectiveness of the diagnostic pathways across different willingness-to-pay values. As the willingness-to-pay value increases, the pathway with genetic testing for index cases and lipid testing for the relatives of genetically confirmed index cases becomes the most cost-effective option, and the probability reached 55.0% and 73.1% at commonly used willingness-to-pay values of $50,000 and $100,000 per QALY gained, respectively.

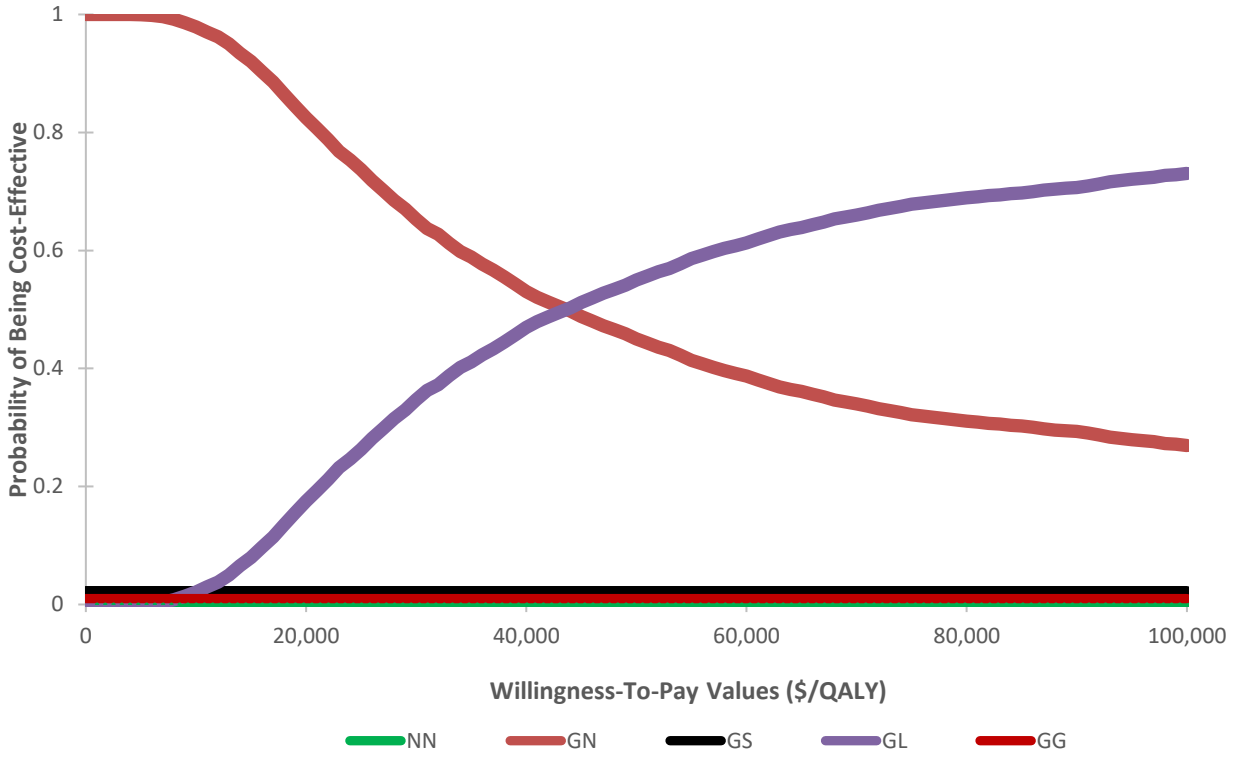

Figure 9: Cost-Effectiveness Acceptability Curve for Diagnostic Pathways

Abbreviation: QALY, quality-adjusted life-year.

Note: GG, genetic testing for index cases followed by cascade screening with genetic testing for relatives; GL, genetic testing for index cases followed by cascade screening with lipid testing for relatives; GN, genetic testing for index cases followed by no cascade screening; GS, genetic testing for index cases followed by cascade screening with sequential testing for relatives; NN, clinical evaluation without genetic testing for index cases followed by no cascade screening. The probability of being cost-effective for other approaches (including NN, GS, and GG) was 0. NG, NL, NS (clinical evaluation without genetic testing for individuals with a FH clinical diagnosis and cascade screening with genetic, lipid, or sequential testing) strategies were dominated and therefore not included in the plot.

Sensitivity Analysis

We conducted scenario analyses to examine the structural model uncertainty regarding the assumptions on the benefit of genetic testing for individuals with a clinical diagnosis of FH. For all research questions, we conducted sensitivity analyses to assess the robustness of results on parameters such as age, genetic testing cost, and lipid-lowering therapy costs.

INDEX CASES WITH AT LEAST A CLINICAL DIAGNOSIS OF POSSIBLE FAMILIAL HYPERCHOLESTEROLEMIA

Considering only costs in the first 5 years, the outcomes (QALYs and CVD events) were similar, though genetic testing was still cost saving in a shorter time horizon (Table 18). The undiscounted treatment cost for the first 5 years was estimated to be $5,899 for people who receive genetic testing and $6,602 for those who do not. The undiscounted health state–related costs were estimated to be $13,056 and $20,651, respectively.

Table 18: Scenario/Sensitivity Analysis Results for Genetic Testing of Index Cases: Shorter Time Horizon

Strategy[a]	Total costs Mean (95% CrI), $	No. FH diagnoses Mean (95% CrI)	No. CVD events Mean (95% CrI)	QALYs mean (95% CrI)	ICER, $/QALY
No genetic testing	23,789 (22,937–24,677)	0.89 (0.83–0.94)	0.13 (0.12–0.14)	3.78 (3.74–3.83)	
Genetic testing	20,339 (19,570–21,241)	0.17 (0.17–0.18)	0.07 (0.07–0.08)	3.82 (3.78–3.86)	
Incremental	−3,450 (−4,144 to −2,739)	−0.72 (−0.77 to −0.66)	−0.06 (−0.07 to −0.05)	0.04 (0.03 to 0.05)	Dominant[b]

Abbreviations: CrI, credible interval; CVD, cardiovascular disease; FH, familial hypercholesterolemia; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.
[a]Treatment strategies are ordered by average total costs, from lowest to highest.
[b]Dominant indicates strategy of genetic testing is less costly and more effective than no genetic testing.

Scenario analyses assuming improved adherence to treatment, increased dose of lipid-lowering therapy, or added therapy of ezetimbe or evolocumab suggested that genetic testing was still dominant compared with no genetic testing for individuals with at least a clinical diagnosis of possible FH, with a 100% probability of being cost saving at a willingness-to-pay value of $50,000 per QALY gained (see Table A6).

CVD risk is age-dependent, with younger people having lower risk. The sensitivity analysis on age suggested that genetic testing was dominant for all age subgroups. However, as the index case ages, the benefits of genetic testing (e.g., QALY gains) decreases (see Table A7). According to the sensitivity analyses, the cost-effectiveness results were robust to the genetic testing cost or lipid-lowering therapy costs.

FIRST-, SECOND-, AND THIRD-DEGREE RELATIVES OF GENETICALLY CONFIRMED FAMILIAL HYPERCHOLESTEROLEMIA CASES

According to the sensitivity analyses, the cost-effectiveness of cascade screening strategies was robust. As age increases, the risk of CVD events increases. Also, younger people with FH would be monitored longer to prevent future CVD events. Given this, the benefit of early identification of people with FH who are yet to experience a CVD event is larger for older people than younger. As a result, as age increases, the ICER decreases. Compared with no screening, the ICER for lipid screening was estimated to be $48,542, $40,507, and $35,061 per QALY gained for three age groups (18, 28, and 38 years, respectively) of first-degree relatives who are younger than our index case in the reference case.

Figure 10 shows the cost-effectiveness acceptability curves for the lipid cascade screening strategy across different age groups. The results showed that, in general, the older the relatives are, the more cost-effective cascade screening is. This is because the older relatives have a higher CVD risk; early identification and intervention after cascade screening has a larger benefit for them than for younger relatives. At a willingness-to-pay value of $100,000 per QALY gained, the probability of lipid cascade screening being cost-effective ranged from 74.6% to 80.6% for relatives aged 18 to 58 years.

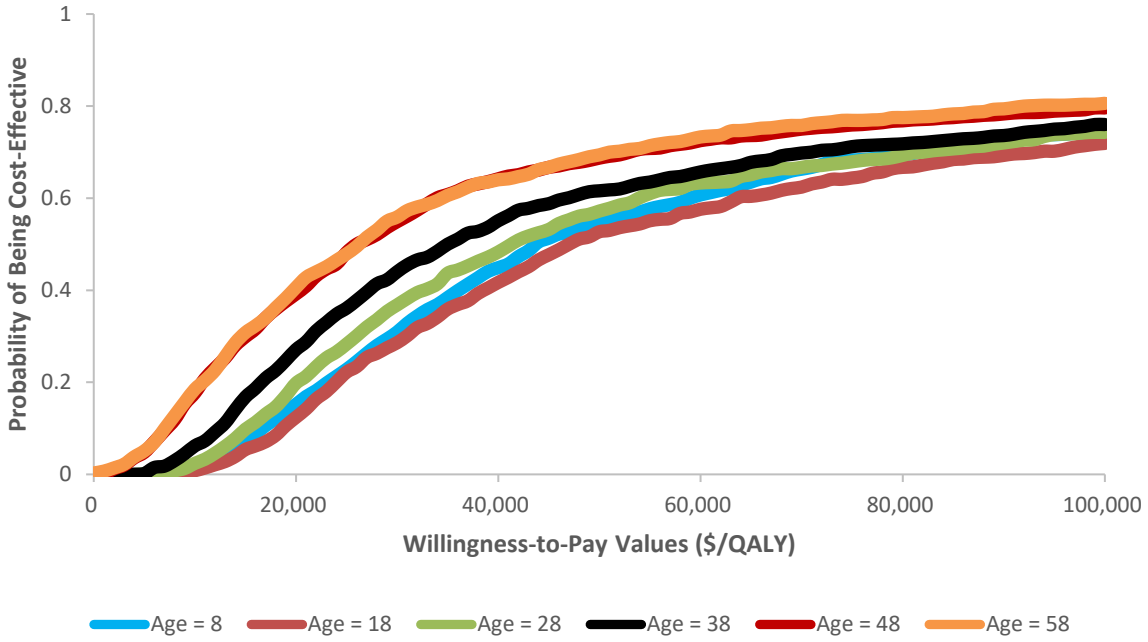

Figure 10: Cost-Effectiveness Acceptability Curve of Lipid Screening for First-Degree Relatives of Genetically Confirmed Cases by Age Group

Abbreviation: QALY, quality-adjusted life-year.
Note: ages listed represent the median of the relevant grouping; e.g., 8 includes children aged 5–12 years, 18 includes people aged 13–22 years.

As the genetic testing cost was applied only once, the testing cost had limited impact on the cost-effectiveness results during the lifetime horizon (see Table A8). In contrast, the cost-effectiveness of screening strategies was sensitive to the lipid-lowering therapy costs. If lipid-lowering therapy costs increase by 50%, the ICER was estimated to be $75,461 per QALY gained for first-degree relatives (compared with $45,754 per QALY gained in the reference case).

GENETIC TESTING IN THE DIAGNOSTIC PATHWAY

All results of the sensitivity analyses were consistent with the reference case findings: the most cost-effective strategy was the pathway with genetic testing for index cases but no cascade screening. As the willingness-to-pay values increase, genetic testing for index cases and cascade screening with lipid testing becomes the most cost-effective strategy. In the reference case, we calculated the ICER based on the aggregate costs and outcomes of three people: one index case and two first-degree relatives. Regardless of the number of relatives or consanguinity (e.g., second or third degree), the two most cost-effective strategies stayed the same. As the willingness-to-pay value surpasses $50,000 per QALY gained, the pathway of genetic testing for index cases and cascade screening with lipid testing becomes the most cost-effective strategy.

Discussion

We conducted a primary economic evaluation to determine the cost-effectiveness of genetic testing for index cases with at least a clinical diagnosis of possible FH and cascade screening of relatives of index cases in the Ontario setting. Our analyses suggested that a combination of genetic testing for individuals with at least a clinical diagnosis of possible FH and lipid cascade screening for relatives of genetically confirmed cases appeared to be the most favourable option from an economic perspective.

For confirmatory diagnosis of index cases with at least a clinical diagnosis of possible FH, our analysis found that genetic testing was a highly cost-effective strategy. It was dominant compared to no genetic testing: less costly and more effective. The genetic testing led to 7,177 fewer FH diagnoses for every 10,000 individuals suspected of FH, with a lifetime cost saving of $27,194 and a gain of 2.06 QALYs for each individual with at least a clinical diagnosis of possible FH. Sharma and colleagues[65] compared a genetic testing strategy (comprehensive genomic analysis) to lipid testing for individuals with a clinical diagnosis. In this study, the target population was index cases aged 50 years. In terms of costs, the results were similar to those in our analysis for index cases aged 48 years with a clinical diagnosis. However, in terms of QALYs, this analysis suggested that genetic testing led to a small QALY loss due to missed treatment and lost benefit for those who met the clinical diagnosis of FH but did not have the pathological variants. Nevertheless, our analysis led to larger QALY gains and cost savings. The large savings from the genetic testing is due to fewer FH diagnoses and improved outcomes (i.e., fewer CVD events). The breakdown estimates of cost in the scenario analysis with a 5-year time horizon suggested that improved outcomes was the main driver of dominance.

We conducted a further series of scenario analyses to examine structural uncertainty, including scenarios with explicit consideration of improved adherence or more aggressive treatment after genetic confirmation of FH diagnosis. The results from scenario analyses were consistent with the reference case. For our model-based analysis, we used data from a large Danish registry. We extracted the relative effects of untreated or treated FH patients (either possible FH, or probable or confirmed FH, according to the DLNC criteria) versus the general population. Notably, this study suggested that, among people on lipid-lowering therapy, those with possible FH had higher risk of CVD events than people with probable or confirmed FH. This might be because of less aggressive treatment or management of other cardiovascular risk factors for those with a less certain diagnosis. However, the registry study did not examine this hypothesis.

For relatives of genetically confirmed cases, lipid testing becomes the most cost-effective testing strategy as the willingness-to-pay value increases. The ICER was estimated to be $45,754 per QALY gained for lipid testing versus no cascade screening for first-degree relatives. The ICER estimate was influenced by age, and our reference case considered 8-year-old first-degree relatives, who had higher risk of FH but relatively lower risk of CVD events due to their young age. Our sensitivity analyses by age suggested the estimated ICER values decreased for older age groups. Cascade screening with lipid, sequential, and genetic approaches had equivalent outcomes in our analysis. This was because FH-relevant pathogenic variants in first-degree relatives is one criterion that led to a probable FH diagnosis.[71] For first-degree relatives of a genetically confirmed FH case, the clinical diagnosis has a certainty similar to genetic testing. Targeted sequencing, which sequences only the coding regions of genes known to cause FH, rather than the whole genome, is cost saving compared to whole-genome sequencing. Our analysis did not consider this scenario because, for relatives of genetically confirmed cases, this strategy would be equivalent to other cascade screening strategies regarding the outcomes, but more costly compared with lipid testing. Our results are similar to the previous US study, suggesting that, although genetic cascade screening may be cost-effective compared to no screening, it may not be cost-effective when compared to lipid cascade screening. However, cost-effectiveness of genetic cascade screening may have been underestimated since values for all measures of effectiveness were assumed to be equal for the three cascade testing options.

We further analyzed the relative merits of different diagnostic pathways. Our analysis demonstrated that pathways starting with genetic testing for individuals with at least a clinical diagnosis of possible FH dominated other options. When the willingness-to-pay value was $50,000 per QALY gained or above, the most cost-effective diagnostic pathway was to start with genetic testing for individuals with at least a clinical diagnosis of possible FH and then use lipid testing to screen the relatives of index cases with FH-relevant pathogenic variants.

Strengths and Limitations

Our modelling study examined the role of genetic testing in the diagnosis of FH in Ontario. We filled the evidence gap by considering the cost-effectiveness of genetic testing for individuals with a FH clinical diagnosis alone, for relatives of genetically confirmed index cases alone, and for both. Our analysis shed light on the optimal use of genetic testing in the diagnostic pathway of FH. Nevertheless, our analyses are limited by our parameter availability and structural model assumptions in the following important respects.

First, we assumed the diagnostic test accuracy of genetic testing was perfect, with sensitivity and specificity of 100%. However, the false negative rate of FH genetic testing can vary depending on the performance attributes of the testing panels. Furthermore, there could be relevant unknown pathogenic variants that are not accessible with current panels. We assumed in our reference case that, even without relevant pathogenic variants, the majority of people would still be treated due to hypercholesterolemia conditions other than FH, and so we did not conduct a sensitivity analysis on this assumption.

Second, our analysis is limited by the parameter availability. There is limited evidence regarding the adherence, treatment choice, and, most importantly, the long-term effect on CVD events after genetic testing. Additionally, there is limited evidence on the health state utility associated with long-term use of lipid-lowering therapy for those diagnosed with FH. In our analysis, we used the HUI values from the general Canadian population and converted these to EQ-5D utilities. This means that utility was not 1, even for those people who had no CVD events. This approach may underestimate the QALYs through the lifetime horizon.

There are also important structural model uncertainties. Our model considered CVD events aggregately, including ischemic heart disease, peripheral arterial disease, and stroke. This means we also considered the costs and outcomes in an aggregate manner. This analysis used a simplified post-CVD state to represent the survival state after CVD events. Further, our model assumed that no lifetime included more than three CVD events. Additionally, our model did not distinguish between the rationales of benefit incurred by genetic testing, which may be due to better lipid-lowering therapy adherence or more aggressive management of hypercholesterolemia. In Ontario, medication costs are not fully covered by the Ontario Health Insurance Plan (OHIP); coverage is dependent on access to extended benefits or individual eligibility for specific programs. For example, *PCSK9* inhibitors are funded on a case-by-case basis by the Ministry of Health under Limited Use Benefits for individuals who are not responsive to conventional medications.[15,16] For the simplicity of the model-based analysis, we considered all medication costs for lipid-lowering therapy. Nevertheless, according to the sensitivity analysis, the results were robust to the medication costs.

Finally, clinical pathways may be more complicated, depending on such factors as age, sex, LDL-C level, gene mutations, and disease history, among others. Thus, our model structure based on DLCN criteria may be oversimplified when predicting who should be treated, at what time, and through what method and what outcomes may be achieved by this complicated pathway. For example, the diagnosis could be based on age-specific LDL-C threshold. Treatment may differ for children with pathogenic variants, and the responsiveness to treatment may differ. Another example is that our model did not distinguish between probable and confirmed FH. Regardless of the certainty of diagnosis, individuals diagnosed with FH will be treated according to national clinical practice guidelines. However, this may be a limitation of our analysis, considering the certainty of diagnosis may impact the adherence to treatment or compliance of relatives identified through cascade screening. We conducted scenario and sensitivity analyses (i.e., sensitivity analyses by age) to account for the structural uncertainty, and the cost-effectiveness results remained robust.

Conclusions

For individuals with at least a clinical diagnosis of possible FH (index cases), genetic testing would be a cost-effective diagnostic strategy compared with no genetic testing. For the first-degree relatives of index cases confirmed through genetic testing, both genetic and lipid cascade screening strategies are cost-effective compared with no cascade screening. The ICERs for cascade screening compared to no cascade screening were estimated to be between $45,754 and $58,390 per QALY gained, with lipid screening as the most cost-effective cascade screening strategy. The findings of our economic analyses are generalizable to individuals with at least a clinical diagnosis of possible FH and their relatives in Ontario.

Budget Impact Analysis

Research Question

What is the potential 5-year budget impact for the Ontario Ministry of Health of publicly funding:

1. Genetic testing for individuals with a clinical diagnosis of familial hypercholesterolemia (FH), defined as at least a clinical diagnosis of possible FH according to the Dutch Lipid Collaborative Network (DLCN) criteria
2. Genetic cascade screening of FH for first-, second-, or third-degree relatives of an index case with FH confirmed through genetic testing?

Methods

Analytic Framework

We separately estimated the budget impact of these two research questions. Our analysis considers the budget impact of publicly funding genetic testing using the cost difference between two scenarios:
(1) the current clinical practice without public funding for genetic testing (the current scenario), and
(2) the anticipated clinical practice with public funding for genetic testing (the new scenario) for individuals with a diagnosis of FH (possible, probable, or confirmed cases for the first research question) and for relatives of an index case with FH confirmed through genetic testing (the second research question). Figure 11 presents the budget impact model schematic, which is applicable to both research questions.

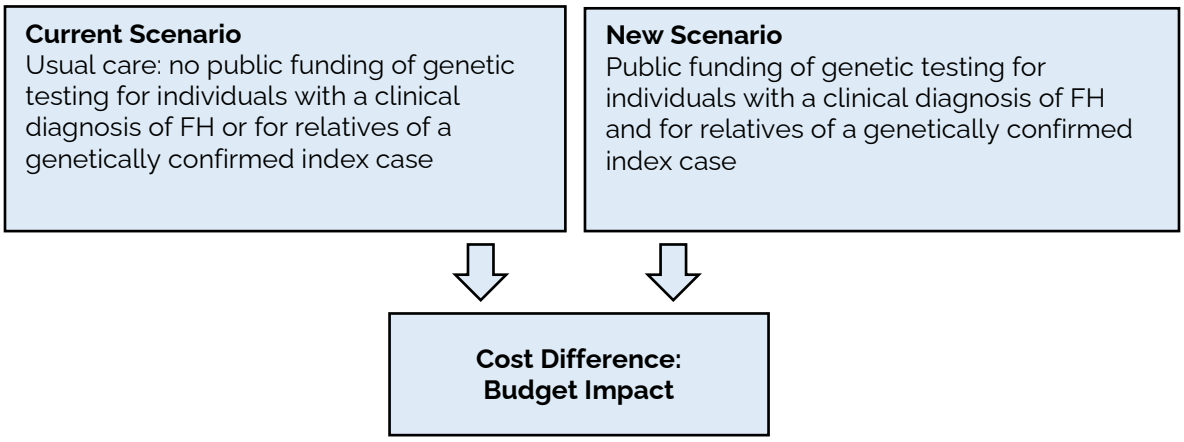

Figure 11: Schematic Model of Budget Impact

Key Assumptions

The assumptions in our cost-effectiveness analyses also apply to our budget impact analyses. In addition, we also assume:

- The diagnostic accuracy of genetic testing will stay constant over the next 5 years. We did not consider new pathogenic variants or the potential for new versions of the test
- Genetic testing costs will stay constant over the next 5 years
- We do not consider start-up and implementation costs, including training, lab renovation, and credentialing

- No genetic testing is used under the current scenario for diagnosis or cascade screening in Ontario
- Those individuals who do not present themselves to physicians to seek a diagnosis of FH, or who are not referred for cascade screening, will not incur any costs and will be excluded from the budget impact analyses
- A large proportion of people with FH will not be diagnosed because they are asymptomatic and unaware of their condition

Target Population

The size of the target population was estimated based on registry data, prevalence, and expert opinion.[18,94] We estimated that in Canada, about 1,300 individuals were recruited in the FH Canada registry.[94] According to Statistics Canada, about 37.07 million people lived in Canada in 2018, with 14.31 million in Ontario.[78] If this estimate holds across all provinces and territories, then about 500 individuals recruited in the FH Canada registry were from Ontario. The prevalence of FH was estimated to be about 1 in 250 individuals (0.4%).[18] That leads to an estimate of about 57,000 cases in Ontario, with a large proportion (over 90%) undiagnosed.[95]

For our first research question, the target population is individuals with at least a clinical diagnosis of possible FH (including possible, probable, or confirmed case) . To estimate the population from 2022 to 2026, we first obtained the Ontario population projection based on data from Statistics Canada.[96] With the population projection for the next 5 years, the prevalence of FH in the general population and the proportion of positive clinical diagnoses among prevalent cases, we estimate the number of individuals with a clinical diagnosis (possible, probable, or confirmed) who are true FH cases. Empirical data suggested that less than 1% of individuals with FH had been diagnosed.[97] For this analysis, we assumed that 3% (1,804) of the prevalent cases will present to physicians and receive a FH diagnosis in year 1. We assumed a slow increase (0.5% annually) because a large proportion of cases will remain undiagnosed. Most of these undiagnosed cases are asymptomatic; the affected people are unaware of their health issue (see Table 19).

With a sensitivity of 0.967, a specificity of 0.125, and a prevalence of 0.4%, we estimated the positive predictive value (PPV) of clinical diagnosis to be 0.195 (PPV = sensitivity × prevalence / [sensitivity × prevalence + {1 – specificity} × {1 – prevalence}]). We then estimated the total number of people with a clinical diagnosis, regardless of whether they are true cases or had received a false positive diagnostic result. In the current scenario in year 1, to identify 1,804 prevalent true cases, we estimated that 9,242 individuals will have at least a clinical diagnosis of possible FH. In the new scenario with genetic testing publicly funded, these individuals were offered genetic testing for FH after the clinical diagnosis (see Table 19).

Table 19: Target Population

	2022	2023	2024	2025	2026
Target population (n)	15,036,100	15,213,600	15,390,200	15,565,800	15,740,100
Prevalent cases	60,144	60,854	61,561	62,263	62,960
Proportion of prevalent cases receiving a clinical diagnosis (%)[a]	3.0%	3.5%	4.0%	4.5%	5.0%
Number of prevalent cases receiving a confirmed diagnosis[b]	1,804	2,130	2,462	2,802	3,148
Number of individuals referred to genetic testing[c]	9,242	10,910	12,613	14,351	16,125

[a]We assume this proportion represents those who present themselves to physicians for diagnosis. However, individuals who present to physicians are not equivalent to individuals who have a possible, probable, or confirmed clinical diagnosis. Individuals presenting to physicians may not belong to the prevalent cases.
[b]This represents the true number of people with FH who present themselves to physicians for diagnosis and a receive clinical diagnosis.
[c]We assumed this represents the size of target population for the first research question. The number of individuals referred to genetic testing = the number of prevalent cases receiving a clinical diagnosis/positive predictive value.

For our second research question, cascade screening for relatives of genetically confirmed cases, the target population is the first-, second-, and third-degree relatives of index cases whose diagnosis was confirmed by genetic testing. With the estimated number of index cases and our assumption of uptake among relatives, we estimated the size of the target population for the cascade screening program. We assumed that for each genetically confirmed case, there were five relatives offered cascade screening (see Current Intervention Mix).

Current Intervention Mix

We assumed that no genetic testing is used for diagnosis or cascade screening in the current scenario in Ontario. For all index cases, the diagnosis includes lipid testing and no genetic testing.

We assumed that for each genetically confirmed index case, two first-degree relatives, two second-degree relatives, and one third-degree relative will receive cascade screening. We assumed in the current scenario that no genetic cascade screening means that these relatives will receive lipid testing as the cascade screening strategy.

Uptake of the New Intervention and New Intervention Mix

In the new scenario, we considered that genetic testing will replace the approach for diagnosis and cascade screening in the current scenario. We assumed those who are not referred for a diagnosis or cascade screening will have no budget impact. We did not consider the number of people who are not referred for testing (for confirmation of a clinical diagnosis or for cascade screening). The genetic testing is offered to those seeking diagnosis either because they are potential index cases with a clinical diagnosis or because they have a relative(s) with a confirmed FH diagnosis through genetic testing. Therefore, we assumed that the uptake of genetic testing will be high once the individuals are offered the test in the new scenario. For our first research question, we assume that 60% of people with possible FH will receive the genetic testing in the first year of publicly funding. The uptake rate will increase 10% each year, achieving 100% over a 5-year period. Table 20 summarizes the estimate of the volume of genetic testing for people with a clinical diagnosis of FH. It was estimated that 5,545 people in year 1, increasing to 16,125 people in year 5, would receive genetic testing. Assuming a PPV of 0.195, 1,083 people in year 1, increasing to 3,148 in year 5, would be genetically confirmed and their relatives would be offered cascade screening.

Table 20: Volume of Genetic Testing for Index Cases

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of individuals referred for genetic testing	9,242	10,910	12,613	14,351	16,125
Current scenario					
Uptake (%)	0	0	0	0	0
Genetic testing	0	0	0	0	0
No genetic testing	9,242	10,910	12,613	14,351	16,125
New scenario					
Uptake (%)	60	70	80	90	100
Genetic testing	5,545	7,637	10,090	12,916	16,125
• Genotype +[a]	1,083	1,491	1,970	2,522	3,148
No genetic testing	3,697	3,273	2,523	1,435	0

[a]Assumed number of index cases confirmed by genetic testing. This number represents the number of individuals referred to genetic testing × the uptake of genetic testing × the positive predictive value (PPV) of clinical diagnoses. The PPV equals 0.195.

Table 21 summarizes the estimate of the volume of genetic cascade screening for relatives of index cases confirmed through genetic testing. For our second research question, we assumed that for each genetically confirmed index case, five relatives will receive genetic cascade screening. However, as in the cost-effectiveness analysis, the genetic cascade screening strategy could be employed according to a sequential testing algorithm, which is lipid testing followed by genetic testing for those with elevated LDL-C levels, or a cascade screening strategy with genetic testing. We assume that 60% of relatives will receive genetic cascade screening in year 1 (half of them receive cascade screening with sequential testing and the other half with genetic testing). The remaining 40% will receive cascade lipid screening. The proportion of cascade genetic testing will increase from 60% in year 1 to 100% in year 5. In year 1, 3,248 relatives would receive cascade screening with genetic testing, increasing to 15,740 in year 5 (Table 21).

Table 21: Volume of Genetic Cascade Screening for Relatives of Genetically Confirmed FH Cases

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of index cases	1,083	1,491	1,970	2,522	3,248
Number of relatives receiving cascade screening per index case	5	5	5	5	5
Current scenario					
Uptake of genetic cascade screening (%)	0	0	0	0	0
• Sequential testing	0	0	0	0	0
• Genetic testing only	0	0	0	0	0
No genetic cascade screening	100%	100%	100%	100%	100%
• Lipid testing only	2,706	3,727	4,925	6,304	7,870
• No testing	2,706	3,727	4,925	6,304	7,870
New scenario					
Uptake of genetic cascade screening (%)	60%	70%	80%	90%	100%
• Number receiving sequential testing	1,624	2,609	3,940	5,674	7,870
• Number receiving genetic testing only	1,624	2,609	3,940	5,674	7,870
No genetic cascade screening (%)	40%	30%	20%	10%	0%
• Lipid testing only	1,083	1,118	985	630	0
• No testing	1,083	1,118	985	630	0

Abbreviation: FH, familial hypercholesterolemia.
Note: Sequential testing: sequential algorithm, lipid testing followed by genetic testing for those with elevated LDL-C levels; Genetic testing: for eligible relatives regardless of lipid testing results.

Resources and Costs

We used inputs on health care resource use and costs from our cost-effectiveness analyses, applying them over a 5-year period (Table 22). We considered both resource use associated with health technology and health states, including genetic testing costs for individuals with a clinical diagnosis and relatives of index cases, short-term costs due to lipid-lowering therapy, and long-term costs related to CVD events and CVD-related death. We estimated undiscounted annual costs per person from year 1 to year 5 and use these costs in our budget impact calculation, separate for research questions on index cases and relatives. The average total cost was estimated to be $6,253 for each person who received genetic testing and $6,984 for each person who did not. All costs were presented in 2021 CAD.

Table 22: Unit Costs Used in Budget Impact Analyses: Reference Case

Scenario	Year 1	Year 2	Year 3	Year 4	Year 5
Index cases					
No genetic testing	6,984	1,544	5,013	5,160	5,289
Genetic testing	6,623	1,126	3,271	3,351	3,424
First-degree relatives					
No screening	252	545	627	706	783
Lipid	1,461	1,062	988	1,057	1,122
Sequential	2,485	917	988	1,057	1,122
Genetic	2,738	977	1,046	1,114	1,179
Second-degree relatives					
No screening	153	331	382	431	479
Lipid	1,235	734	562	606	648
Sequential	2,093	517	562	606	648
Genetic	2,290	547	591	635	677
Third-degree relatives					
No screening	103	224	259	293	327
Lipid	1,123	570	349	381	412
Sequential	1,898	317	349	381	412
Genetic	2,066	332	364	395	426

Internal Validation

A secondary health economist conducted formal internal validation. This process included checking for errors and ensuring the accuracy of parameter inputs and equations in the budget impact analysis.

Analysis

We conducted a reference case analysis and scenario and sensitivity analyses. Our reference case represents the analysis with the most likely set of input parameters and model assumptions. Our scenario and sensitivity analyses examined how the results are affected by varying input parameters and model assumptions.

Scenario or sensitivity analyses related to both research questions:

Scenario 1: genetic testing cost

- This sensitivity analysis examined the budget impact for various levels of genetic testing cost

Scenario 2: cost of lipid-lowering therapy

- As in the cost-effectiveness analysis, this scenario analysis intended to assess the robustness of the budget impact analysis to changes in lipid-lowering therapy cost

Scenario or sensitivity analyses related to the first research question:

Scenario 3: out-of-country testing as the comparator

- We assessed the budget impact of the new scenario of publicly funding versus the current scenario of out-of-country testing. We assumed 20% of people (either index cases or relatives of index cases) would receive genetic testing through the out-of-country program, with an average cost of $1,000

Scenario 4: the proportion of individuals seeking a diagnosis

- We assumed that 3% of individuals present themselves to physicians for diagnosis, relative to the prevalent cases (i.e., both new and existing FH cases). This sensitivity analysis aims to assess the budget impact if only 1% of individuals seek a diagnosis

Scenario 5: various uptake rates in individuals with a clinical diagnosis

- In the reference case, we assumed a gradual increase in uptake from 60% to 100% over 5 years. In this scenario, we assess the budget impact of low uptake (increasing from 30% to 50% over 5 years)

Scenario or sensitivity analyses related to the second research question:

Scenario 6: number of relatives receiving cascade screening

- In the reference case, we assumed on average 5 relatives of index cases will receive cascade screening and the proportion of these relatives receiving genetic cascade screening will increase from 60% in year 1 to 100% in year 5. In this scenario, we explored the budget impact of considering only first-degree relatives, or only first- and second-degree relatives, for cascade screening

Scenario 7: various uptake rates in cascade screening

- In the reference case, we assumed that half of the people in the genetic cascade screening strategy will use cascade screening with sequential testing, and the other half will use genetic screening. In the no genetic cascade screening alternative, half will use lipid screening and the other half will not be screened. This scenario will explore the budget impact of implementing different genetic cascade screening strategies

Results

Reference Case

INDEX CASES WITH AT LEAST A CLINICAL DIAGNOSIS OF POSSIBLE FAMILIAL HYPERCHOLESTEROLEMIA

Table 23 shows the budget impact of publicly funding genetic testing for individuals with a clinical diagnosis of possible FH. Publicly funding genetic testing for individuals with at least a clinical diagnosis of possible FH at a high uptake of 60% in year 1, increasing to 100% in year 5, would lead to a cost saving of $2.0 million in year 1 and $64.42 million in year 5. The total 5-year budget impact was estimated to be a cost saving of $140.89 million.

As the breakdown in Table A12 shows, the cost saving was driven by a reduction in treatment costs and improvement in health outcomes. The savings due to improved health outcomes (i.e., health state costs) accounted for most of the estimated cost savings. If we only considered the testing

costs, the budget impact was estimated to be $6.74 million in year 1, increasing to $19.59 in year 5, for a total budget impact of $63.57 million.

Table 23: Budget Impact Analysis Results—Reference Case, Index Cases

	Budget impact, $ million[a,b,c]					
Scenario	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Current scenario						
Testing costs	0.00	0.00	0.00	0.00	0.00	0.00
Treatment costs	13.24	28.33	45.25	63.96	84.45	235.24
Health state costs	51.30	92.30	141.63	199.29	265.56	750.08
Total costs	64.55	120.63	186.87	263.25	350.01	985.32
New scenario						
Testing costs	6.74	9.28	12.26	15.70	19.59	63.57
Treatment costs	13.33	28.68	44.17	61.04	79.22	226.45
Health state costs	42.48	72.66	107.16	145.33	186.77	554.41
Total costs	62.54	110.63	163.59	222.07	285.59	844.43
Budget impact						
Testing only	6.74	9.28	12.26	15.70	19.59	63.57
Treatment	0.08	350.36	−1.08	−2.92	−5.23	−8.79
Health states	−8.82	−19.63	−34.47	−53.96	−78.79	−195.67
Total	−2.00	−10.00	−23.28	−41.18	−64.42	−140.89

[a]In 2021 CAD. All costs were calculated using the mean cost from the Primary Economic Evaluation's probabilistic results.
[b]Negative costs indicate savings.
[c]Results may appear inexact due to rounding.

FIRST-, SECOND-, AND THIRD-DEGREE RELATIVES OF GENETICALLY CONFIRMED FAMILIAL HYPERCHOLESTEROLEMIA CASES

Table 24 presents the budget impact of publicly funding genetic cascade screening strategies in first-, second-, and third-degree relatives of genetically confirmed FH cases. Our reference case assumed that for each genetically confirmed cases, there would be five relatives referred for cascade screening. In a high-uptake scenario (60% in year 1, increasing to 100% in year 5), funding genetic cascade screening strategies (either sequential or genetic approach) would lead to an additional cost of $5.11 million in year 1, increasing to $27.46 million in year 5, for a total cost of $73.36 million.

If we consider only testing costs, the budget impact was estimated to be an additional of $4.95 million in year 1, increasing to an additional $23.99 million in year 5, for a total cost increase of $66.18 in the next 5 years.

Table 24: Budget Impact Analysis, Reference Case Results—Cascade Screening in First-, Second-, and Third-Degree Relatives of Genetically Confirmed Index Cases

	Budget impact, $ million[a,b,c]					
Scenario	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Current scenario						
Testing costs	1.80	2.49	3.28	4.20	5.25	17.02
Treatment costs	1.25	2.97	4.69	6.83	9.44	25.18
Health state costs	0.96	3.41	7.02	12.04	18.75	42.18
Total costs	4.02	8.86	14.99	23.08	33.43	84.38
New scenario						
Testing costs	6.75	10.44	15.29	21.49	29.23	83.21
Treatment costs	1.44	3.43	5.89	9.14	13.32	33.22
Health state costs	0.95	3.35	6.88	11.80	18.34	41.31
Total costs	9.14	17.22	28.07	42.43	60.89	157.74
Budget impact						
Testing only	4.95	7.95	12.01	17.29	23.99	66.18
Treatment	0.18	0.47	1.20	2.31	3.89	8.04
Health states	−0.02	−0.06	−0.13	−0.25	−0.41	−0.87
Total	5.11	8.36	13.08	19.35	27.46	73.36

[a]In 2021 CAD. All costs were calculated using the mean cost from the Primary Economic Evaluation's probabilistic results.
[b]Negative costs indicate savings.
[c]Results may appear inexact due to rounding.

Sensitivity Analysis

INDEX CASES WITH AT LEAST A CLINICAL DIAGNOSIS OF POSSIBLE FAMILIAL HYPERCHOLESTEROLEMIA

Table 25 presents findings for the scenario analyses for index cases. For all scenario analyses, we report the testing and total costs for the current and the new intervention mixes.

Assuming that 1,109 individuals with at least a clinical diagnosis of possible FH in year 1, increasing to 3,225 in year 5, would receive out-of-country testing, funding genetic testing in Ontario would lead to more genetic testing, but a cost saving of $2.17 million in year 1, increasing to $53.19 million in year 5, for a total cost saving of $118.05 million over the next 5 years. The difference between this scenario and the reference case was driven by the genetic testing cost difference between testing in Ontario and abroad. Out-of-country testing–related budget costs were estimated to be between $1.91 million (year 1) and $5.56 million (year 5) annually. This cost increases to $6.74 million and $19.59 million, respectively, if the genetic testing is conducted in Ontario.

Table 25: Budget Impact Analysis, Scenario Analysis Results—Genetic Testing in People With a Clinical Diagnosis of FH

		Budget impact, $ million[a,b,c]					
	Scenario	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Out-of-country testing as comparison	Current scenario: total costs	64.71	119.41	183.25	256.33	338.78	962.48
	Current scenario: testing costs	1.91	2.64	3.48	4.46	5.56	18.05
	New scenario: total costs	62.54	110.63	163.59	222.07	285.59	844.43
	New scenario: testing costs	6.74	9.28	12.26	15.70	19.59	63.57
	Budget impact	−2.17	−8.78	−19.65	−34.26	−53.19	−118.05
Low proportion of clinical diagnosis	Current scenario: total costs	21.52	47.47	81.97	125.34	177.94	454.23
	Current scenario: testing costs	0.00	0.00	0.00	0.00	0.00	0.00
	New scenario: total costs	20.85	43.87	72.65	107.11	146.91	391.39
	New scenario: testing costs	2.25	3.98	6.13	8.72	11.76	32.83
	Budget impact	−0.67	−3.60	−9.32	−18.23	−31.02	−62.83
Low uptake	Current scenario: total costs	64.55	120.63	186.87	263.25	350.01	985.32
	Current scenario: testing costs	0.00	0.00	0.00	0.00	0.00	0.00
	New scenario: total costs	63.54	115.63	175.23	242.66	317.80	914.87
	New scenario: testing costs	3.37	4.64	6.13	7.85	9.80	31.79
	Budget impact	−1.00	−5.00	−11.64	−20.59	−32.21	−70.44

[a]In 2021 CAD. All costs were calculated using the mean cost from the Primary Economic Evaluation's probabilistic results.
[b]Negative costs indicate savings.
[c]Results may appear inexact due to rounding.

In the scenario in which a low proportion of individuals suspected of having FH receive a clinical diagnosis and genetic testing, the budget impact was estimated to be a cost saving of $0.67 million in year 1, increasing to $31.02 million in year 5. The annual cost increase is between $2.25 million and $11.76 million. The budget impact due to genetic testing was estimated to be an additional $2.25 million in year 1, increasing to $11.76 million in year 5.

Assuming a low uptake of 30% in year 1, increasing to 50% in year 5, funding genetic testing for individuals with a clinical diagnosis of FH was predicted to save $1.00 million in year 1, increasing to $32.21 million in year 5. The budget increase due to genetic testing was estimated to be $3.37 million in year 1, increasing to $9.80 million in year 5.

Tables A13 and A14 show the sensitivity analysis of genetic testing and lipid-lowering therapy costs. As the genetic testing cost increased from $200 to $1,600, the budget impact was estimated to

decrease from a cost saving of $156.04 million over the next 5 years to a cost saving of $82.80 million. In the case of providing additional treatment of ezetimbe, the budget impact was estimated to be an additional $4.51 million in year 1, reducing the costs saving to $27.82 million in year 5; and if the added treatment was evolocumab, the funding of genetic testing for individuals with a clinical diagnosis of FH would lead to an additional cost of $9.01 million in year 1, with the annual cost decreasing slightly to $8.17 million in year 5.

RELATIVES OF GENETICALLY CONFIRMED FAMILIAL HYPERCHOLESTEROLEMIA CASES

If we screen only first-degree relatives of genetically confirmed cases, we estimate the budget impact to be an additional of $2.28 million in year 1, increasing to $13.05 million in year 5. Testing-related costs are the main driving factor, increasing from an additional of $2.08 million to $10.07 million from year 1 to year 5. If we also screen second-degree relatives, we estimate the budget impact to be an additional of $4.23 million in year 1, increasing to $23.15 million in year 5 (Table 26).

Table 26: Budget Impact Analysis, Scenario Analysis Results: Cascade Screening of Relatives of Genetically Confirmed Index Cases

		Budget impact, $ million[a,b,c]					
	Scenario	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
First-degree relatives only	Current scenario: total costs	1.85	4.29	7.52	11.80	17.32	42.78
	Current scenario: testing costs[d]	0.72	0.99	1.31	1.68	2.10	6.81
	New scenario: total costs	4.13	8.14	13.62	20.92	30.36	77.19
	New scenario: testing costs	2.80	4.33	6.35	8.94	12.16	34.59
	Budget impact	2.28	3.85	6.11	9.12	13.05	34.41
First- and second-degree relatives only	Current scenario: total costs	3.36	7.52	12.86	19.93	29.00	72.66
	Current scenario: testing costs	1.44	1.99	2.63	3.36	4.20	13.62
	New scenario: total costs	7.58	14.49	23.82	36.20	52.14	134.24
	New scenario: testing costs	5.46	8.44	12.37	17.39	23.66	67.31
	Budget impact	4.23	6.98	10.96	16.27	23.15	61.58
Low uptake (including first-, second-, and third-degree relatives)	Current scenario: total costs	4.02	8.86	15.00	23.08	33.43	84.38
	Current scenario: testing costs	1.80	2.49	3.28	4.20	5.25	17.02
	New scenario: total costs	6.58	13.04	21.53	32.75	47.16	121.06
	New scenario: testing costs	4.28	6.46	9.29	12.85	17.24	50.12
	Budget impact	2.56	4.18	6.54	9.68	13.73	36.68

[a]In 2021 CAD. All costs were calculated using the mean cost from the primary economic evaluation's probabilistic results.
[b]Negative costs indicate savings.
[c]Results may appear inexact due to rounding.
[d]In the current scenario, lipid testing is used in cascade screening.

If the genetic testing cost is $200, we estimated the budget impact to be an additional of $3.71 million in year 1, increasing to $20.62 million in year 5. If the genetic testing cost is increased to $1,600, we estimated the budget impact to be an additional $6.22 million in year 1, increasing to $29.14 million in year 5 (see Table A15).

Discussion

We conducted a model-based budget impact analysis to examine the range of costs related to publicly funding genetic testing in the diagnosis of FH and in the cascade screening of relatives of people with genetically confirmed cases of FH. Assuming an annual prevalence of 3% of FH cases being diagnosed, and the uptake rate for testing increasing from 60% to 100% over 5 years, publicly funding genetic testing in Ontario would lead to a cost saving of $2.00 million in year 1, increasing to $64.42 million in year 5, for a total savings of $140.89 million over the next 5 years. In contrast, assuming five relatives of genetically confirmed FH cases would be referred for cascade screening, and the uptake increases from 60% to 100%, then funding genetic testing in the cascade screening program (with either a sequential or genetic testing approach) would lead to an additional $5.11 million in year 1, increasing to $27.46 million in year 5, for a total cost of $77.36 million over the next 5 years. We also report the budget impact of considering only genetic testing–related costs. Currently, genetic testing is available through Ontario's out-of-country program. Our budget impact analysis may help estimate the resources needed to deliver testing to individuals with a clinical diagnosis of FH and the relatives of people with genetically confirmed cases of FH in Ontario.

In further scenario and sensitivity analyses, we examined the robustness of our budget impact estimates to our assumptions and parameters. For individuals with at least a clinical diagnosis of possible FH, the cost saving was mainly driven by the health state–related cost savings due to improved outcomes. However, there is uncertainty around the long-term outcomes after genetic testing. This finding underscores the importance of accounting for treatment adherence and health outcomes for people with at least a clinical diagnosis of possible FH or genetically confirmed FH. For both populations, the budget impact was sensitive to the uptake of the genetic testing. However, it is challenging to predict the uptake of genetic testing in Ontario. This is mainly due to the current limited data on FH underdiagnosis and the somewhat speculative change in uptake of genetic testing in the next 5 years. Between the low uptake scenario and our reference case, about 500 to 1,100 additional cases of FH would be genetically confirmed in year 1 (excluding case identification from cascade screening), which is similar to the empirical evidence suggesting that about 500 individuals recruited in the FH Canada registry annually are from Ontario.[18]

Our budget impact analysis did not account for the uptake of the diagnostic pathway. According to our analysis, the most cost-effective strategy when the willingness-to-pay value was $0 is the pathway with genetic testing for index cases but no cascade screening, which was replaced by genetic testing for index cases and cascade screening with lipid testing as the willingness-to-pay values increased. Neither strategy included genetic testing. This means that the budget impact of funding genetic testing for people with at least a clinical diagnosis of possible FH plus not funding genetic testing for the relatives could represent the two most cost-effective pathways (genetic testing for people with a clinical diagnosis of FH followed by either no or lipid screening for relatives).

Strengths and Limitations

There were several strengths in our budget impact analysis. First, this analysis was based on a model-based budget impact analysis, which considered genetic testing–related costs, treatment costs, and health state costs. Second, we conducted scenario analyses to examine the budget impact of different potential scenarios, especially the impact of underdiagnosis assumptions and various uptake levels. Additionally, our cost parameters were mainly derived from Ontario or Canada settings.

Our budget impact analysis was limited by some uncertainties. First, it was based on our economic model for the cost-effectiveness analysis (above), so it has the same limitations as in that analysis.

Second, there is uncertainty related to clinical and cost parameters, resulting primarily from uncertainty around the long-term treatment adherence and health outcomes after a clinical or genetic diagnosis of FH. To overcome this limitation, we analysed the budget impact if we considered only genetic testing–related costs. Third, there is very limited evidence regarding the use of genetic testing, especially the uptake of cascade screening among relatives of people with genetically confirmed FH. Our analysis was based on assumptions around how many true prevalent cases would be diagnosed, without considering the number of cases already detected in the previous year of the program. Thus, we may have overestimated the uptake of genetic testing. Cascade screening could be conducted with lipid testing only, which is another layer of uncertainty on the uptake of genetic testing. We have limited knowledge of the capacity of current Ontario laboratories to conduct genetic testing. Lastly, we have limited knowledge of the demographic characteristics of likely users of publicly funded genetic testing. For example, CVD risk profiles, treatment, and adherence probably have demographic characteristics. Our budget impact analysis was based on the reference case in our model-based cost-effectiveness analysis, which included index cases of people aged 43 years, and relatives of people aged 8 years.

Conclusions

Our budget impact analysis suggests that publicly funding genetic testing of people in Ontario with at least a clinical diagnosis of possible FH would save $2 million in year 1 (60% uptake), increasing to $64 million in year 5 (100% uptake), for a total saving of $141 million over the next 5 years. The estimated cost saving was mainly due to improved health outcomes after genetic diagnosis. If only genetic testing–related costs were considered, the budget impact would be an additional cost of $7 million in year 1, increasing to $20 million in year 5, for a total budget impact of $64 million.

Publicly funding genetic testing in the cascade screening program for relatives (two first-degree, two second-degree, and one third-degree relative) of genetically confirmed FH cases would lead to a cost increase of $5 million in year 1, increasing to $27 million in year 5, for a total of $73 million over the next 5 years, which is mainly driven by the genetic testing–related costs.

Preferences and Values Evidence

Objective

The objective of this analysis was to explore the underlying values, needs, and priorities of those who had lived experience of high cholesterol and had considered (or undergone) genetic testing for familial hypercholesterolemia (FH). We also sought to understand patients' perceptions of value and impact of a genetic diagnosis of FH on themselves and on their relatives.

Background

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

Information shared from lived experience can also identify gaps or limitations in published research (e.g., outcomes important to those with lived experience that are not reflected in the literature).[98-100] Additionally, lived experience can provide information and perspectives on the ethical and social values implications of health technologies or interventions.

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

For this analysis, we examined the preferences and values of people with a diagnosis of high cholesterol, some of whom have been diagnosed with FH, in two ways:

- A review by Ontario Health of the quantitative evidence on patient preferences and values
- Direct engagement by Ontario Health with people who have had or may have genetic testing for FH this genetic diagnosis, or who may encounter this diagnosis, through interviews

Quantitative Evidence

Research Questions

1. What is the relative preference of patients for genetic testing for familial hypercholesterolemia?
2. What is the importance of key attributes of genetic testing for familial hypercholesterolemia, and what trade-offs between different attributes are patients willing to make?

Methods

Literature Search

We performed a literature search for quantitative evidence of preferences and values on February 17, 2021, to retrieve studies published from database inception until the search date. We used the Ovid interface to search MEDLINE and the EBSCOhost interface to search the Cumulative Index to Nursing & Allied Health Literature (CINAHL).

The search was based on the population and intervention of the clinical search strategy with a methodological filter applied to limit retrieval to quantitative evidence of preferences and values (modified from Selva et al[101]). We created database auto-alerts in MEDLINE and CINAHL and

monitored them for the duration of the assessment period. See Appendix 1 for our literature search strategies, including all search terms.

ELIGIBILITY CRITERIA

Studies

Inclusion Criteria

- English-language full-text publications
- Studies published from database inception until February 17, 2021
- Cross-sectional/survey studies

Exclusion Criteria

- Animal and in vitro studies
- Narrative reviews, abstracts, editorials, letters, case reports, commentaries, and qualitative studies

Participants

Inclusion Criteria

- People identified to have FH using a genetic test or according to clinical criteria

Interventions

Inclusion Criteria

- Genetic testing
- Any nationally or internationally recognized clinical criteria for diagnosing familial hypercholesterolemia (e.g., Canadian Cardiovascular Society, Simon Broome Register, Dutch Lipid Clinic Network)

Literature Screening

A single reviewer conducted an initial screening of titles and abstracts using Covidence[20] and then obtained the full text of studies that appeared eligible for review according to the inclusion criteria. A single reviewer then examined the full-text articles and selected studies eligible for inclusion.

Data Extraction

We extracted relevant data on study characteristics using a data form to collect information about the following:

- Source (e.g., citation information, contact details, study type)
- Methods (e.g., study design, study duration, participant recruitment)

STATISTICAL ANALYSIS

Results are summarized narratively. No additional statistical analyses were conducted beyond those reported in the primary studies.

CRITICAL APPRAISAL OF EVIDENCE

We did not undertake a formal critical appraisal of the included studies.

Results

LITERATURE SEARCH

The literature search of the quantitative evidence of preferences and values yielded 403 citations published from database inception until February 17, 2021, after duplicates were removed. One additional record was identified through consultation with a clinical expert, for a total of 404 citations.

Of these, two studies were eligible for this review. Figure 12 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the literature search for quantitative evidence of preferences and values.

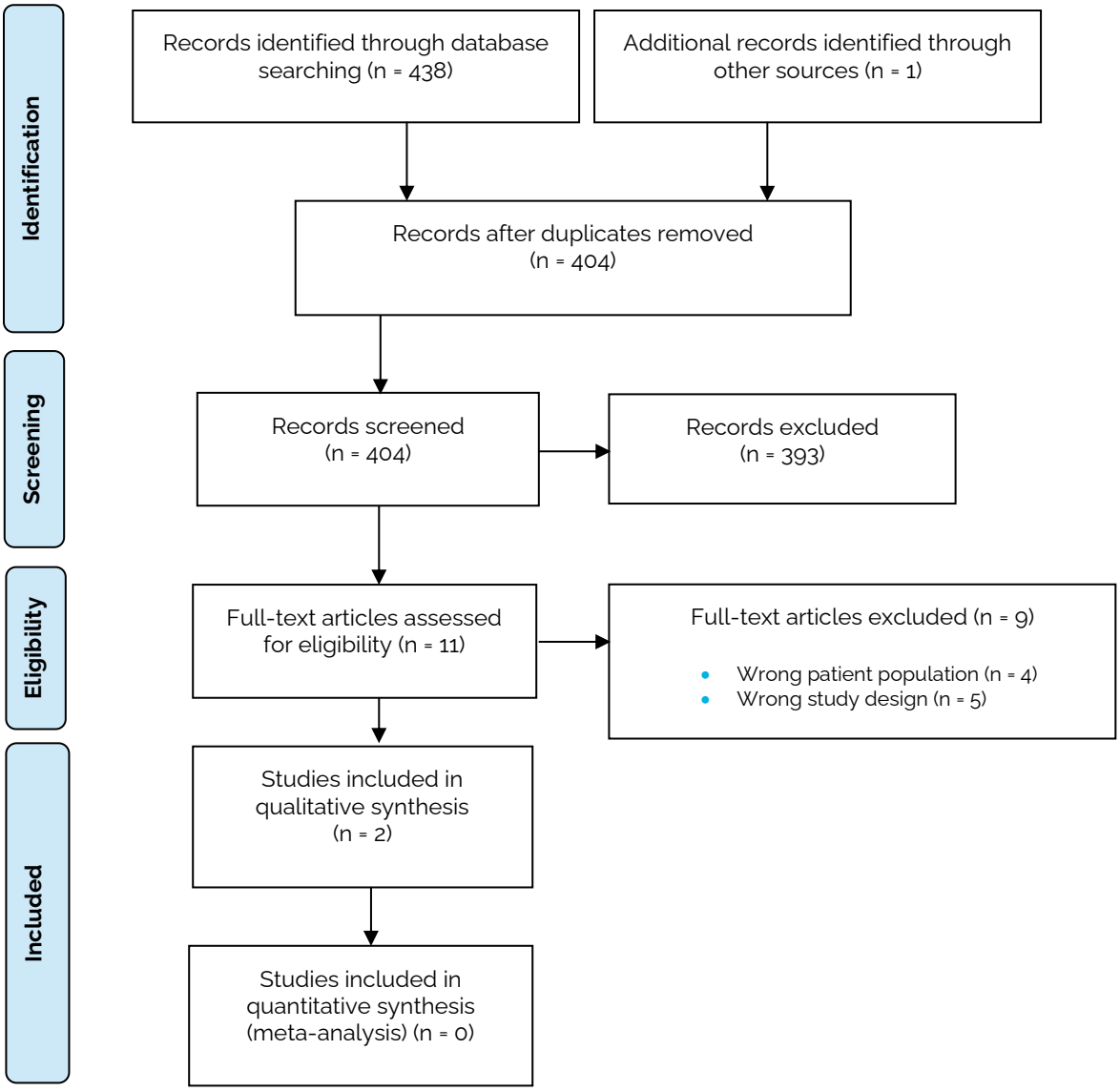

Figure 12: PRISMA Flow Diagram—Quantitative Evidence of Preferences and Values Search Strategy

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.
Source: Adapted from Page et al.[22]

CHARACTERISTICS OF INCLUDED STUDIES

Jones et al[32] conducted a pilot study in the United States on seven individuals who consented to participate in a semi-structured interview. The study assessed healthcare use and patients' perspectives after receiving a positive genetic test for familial hypercholesterolemia. All seven participants were satisfied with the treatment of high cholesterol, but one person expressed

confusion and uncertainty regarding future medical care (e.g., how often to check for cholesterol level and whether to stick with the same cardiologist).

Marchand et al[102] conducted an online survey of participants in the British Columbia Familial Hypercholesterolemia Registry who underwent research-based genetic testing for FH. The survey assessed patient experience with the genetic testing process, their willingness to recommend genetic screening, and their motivation to lower their cholesterol levels. Among 183 respondents, 38 (20.7%) had a positive genetic test result, 27 (14.8%) had a negative result, and 118 (64.4%) were still awaiting their results. Compared with the individuals waiting for results, participants with a positive genetic test were more likely to believe lipid-lowering therapy was highly important (74.3% vs. 55.4%). They were also more likely to strongly agree that a diagnosis of FH was important to them (71.1% vs. 46.2%), were more likely to recommend genetic screening to their relatives (85.9% vs. 72.9%), and were more likely to perceive genetic testing for patients with high cholesterol as "very important" (81.6% vs. 56.8%). They also reported a better overall experience with the genetic testing process compared with those with a negative test or who were still awaiting their results (86.8% vs. 65.4% and 52.2%, respectively). No notable differences were observed between groups regarding concerns of the effect of a genetic diagnosis on insurance and employment opportunities.

Conclusions

Most people with a positive FH genetic test perceived the screening, diagnosis, and treatment of FH more positively.

Direct Patient Engagement

Methods

PARTNERSHIP PLAN

The partnership plan for this health technology assessment focused on consultation to examine the experiences of people with high cholesterol and their experience with genetic testing for FH. We engaged people via phone interviews.

We used a qualitative interview, as this method of engagement allowed us to explore the meaning of central themes in the experiences of people with thyroid nodules.[103] The sensitive nature of exploring people's experiences of a health condition and their quality of life are other factors that support our choice of an interview methodology.

PARTICIPANT OUTREACH

We used an approach called purposive sampling,[104-107] which involves actively reaching out to people with direct experience of the health condition and health technology or intervention being reviewed. We approached a variety of partner organizations and clinical experts to spread the word about this engagement activity and to contact people with experience with high cholesterol and molecular testing for FH.

Inclusion Criteria

We sought to speak with adults with lived experience of high cholesterol and genetic testing for FH or who may seek out this testing in the future. Participants did not need to have direct experience with genetic testing for FH.

Exclusion Criteria

We did not set specific exclusion criteria.

Participants

For this project, we spoke with 15 people who had high cholesterol, all of whom lived in Ontario. Twelve of these individuals had a genetic diagnosis of FH. Participants with genetic diagnosis were

primarily found through a genetic research clinic in London, Ontario, and lived in southern Ontario. Some individuals lived in Northwest Ontario and the Kingston area.

APPROACH

At the beginning of the interview, we explained the role of our organization, the purpose of this health technology assessment, the risks of participation, and how participants' personal health information would be protected. We gave this information to participants both verbally and in a letter of information (Appendix 8), if requested. We then obtained participants' verbal consent before starting the interview. With participants' consent, we audio-recorded and then transcribed the interviews.

Interviews lasted approximately 15 to 40 minutes. The interview was loosely structured and consisted of a series of open-ended questions. Questions were based on a list developed by the Health Technology Assessment International Interest Group on Patient and Citizen Involvement in Health Technology Assessment.[108] Questions focused on the diagnosis of high cholesterol, participants' care journey and their perceptions of genetic testing, and the ultimate impact of the diagnosis of FH and potential for cascade screening. See Appendix 9 for our interview guide.

DATA EXTRACTION AND ANALYSIS

We used a modified version of a grounded-theory methodology to analyze interview transcripts. The grounded-theory approach allowed us to organize and compare information on experiences across participants. This method consists of a repetitive process of obtaining, documenting, and analyzing responses while simultaneously collecting, analyzing, and comparing information.[109,110] We used the qualitative data analysis software program NVivo[111] to identify and interpret patterns in the data. The patterns we identified allowed us to highlight the impact of high cholesterol and the diagnosis of FH from those we interviewed.

Results

DIAGNOSIS OF HIGH CHOLESTEROL

Participants reported a variety of circumstances leading to the diagnosis of high cholesterol. For some, the news of their condition came from routine blood work and was completely unexpected. Others learned that their cholesterol was an issue through a larger medical event—such as cardiac arrest—for which their cholesterol levels may have been a contributing factor. The age at which participants reported discovering that they had high cholesterol levels also varied. Some participants discovered their condition as children or young adults, while others did not learn of it until well into adulthood.

> *We were kind of new to [the city] at the time and with a new doctor. So they just ran some blood tests, routine blood tests, and in that I think it was flagged that my cholesterol was through the roof and I was a young adolescent and that shouldn't happen.*
>
> *My sister's and [my] cholesterol came back through the roof. And we were 12…. [The doctor] thought, "Well, that's really odd." So she ran the results again. Not normal to run these types of tests on 10- to 12-year-olds at the time…came back as high again.*
>
> *But, really, as far as daily life went everything was normal. And then I dropped and had a heart attack. I had a stent placed. And it was found that I had the enormous cholesterol level.*

Given that most participants were eventually diagnosed with familial hypercholesterolemia, it is not surprising that many reported high cholesterol in other relatives and subsequent health issues caused by high cholesterol levels. Family history was the most reported reason for checking cholesterol levels. Many participants spoke of high cholesterol in their family going back generations. Many reported receiving encouragement from relatives to be tested.

> *Because of my older brother having a heart attack, both my other brother and [I] had some cardiac testing. We had our cholesterol tested; we had an echocardiogram. Just kind of as a baseline to make sure that there was nothing going on yet and that we would both be okay.*
>
> *When I was 18, my dad was really into health, and so he said, "You guys should all get checked because you know it could be a familial thing." So we did, and actually I was the only one out of three [siblings] that had high cholesterol.*
>
> *But my father as a young man in his late 40s had been diagnosed with high cholesterol. And I happen to have a GP who was really on top of things and who attended a lot of extra education sessions and what have you. So he was checking me, given the family history, and my cholesterol just kind of kept creeping up and up.*

Most participants commented that, prior to their diagnosis of high cholesterol, there were typically few or no indications that something was amiss. A few participants reported having spots or bumps around the eyes, which can sometimes be associated with high cholesterol levels, but this symptom was not widely shared. One participant reported a feeling of gradual decline until a significant health event prompted testing, which uncovered their high cholesterol levels. This patient attributed their health decline and increased fatigue to increasing cholesterol levels.

> *So anyway, health-wise, at the time, I didn't even know I was sick with high cholesterol or anything like that. I knew I had marks on my eyes, but my mom had these marks so to us it was just a natural thing, like I take after Mom, right?*
>
> *In retrospect, being able to reflect, there should have been some things that would have tipped me off in regard to the possibility of a serious health condition.*

Despite the fact that most participants had multiple occurrences of high cholesterol in their family, some reported that obtaining a diagnosis was a challenge; some physicians were hesitant to test for cholesterol given the general good health or young age of the individual. Even when a person reported familial occurrences of high cholesterol to their physician, there could be resistance to ordering the bloodwork necessary to have cholesterol levels tested.

> *I was in shape, and I approached my family doctor about this. And he goes, "Oh, you're in such good shape, don't even worry about cholesterol." Over the next four years, I kept telling him about this and asking him, [and he said,] "No, no we can't waste money on cholesterol checks that are totally unnecessary. You don't need this test."*
>
> *Anyway, I got my kids checked. My family doctor at first didn't want to do it; he's going, "Oh, kids, blah blah blah." But, sure enough, my kids' cholesterol was sky high, and then they got referred to a pediatrician.*
>
> *I just kept hearing from my doctor that I'm too young to have [high cholesterol]. I think they just had a stereotypical image of someone that was overweight, which I wasn't. So they were reluctant to prescribe.*

CARE JOURNEY

Following the diagnosis of high cholesterol, participants discussed various treatment methods that they followed to attempt to control or lower their cholesterol levels. These treatment methods typically involved active monitoring, adjustment of food intake, and increased exercise. Additional changes to lifestyle, such as quitting smoking, were suggested where needed. Participants reported that each step or adjustment to these treatment methods would be made in consultation with their health care providers and their cholesterol levels would continue to be monitored to track the effects of the treatment regimen.

> *My diet changed; I introduced more vegetables, more fruit, more exercise. You know, being more mindful of what I was putting in my mouth. It's not like I didn't before that, but now I'm very selective.*
>
> *You try to change your diet, you try to do your exercise…you quit smoking, obviously. But you do have to change your lifestyle as far as your eating, your exercising.*

Participants also reported that medications to treat their cholesterol would often come later in the treatment pathway, if diet and exercise were unsuccessful. Some participants reported preferring to avoid medications as long as possible and attempted to control their cholesterol through exercise and diet only. Others tried different medications and often adjusted or changed their regimen depending on their success controlling cholesterol levels.

> *There's not a medication that I was not on, let's put it that way…I tried every medication.*
>
> *Yeah, I'd rather not have to take meds if I don't have to. So I'd really like to control it with the diet and exercise if at all possible. I figure it's inevitable in my future anyway, but holding it off for as long as I can is my goal.*
>
> *I went to see a dietician, to watch the diet. Which is the one thing. And then we started with the medications, we started with the statin medications.*

Most of the people we interviewed were eventually diagnosed with FH, which means that diet and exercise are somewhat limited in their ability to control cholesterol levels, which is why most progressed to medication. This genetic condition is not responsive to some cholesterol-lowering medications, adding an extra treatment burden. This was reflected in participants' comments that diet and lifestyle changes were often ineffective, and some participants complained about side effects from the medications.

> *I tried to make sure I was exercising regularly and adjusted my diet and do all the things that that you should do. But [my cholesterol level] continued to climb. Just very gradually, up and up.*
>
> *Medication didn't work, really, to control the levels, and then they started coming out with statins after that…so we went on a statin. And my sister was on it longer than me because I had bad reactions to it.*

DIAGNOSIS OF FAMILIAL HYPERCHOLESTEROLEMIA

Most of the people we interviewed were recruited from a clinical research centre focusing on cholesterol and FH. Prior to receiving their diagnosis, participants reported varying degrees of information and knowledge about the condition. Some had relatives who had previously been diagnosed with FH and were more knowledgeable about the topic and its implications. Others reported a general lack of information or awareness of the condition and that the genetic component can be tested for. Some participants with relatives who had high cholesterol reported being unaware of the potential genetic cause of this condition until information was provided by the genetic clinic.

> *My family did have the genetic testing done, and they were definitely aware of it. It really didn't register with me until it was kind of explained to me. [The doctor] has been nothing but great in terms of explaining it.*
>
> *Put it in a nutshell, I think education is a big part of it. And, you know, having an understanding of it…. It's just a blood test, so it's not a big deal, and it was explained to me as being a genetic issue that I had no control over other than [with] the medication.*

The diagnosis of FH could be emotionally impactful for participants, in both positive and negative ways. Several participants spoke about how the diagnosis allowed them to gain a measure of control and understanding of their condition, where previously their cholesterol had been high for unknown reasons. Some found this knowledge valuable, both emotionally and intellectually. Others reported that the diagnosis could be challenging to deal with, feeling as though the condition was permanent and could not be improved.

> *It arms me with the knowledge that I need to be able to live the best lifestyle that I can [and] to be able to manage what I'm dealing with.*

> *My son was devastated when he found out he had high cholesterol because [he] is very active, very athletic, and he was like, "I'm not going to have it, I'm not going to have it." And then he was really quite upset when he found out he had it.*

> *But the [heart] blockages are massive. Now to understand why they're there and to have a name put on a monster really helps. Because, psychologically, it helps you tackle it.*

Upon learning of their diagnosis, a number of participants expressed regret that they did not learn of their condition sooner. Additionally, some participants expressed regret that previous generations of relatives had not been tested, so as to prepare them earlier for the potential of high cholesterol earlier in their lives. Many felt that even some subsequent health events could have been prevented through an earlier diagnosis.

> *Yeah, you must think back. You know, if I'd had the test, if my parents [had] said, "You should get her cholesterol tested."…. What a difference that could have made.*

> *This should have been picked up. Had it been picked up, and had it been managed earlier, there is no question that my life would be at a much better state than what it is now. I would have been able to at least have the heads-up to be able to stop, or at least slow down if not stop, the development of the blockages of the plaque in the arteries of my heart.*

> *I'm sure at a younger age I would have probably taken it a lot more seriously, and I would have looked a little closer at following dietary recommendations, probably accepted medications sooner.*

IMPACT OF FH DIAGNOSIS—CLINICAL

Many participants reported that their clinical diagnosis of FH served as a turning point in their care and their ability to control their cholesterol levels. Understanding the genetic condition allowed for further refinement of diet, exercise, and medication protocols that would be most effective.

> *But anyway, through that they got put on cholesterol medication. So, for my kids, I found it was very beneficial, because they've been on cholesterol medications for a long time and…even then they said diet, because we're missing a certain something that we don't produce; we don't get rid of the cholesterol like most people do. So even though we could [follow a] low-cholesterol diet,…we need help. We need to be on medication.*

Additionally, participants within clinical research trials reported that having a genetic diagnosis of FH allowed them to access new and more effective medications. These medications were often able to control cholesterol levels better than those tried previously. Many people reported that their newfound ability to control their cholesterol was a major benefit of their FH diagnosis.

> *I think that this has had a really big impact in being able to get me connected to some of the latest drugs that have come out on the market…. And having that specific diagnosis really allowed me to be able to access that.*

> *Well, the major impact was I had to make sure I took my medications regularly. And being much more conscientious about what I eat. Sometimes that was challenging, sometimes it wasn't…I had to make conscious choices.*
>
> *Just allowing you to be able to have different options from the diagnosis, rather than just getting a blood test and having high cholesterol, really opened the door for me to get into [a new medication], and I'm still on it today.*

The newfound ability of participants to control their cholesterol levels provided comfort that they may be able to avoid future cholesterol-related health issues. One participant also commented that the symptoms and impacts of high cholesterol were lessened through the use of new and effective medications.

> *I can say my quality of life has improved. I was gradually getting worn out. And I would say the last seven years have been much better than the previous five [before] the heart attack. It was just kind of degrading a little bit by little bit all along, and then so once the cholesterol was actually remedied and the artery was unblocked, I would say that my quality of life has been high.*

The diagnosis served other positive functions as well. A few participants mentioned that having a clinical diagnosis was beneficial when applying for insurance benefits and in dealing with other health-related issues. Having a genetic diagnosis was seen as valuable compared to the previous unknown etiology of their high cholesterol.

> *Hypothetically, if I didn't get the test, have the working meds, I could have faced insurance issues down the road.*
>
> *With a letter indicating what my medical condition is, [I was] able to get some support through my insurance so that I don't have to pay because it is a very high-cost drug.*

IMPACT OF FH DIAGNOSIS—FAMILY

Many participants reported that the diagnosis of FH had a positive impact on their family planning and ability to inform relatives of the nature of their condition. Upon receiving a diagnosis of FH, many participants reported that they subsequently urged other relatives to be tested for high cholesterol or they supported relatives in receiving genetic testing. "Relatives" included siblings, aunts, uncles, nieces, nephews, and children. Participants reported feeling that their own diagnosis was of great value because it allowed them to protect their loved ones from future complications from high cholesterol.

> *My son has it, too, so he's on a cholesterol-lowering drug. And if you looked at him, he's the picture of health…but he has high cholesterol. So [my diagnosis of FH] has made one heck of a big difference in his life because he won't be faced with the same decisions and the same things that I went through…my son is going to avoid all of that thanks to this genetic testing.*
>
> *But it's also something that they'll know…my son actually is having a baby in the fall. It's something he can keep in the back of his mind for his little one once they're born, so I think it's a good thing to know.*
>
> *So for me…having this diagnosis, I just keep wondering, "Okay, my son and his kids, it's just going to keep on going, keep on going…." And this is why hopefully with all these studies and whatever's going on, maybe they can find out earlier, be able to do something for my grandkids, right?*

Despite the perceived benefits of FH testing and diagnosis, some participants reported that some relatives were resistant to testing or outright refused to be tested for cholesterol or FH. The reasons for this resistance included a disbelief in the presence of high cholesterol due to age or perceived health, perceived cost of the testing, or a lack of understanding of the genetic nature of FH. One participant who initially refused to consider testing reported that the refusal was motivated by a lack of knowledge and understanding of the medical condition and the seriousness of high cholesterol. If larger-scale cascade screening is to be considered, these results indicate a need for increased education and awareness of the dangers of high cholesterol and the nature of FH.

> *Here's where I sit on this, because I have two boys, but they think I'm paranoid. But I am, because their father died so young of heart disease, so I worry about them, because they could have the same thing, right? I've asked both of them to have their cholesterol checked, and both of [them] told me, "Mom, you worry too much." If I said to them, "Look, why don't we do a genetic test?" one son would do it. The other one would definitely not because he doesn't want to know anything. He just wants to live his life large, not knowing anything that could possibly happen down the line.*
>
> *There's no question that there's a business case, whatever it costs, but how do you convince somebody of a business case before you know that you've got a problem?*
>
> *So I wasn't getting it, in terms of I didn't understand the science behind it, and I felt fine. So why would I even worry about it? But it was my own ignorance and, probably, a lack of knowledge that caused me not to [take it seriously].*

BARRIERS

Participants reflected on the barriers they encountered in accessing and receiving a diagnosis of FH. Since most people we interviewed were recruited from a single clinical research centre, there was an inherent access issue affecting the make-up of the pool of potential participants. Learning about and getting referrals to the clinic were barriers that required time and effort to overcome. Participants acknowledged that they were unsure how they would have received this genetic diagnosis without access to the clinic.

> *Unless my family was involved with [the clinic], I probably wouldn't have been steered towards that test or that drug. So there's a real lack of education, I think, even in the medical community, as to the severity of the issue and the treatments available.*

Because most participants received a FH diagnosis through the research clinic, the cost of the test was not passed on to them. However, they reported that the cost of the test would have been an issue if they were required to pay for it out-of-pocket. Some people reflected that, at the time of their diagnosis, their lifestyle and employment status were such that paying for the cost of the genetic test would have been impossible financially.

> *At any time of my life, but particularly at that time of my life: I had two teenage kids. It absolutely would have been a real barrier for me.*
>
> *And the thing is, too…if I had known when I was in my 20s…if they had this test and the government didn't pay for it, then I couldn't afford to get it anyway…. Nobody could help us out at that time.*

Other participants reflected that, even if cost wasn't an issue for them, being convinced that the test was of value could be a barrier for those who would have to pay for the test. Without knowing that cholesterol was indeed a personal health concern, it would be hard to justify the cost of the test.

> *In hindsight, I wouldn't balk at the cost of it. But I probably would have had I not understood the results, so it's a bit of a chicken-and-egg situation. I think I can see the average person not wanting to spend $2,000 to $4,000 to find out if they've got a problem, but by the same token, finding out you've got a problem and then the actual results of the treatment for such that it's probably extending your life significantly. So then it's worth it.*

Discussion

Engaging with people directly through interviews allowed us to perform a robust examination of the preferences and values surrounding the diagnosis of high cholesterol and the genetic condition of familial hypercholesterolemia. All participants had been diagnosed with high cholesterol, and most had confirmed FH diagnosed through genetic testing at a research clinic. Therefore, participants were able to speak to the impacts of their diagnosis, both for themselves and for their relatives.

Participants represented a spectrum of people who had managed their cholesterol for various lengths of time. Some had attempted to manage cholesterol for many years through exercise, diet, or medication prior to their diagnosis of FH. Some learned of their condition only after a drastic health event, such as a cardiac arrest. In this way, direct engagement allowed for analysis of a wide variety of perspectives and for a thorough analysis of the benefits and challenges of genetic testing for FH. They were also able to reflect on the impact of their diagnosis on relatives, providing insight into potential strengths and limitations of widespread cascade screening.

Participants were able to speak regarding barriers they may have faced in accessing and choosing to undergo genetic testing for FH. This context can provide insight into the use of the genetic test in the province and help to illuminate when and how people who suspect they may have the condition can access the test and what supports may be most valued.

Testing is not widely available in Ontario. Most participants were recruited from a single research clinic in southwestern Ontario, perhaps limiting some provincial context in access and information surrounding FH genetic testing. The limited number of Ontarians who have received a genetic diagnosis of FH was also a limitation of this engagement.

Conclusions

High cholesterol can precipitate a serious health event and its discovery can lead people to change their diet and lifestyle in an effort to control their cholesterol levels. A genetic diagnosis of FH can provide people who have high cholesterol with greater access to effective medications that, combined with diet and exercise, can help them to better control their cholesterol levels. While this diagnosis often provides people an opportunity to inform and warn relatives of the potential health risks of high cholesterol, it was felt that greater awareness and education would allow for more efficient uptake of cascade screening.

Conclusions of the Health Technology Assessment

Our review found that genetic testing for FH has a higher clinical utility than does clinical evaluation without a genetic test. It also results in a high diagnostic yield of FH through cascade screening, allowing for earlier diagnosis and treatment.

Genetic testing can improve four outcomes measuring treatment change (increased statin dose, initiating statin treatment, adding ezetimibe to existing LDL-C lowering therapy, and remain untreated with cholesterol-lowering drugs), one outcome measuring LDL-C control (LDL-C level), and one outcome measuring total cholesterol control (total cholesterol level). There were no studies that evaluated the clinical utility of genetic testing on the outcomes measuring lifestyle change, atherosclerotic cardiovascular disease, quality of life, or mortality.

For individuals with a clinical diagnosis of FH, genetic testing would probably be a cost-saving diagnostic strategy. However, lipid cascade screening is the most cost-effective strategy for relatives of index cases confirmed through genetic testing. We estimated that publicly funding genetic testing for individuals with a clinical diagnosis of FH in Ontario would save $140.89 million (including cost savings from improved health outcomes after diagnosis), and publicly funding genetic testing in a cascade screening program for relatives would cost an additional $73.36 million, over the next five years.

People interviewed shared that learning they had high cholesterol led them to modify their diet and lifestyle in an effort to control their cholesterol levels. People we interviewed who had FH felt that greater awareness and education would allow for more efficient uptake of cascade screening.

Abbreviations

CADTH	Canadian Agency for Drugs and Technologies in Health
CI	Confidence interval
CK	Creatine kinase
CVD	Cardiovascular disease
DLCN	Dutch Lipid Collaborative Network
FH	Familial hypercholesterolemia
FH	Familial hypercholesterolemia
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HUI	Health Utility Index
ICER	Incremental cost-effectiveness ratio
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LDLR	LDL receptor
NGS	Next-generation gene sequencing
PPV	Positive predictive value
QALY	Quality-adjusted life-year

Glossary

Adverse event	An adverse event is an unexpected medical problem that happens during treatment for a health condition. Adverse events may be caused by something other than the treatment.
Budget impact analysis	A budget impact analysis estimates the financial impact of adopting a new health care intervention on the current budget (i.e., the affordability of the new intervention). It is based on predictions of how changes in the intervention mix will impact the level of health care spending for a specific population. Budget impact analyses are typically conducted for a short-term period (e.g., 5 years). The budget impact, sometimes referred to as the net budget impact, is the estimated cost difference between the current scenario (i.e., the anticipated amount of spending for a specific population without using the new intervention) and the new scenario (i.e., the anticipated amount of spending for a specific population following the introduction of the new intervention).
Causative mutation	A gene containing a mutation that is related to (contributes to or causes) the disease condition under investigation in a person with a genetic condition.
Cost-effective	A health care intervention is considered cost-effective when it provides additional benefits, compared with relevant alternatives, at an additional cost that is acceptable to a decision-maker based on the maximum willingness-to-pay value.
Cost-effectiveness acceptability curve	In economic evaluations, a cost-effectiveness acceptability curve is a graphical representation of the results of a probabilistic analysis. It illustrates the probability of health care interventions being cost-effective over a range of willingness-to-pay values. Willingness-to-pay values are plotted on the horizontal axis of the graph, and the probability of the intervention of interest and its comparator(s) being cost-effective at corresponding willingness-to-pay values is plotted on the vertical axis.
Cost-effectiveness analysis	Used broadly, "cost-effectiveness analysis" may refer to an economic evaluation used to compare the benefits of two or more health care interventions with their costs. It may encompass several types of analysis (e.g., cost-effectiveness analysis, cost–utility analysis). Used more specifically, "cost-effectiveness analysis" may refer to a type of economic evaluation in which the main outcome measure is the incremental cost per natural unit of health (e.g., life-year, symptom-free day) gained.
Cost-minimization analysis	In economic evaluations, a cost-minimization analysis compares the costs of two or more health care interventions. It is used when the intervention of interest and its relevant alternative(s) are determined to be equally effective.
Cost–utility analysis	A cost–utility analysis is a type of economic evaluation used to compare the benefits of two or more health care interventions with their costs. The benefits are measured using quality-adjusted life-years, which capture both the quality and quantity of life. In a cost–utility analysis, the main outcome measure is the incremental cost per quality-adjusted life-year gained.

Decision tree	A decision tree is a type of economic model used to assess the costs and benefits of two or more alternative health care interventions. Each intervention may be associated with different outcomes, which are represented by distinct branches in the tree. Each outcome may have a different probability of occurring and may lead to different costs and benefits.
Discounting	Discounting is a method used in economic evaluations to adjust for the differential timing of the costs incurred and the benefits generated by a health care intervention over time. Discounting reflects the concept of positive time preference, whereby future costs and benefits are reduced to reflect their present value. The health technology assessments conducted by Ontario Health use an annual discount rate of 1.5% for both future costs and future benefits.
Disutility	A disutility is a decrease in utility (i.e., a decrease in preference for a particular health outcome) typically resulting from a particular health condition (e.g., experiencing a symptom or complication).
Dominant	A health care intervention is considered dominant when it is more effective and less costly than its comparator(s).
EQ-5D	The EQ-5D is a generic health-related quality-of-life classification system widely used in clinical studies. In economic evaluations, it is used as an indirect method of obtaining health state preferences (i.e., utility values). The EQ-5D questionnaire consists of five questions relating to different domains of quality of life: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. For each domain, there are three response options: no problems, some problems, or severe problems. A newer instrument, the EQ-5D-5L, includes five response options for each domain. A scoring table is used to convert EQ-5D scores to utility values.
Extended dominance	A health care intervention is considered to be extendedly dominated when it has an incremental cost-effectiveness ratio higher than that of the next most costly or effective comparator. Interventions that are extendedly dominated are ruled out.
Health-related quality of life	Health-related quality of life is a measure of the impact of a health care intervention on a person's health. It includes the dimensions of physiology, function, social life, cognition, emotions, sleep and rest, energy and vitality, health perception, and general life satisfaction.
Health state	A health state is a particular status of health (e.g., sick, well, dead). A health state is associated with some amount of benefit and may be associated with specific costs. Benefit is captured through individual or societal preferences for the time spent in each health state and is expressed in quality-adjusted weights called utility values. In a Markov model, a finite number of mutually exclusive health states are used to represent discrete states of health.

Health Utilities Index Mark 3 (HUI3)	The HUI3 is a generic health-related quality-of-life classification system widely used in clinical studies. In economic evaluations, it is used as an indirect method of obtaining health state preferences (i.e., utility values). The HUI3 was developed in Canada and is used in major Canadian population health surveys. The HUI3 comprises eight attributes: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain and discomfort. Each attribute is associated with five or six defined functional levels, thus producing a total of 972,000 unique health states. A predefined scoring formula is used to convert HUI3 scores to utility values.
Incremental cost	The incremental cost is the additional cost, typically per person, of a health care intervention versus a comparator.
Incremental cost-effectiveness ratio (ICER)	The incremental cost-effectiveness ratio (ICER) is a summary measure that indicates, for a given health care intervention, how much more a health care consumer must pay to get an additional unit of benefit relative to an alternative intervention. It is obtained by dividing the incremental cost by the incremental effectiveness. Incremental cost-effectiveness ratios are typically presented as the cost per life-year gained or the cost per quality-adjusted life-year gained.
Index case	The original patient (the earliest identified occurrence) whose condition sets off an investigation of people who may have come into contact with the index case. In genetics, the investigation focusses on family members of the index case, who may share the genes that are thought to have caused or contributed to the condition.
***LDLR* gene**	Provides instructions for making a protein called a low-density lipoprotein receptor. This receptor binds to low-density lipoproteins (LDLs), which are the primary carriers of cholesterol in the blood, and delivers them to cells where they support cell function. A malfunctioning *LDLR* gene can impair the body's ability to remove cholesterol from the bloodstream and contribute to the development of familial hypercholesterolemia.
Markov model	A Markov model is a type of decision-analytic model used in economic evaluations to estimate the costs and health outcomes (e.g., quality-adjusted life-years gained) associated with using a particular health care intervention. Markov models are useful for clinical problems that involve events of interest that may recur over time (e.g., stroke). A Markov model consists of mutually exclusive, exhaustive health states. Patients remain in a given health state for a certain period of time before moving to another health state based on transition probabilities. The health states and events modelled may be associated with specific costs and health outcomes.
One-way sensitivity analysis	A one-way sensitivity analysis is used to explore uncertainty in the results of an economic evaluation. It is done by varying one model input (i.e., a parameter) at a time between its minimum and maximum values to observe the potential impact on the cost-effectiveness of the health care intervention of interest.

Probabilistic analysis	A probabilistic analysis (also known as a probabilistic sensitivity analysis) is used in economic models to explore uncertainty in several parameters simultaneously and is done using Monte Carlo simulation. Model inputs are defined as a distribution of possible values. In each iteration, model inputs are obtained by randomly sampling from each distribution, and a single estimate of cost and effectiveness is generated. This process is repeated many times (e.g., 10,000 times) to estimate the number of times (i.e., the probability) that the health care intervention of interest is cost-effective.
Quality-adjusted life-year (QALY)	The quality-adjusted life-year (QALY) is a generic health outcome measure commonly used in cost–utility analyses to reflect the quantity and quality of life-years lived. The life-years lived are adjusted for quality of life using individual or societal preferences (i.e., utility values) for being in a particular health state. One year of perfect health is represented by one quality-adjusted life-year.
Reference case	The reference case is a preferred set of methods and principles that provide the guidelines for economic evaluations. Its purpose is to standardize the approach of conducting and reporting economic evaluations, so that results can be compared across studies.
Risk difference	Risk difference is the difference in the risk of an outcome occurring between one health care intervention and an alternative intervention.
Scenario analysis	A scenario analysis is used to explore uncertainty in the results of an economic evaluation. It is done by observing the potential impact of different scenarios on the cost-effectiveness of a health care intervention. Scenario analyses include varying structural assumptions from the reference case.
Sensitivity analysis	Every economic evaluation contains some degree of uncertainty, and results can vary depending on the values taken by key parameters and the assumptions made. Sensitivity analysis allows these factors to be varied and shows the impact of these variations on the results of the evaluation. There are various types of sensitivity analysis, including deterministic, probabilistic, and scenario.
Societal perspective	The perspective adopted in an economic evaluation determines the types of costs and health benefits to include. The societal perspective reflects the broader economy and is the aggregation of all perspectives (e.g., health care payer and patient perspectives). It considers the full effect of a health condition on society, including all costs (regardless of who pays) and all benefits (regardless of who benefits).
Targeted NGS (next-generation gene sequencing)	A technique to analyze specific areas of the genome (an organism's complete set of genetic instructions) in order to locate genetic variants within an area of interest more quickly than is possible with whole-genome sequencing.
Time horizon	In economic evaluations, the time horizon is the time frame over which costs and benefits are examined and calculated. The relevant time horizon is chosen based on the nature of the disease and health care intervention being assessed, as well as the purpose of the analysis. For instance, a lifetime horizon would be chosen to capture the long-term health and cost consequences over a patient's lifetime.

Uptake rate	In instances where two technologies are being compared, the uptake rate is the rate at which a new technology is adopted. When a new technology is adopted, it may be used in addition to an existing technology, or it may replace an existing technology.
Utility	A utility is a value that represents a person's preference for various health states. Typically, utility values are anchored at 0 (death) and 1 (perfect health). In some scoring systems, a negative utility value indicates a state of health valued as being worse than death. Utility values can be aggregated over time to derive quality-adjusted life-years, a common outcome measure in economic evaluations.
Willingness-to-pay value	A willingness-to-pay value is the monetary value a health care consumer is willing to pay for added health benefits. When conducting a cost–utility analysis, the willingness-to-pay value represents the cost a consumer is willing to pay for an additional quality-adjusted life-year. If the incremental cost-effectiveness ratio is less than the willingness-to-pay value, the health care intervention of interest is considered cost-effective. If the incremental cost-effectiveness ratio is more than the willingness-to-pay value, the intervention is considered not to be cost-effective.

Appendices

Appendix 1: Literature Search Strategies

Clinical Evidence Search

Search date: February 11, 2021

Databases searched: Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, CRD Health Technology Assessment Database, and NHS Economic Evaluation Database

Database segments: EBM Reviews - Cochrane Central Register of Controlled Trials <January 2021>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to February 10, 2021>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2021 Week 05>, Ovid MEDLINE(R) ALL <1946 to February 10, 2021>

Search strategy:

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1 Hyperlipoproteinemia Type II/ (13061)
2 ((hypercholesterol?emia* or hyper cholesterol?emia*) adj2 (familial or autosomal dominant or essential)).ti,ab,kf. (17839)
3 ((familial or hypercholesterol* or FH or hyperlipoprotein?emia* or dysliped?emia* or hyperlipid?emia*) adj2 (xanthomat* or xantomat* or xanthelas*)).ti,ab,kf. (270)
4 (hyper low density lipoprotein?emia* or hyperbetalipoprotein?emia* or hyperbeta lipoprotein?emia* or hyper beta lipoprotein?emia* or (LDL receptor* adj2 (disorder* or mutat* or variant*))).ti,ab,kf. (889)
5 ((hyperlipoprotein?emia* or hyper lipoprotein?emia* or fredrickson) adj2 (type 2 or type 2s or type 2a or type 2as or type 2b or type 2bs or type ii or type iis or type iia or type iias or type iib or type iibs)).ti,ab,kf. (1379)
6 (HeFH or HoFH or (FH adj2 (probable or definite or diagnos* or heterozygo* or homozygo* or genetic or variant* or mutat*))).ti,ab,kf. (5922)
7 Hyperlipidemia, Familial Combined/ (1780)
8 ((hyperlipoprotein?emia* or hyperlipid?emia*) adj2 familial combined).ti,ab,kf. (1685)
9 Apolipoproteins B/ (31645)
10 Apolipoprotein B-100/ (5822)
11 (apolipoprotein b or apolipoproteins b or apo b or apob or apoprotein b or apoproteins b or apolipoprotein b100 or apolipoproteins b100 or apo b100 or apob100 or apoprotein b100 or apoproteins b100).ti,ab,kf. (50128)
12 Receptors, LDL/ (24976)
13 ((LDL or LDL-C or low density lipoprotein*) adj2 (elevat* or raise or raises or raised or raising or higher or rise or rises or rising or increas*)).ti,ab,kf. (26135)
14 Proprotein Convertase 9/ (6389)
15 ((proprotein convertase subtilisin* kexin adj2 9*) or kexin9* or PCSK9*).ti,ab,kf. (10801)
16 or/1-15 (123450)
17 DNA Mutational Analysis/ (62933)
18 Sequence Analysis, DNA/ (165334)
19 (DNA adj2 (variant analy* or mutation* analy* or sequenc* or diagnos*)).ti,ab,kf. (240992)
20 ((gene or genes or genetic) adj2 (variant analy* or mutation* analy*)).ti,ab,kf. (3884)
21 Molecular Diagnostic Techniques/ (28567)
22 molecular diagnos*.ti,ab,kf. (42021)
23 Oligonucleotide Array Sequence Analysis/ (126273)
24 (DNA microarray* or taqman*).ti,ab,kf. (68131)
25 Genetic Testing/ (99955)

26 ((genetic* or gene or genes) adj2 (test* or screen* or panel* or diagnos#s)).ti,ab,kf. (197641)
27 (cascade adj2 (screen* or test*)).ti,ab,kf. (2633)
28 Genetic Predisposition to Disease/ (192300)
29 (genetic adj2 (predisposition* or susceptibil*)).ti,ab,kf. (62645)
30 Genetic Counseling/ (46290)
31 (genetic adj2 counsel*).ti,ab,kf. (46628)
32 exp Whole Genome Sequencing/ (31560)
33 (((exome or transcriptome or genom* or next gen or nextgen or sanger or panel or panels or capillary electrophoresis) adj2 sequenc*) or NGS or whole exome* or WES or parallel sequenc* or whole genom* or WGS).ti,ab,kf. (376585)
34 ((target* or next generation) adj2 (sequenc* or resequenc* or panel*)).ti,ab,kf. (152703)
35 Genotyping Techniques/ (15800)
36 (genotype or genotypes or genotyping or polygenic risk scor*).ti,ab,kf. (684604)
37 lipidseq*.ti,ab,kf. (18)
38 or/17-37 (2016208)
39 16 and 38 (11119)
40 (FH cascade screen* or FH genetic test* or FH genetic screen*).ti,ab,kf. (97)
41 or/39-40 (11119)
42 exp Animals/ not Humans/ (17606786)
43 41 not 42 (8156)
44 Case Reports/ or Comment.pt. or Editorial.pt. or (Letter not (Letter and Randomized Controlled Trial)).pt. or Congress.pt. (5740496)
45 43 not 44 (7784)
46 limit 45 to english language [Limit not valid in CDSR; records were retained] (7265)
47 46 use medall,cctr,coch,clhta,cleed (4047)
48 familial hypercholesterolemia/ (17451)
49 ((hypercholesterol?emia* or hyper cholesterol?emia*) adj2 (familial or autosomal dominant or essential)).tw,kw. (18042)
50 ((familial or hypercholesterol* or FH or hyperlipoprotein?emia* or dysliped?emia* or hyperlipid?emia*) adj2 (xanthomat* or xantomat* or xanthelas*)).tw,kw. (276)
51 (hyper low density lipoprotein?emia* or hyperbetalipoprotein?emia* or hyperbeta lipoprotein?emia* or hyper beta lipoprotein?emia* or (LDL receptor* adj2 (disorder* or mutat* or variant*))).tw,kw. (921)
52 ((hyperlipoprotein?emia* or hyper lipoprotein?emia* or fredrickson) adj2 (type 2 or type 2s or type 2a or type 2as or type 2b or type 2bs or type ii or type iis or type iia or type iias or type iib or type iibs)).tw,kw. (1424)
53 (HeFH or HoFH or (FH adj2 (probable or definite or diagnos* or heterozygo* or homozygo* or genetic or variant* or mutat*))).tw,kw. (5939)
54 familial hyperlipemia/ (970)
55 ((hyperlipoprotein?emia* or hyperlipid?emia*) adj2 familial combined).tw,kw. (1724)
56 apolipoprotein B/ (21479)
57 apolipoprotein B100/ (3787)
58 (apolipoprotein b or apolipoproteins b or apo b or apob or apoprotein b or apoproteins b or apolipoprotein b100 or apolipoproteins b100 or apo b100 or apob100 or apoprotein b100 or apoproteins b100).tw,kw. (50470)
59 low density lipoprotein receptor/ (25708)
60 ((LDL or LDL-C or low density lipoprotein*) adj2 (elevat* or raise or raises or raised or raising or higher or rise or rises or rising or increas*)).tw,kw. (26187)
61 proprotein convertase 9/ (6389)
62 ((proprotein convertase subtilisin* kexin adj2 9*) or kexin9* or PCSK9*).tw,kw. (11019)
63 or/48-62 (123316)
64 dna mutational analysis/ (62933)
65 dna sequencing/ (165287)
66 (DNA adj2 (variant analy* or mutation* analy* or sequenc* or diagnos*)).tw,kw,dv. (243663)
67 ((gene or genes or genetic) adj2 (variant analy* or mutation* analy*)).tw,kw,dv. (3903)

68 molecular diagnosis/ (20742)
69 molecular diagnos*.tw,kw,dv. (44913)
70 DNA microarray/ (127966)
71 (DNA microarray* or taqman*).tw,kw,dv. (70449)
72 genetic screening/ (130240)
73 ((genetic* or gene or genes) adj2 (test* or screen* or panel* or diagnos#s)).tw,kw,dv. (200867)
74 (cascade adj2 (screen* or test*)).tw,kw,dv. (2684)
75 genetic predisposition/ (201906)
76 (genetic adj2 (predisposition* or susceptibil*)).tw,kw,dv. (67941)
77 genetic counseling/ (46290)
78 (genetic adj2 counsel*).tw,kw,dv. (47538)
79 exp whole genome sequencing/ (31560)
80 (((exome or transcriptome or genom* or next gen or nextgen or sanger or panel or panels or capillary electrophoresis) adj2 sequenc*) or NGS or whole exome* or WES or parallel sequenc* or whole genom* or WGS).tw,kw,dv. (379769)
81 ((target* or next generation) adj2 (sequenc* or resequenc* or panel*)).tw,kw,dv. (153366)
82 genotyping technique/ (16913)
83 (genotype or genotypes or genotyping or polygenic risk scor*).tw,kw,dv. (690591)
84 lipidseq*.tw,kw,dv. (18)
85 or/64-84 (2046324)
86 63 and 85 (11395)
87 (FH cascade screen* or FH genetic test* or FH genetic screen*).tw,kw,dv. (97)
88 or/86-87 (11395)
89 (exp animal/ or nonhuman/) not exp human/ (10952173)
90 88 not 89 (10693)
91 Case Report/ or Comment/ or Editorial/ or (letter.pt. not (letter.pt. and randomized controlled trial/)) or conference abstract.pt. or conference review.pt. (11733002)
92 90 not 91 (8568)
93 limit 92 to english language [Limit not valid in CDSR; records were retained] (7979)
94 93 use emez (3974)
95 47 or 94 (8021)
96 95 use medall (3837)
97 95 use emez (3974)
98 95 use cctr (199)
99 95 use coch (1)
100 95 use clhta (5)
101 95 use cleed (5)
102 limit 95 to yr="2010 -Current" (4382)
103 remove duplicates from 102 (2809)
104 limit 95 to yr="1946 - 2009" (3632)
105 remove duplicates from 104 (2312)
106 102 or 104 (8014)
107 95 not 106 (7)
108 103 or 105 or 107 (5128)

Economic Evaluation and Cost Effectiveness Search

Search date: February 16, 2021

Databases searched: Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Centre for Reviews and Dissemination (CRD) Health Technology Assessment Database, and National Health Service (NHS) Economic Evaluation Database

Database segments: EBM Reviews - Cochrane Central Register of Controlled Trials <January 2021>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to February 10, 2021>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2021 Week 06>, Ovid MEDLINE(R) ALL <1946 to February 15, 2021>

Search strategy:

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1 Hyperlipoproteinemia Type II/ (13064)
2 ((hypercholesterol?emia* or hyper cholesterol?emia*) adj2 (familial or autosomal dominant or essential)).ti,ab,kf. (17910)
3 ((familial or hypercholesterol* or FH or hyperlipoprotein?emia* or dysliped?emia* or hyperlipid?emia*) adj2 (xanthomat* or xantomat* or xanthelas*)).ti,ab,kf. (271)
4 (hyper low density lipoprotein?emia* or hyperbetalipoprotein?emia* or hyperbeta lipoprotein?emia* or hyper beta lipoprotein?emia* or (LDL receptor* adj2 (disorder* or mutat* or variant*))).ti,ab,kf. (892)
5 ((hyperlipoprotein?emia* or hyper lipoprotein?emia* or fredrickson) adj2 (type 2 or type 2s or type 2a or type 2as or type 2b or type 2bs or type ii or type iis or type iia or type iias or type iib or type iibs)).ti,ab,kf. (1379)
6 (HeFH or HoFH or (FH adj2 (probable or definite or diagnos* or heterozygo* or homozygo* or genetic or variant* or mutat*))).ti,ab,kf. (5936)
7 Hyperlipidemia, Familial Combined/ (1784)
8 ((hyperlipoprotein?emia* or hyperlipid?emia*) adj2 familial combined).ti,ab,kf. (1685)
9 Apolipoproteins B/ (31734)
10 Apolipoprotein B-100/ (5831)
11 (apolipoprotein b or apolipoproteins b or apo b or apob or apoprotein b or apoproteins b or apolipoprotein b100 or apolipoproteins b100 or apo b100 or apob100 or apoprotein b100 or apoproteins b100).ti,ab,kf. (50212)
12 Receptors, LDL/ (25062)
13 ((LDL or LDL-C or low density lipoprotein*) adj2 (elevat* or raise or raises or raised or raising or higher or rise or rises or rising or increas*)).ti,ab,kf. (26175)
14 Proprotein Convertase 9/ (6409)
15 ((proprotein convertase subtilisin* kexin adj2 9*) or kexing* or PCSK9*).ti,ab,kf. (10843)
16 or/1-15 (123753)
17 DNA Mutational Analysis/ (62954)
18 Sequence Analysis, DNA/ (165442)
19 (DNA adj2 (variant analy* or mutation* analy* or sequenc* or diagnos*)).ti,ab,kf. (241465)
20 ((gene or genes or genetic) adj2 (variant analy* or mutation* analy*)).ti,ab,kf. (3895)
21 Molecular Diagnostic Techniques/ (28707)
22 molecular diagnos*.ti,ab,kf. (42230)
23 Oligonucleotide Array Sequence Analysis/ (126505)
24 (DNA microarray* or taqman*).ti,ab,kf. (68239)
25 Genetic Testing/ (99917)
26 ((genetic* or gene or genes) adj2 (test* or screen* or panel* or diagnos#s)).ti,ab,kf. (198627)
27 (cascade adj2 (screen* or test*)).ti,ab,kf. (2658)
28 Genetic Predisposition to Disease/ (192569)
29 (genetic adj2 (predisposition* or susceptibil*)).ti,ab,kf. (62826)
30 Genetic Counseling/ (46597)
31 (genetic adj2 counsel*).ti,ab,kf. (46907)
32 exp Whole Genome Sequencing/ (31841)
33 (((exome or transcriptome or genom* or next gen or nextgen or sanger or panel or panels or capillary electrophoresis) adj2 sequenc*) or NGS or whole exome* or WES or parallel sequenc* or whole genom* or WGS).ti,ab,kf. (378601)
34 ((target* or next generation) adj2 (sequenc* or resequenc* or panel*)).ti,ab,kf. (153378)
35 Genotyping Techniques/ (15823)

36 (genotype or genotypes or genotyping or polygenic risk scor*).ti,ab,kf. (686333)
37 lipidseq*.ti,ab,kf. (18)
38 or/17-37 (2021936)
39 16 and 38 (11159)
40 (FH cascade screen* or FH genetic test* or FH genetic screen*).ti,ab,kf. (98)
41 or/39-40 (11159)
42 exp Animals/ not Humans/ (17713707)
43 41 not 42 (8161)
44 Case Reports/ or Comment.pt. or Editorial.pt. or (Letter not (Letter and Randomized Controlled Trial)).pt. or Congress.pt. (5766096)
45 43 not 44 (7788)
46 limit 45 to english language [Limit not valid in CDSR; records were retained] (7269)
47 46 use coch,clhta,cleed (11)
48 economics/ (261489)
49 economics, medical/ or economics, pharmaceutical/ or exp economics, hospital/ or economics, nursing/ or economics, dental/ (904533)
50 economics.fs. (444337)
51 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).ti,ab,kf. (1026283)
52 exp "costs and cost analysis"/ (622642)
53 (cost or costs or costing or costly).ti. (292505)
54 cost effective*.ti,ab,kf. (375140)
55 (cost* adj2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab,kf. (244855)
56 models, economic/ (14318)
57 markov chains/ or monte carlo method/ (91535)
58 (decision adj1 (tree* or analy* or model*)).ti,ab,kf. (50135)
59 (markov or markow or monte carlo).ti,ab,kf. (147843)
60 quality-adjusted life years/ (45852)
61 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).ti,ab,kf. (88217)
62 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).ti,ab,kf. (145806)
63 or/48-62 (2851120)
64 46 and 63 (287)
65 64 use medall,cctr (145)
66 or/47,65 (156)
67 familial hypercholesterolemia/ (17538)
68 ((hypercholesterol?emia* or hyper cholesterol?emia*) adj2 (familial or autosomal dominant or essential)).tw,kw. (18113)
69 ((familial or hypercholesterol* or FH or hyperlipoprotein?emia* or dysliped?emia* or hyperlipid?emia*) adj2 (xanthomat* or xantomat* or xanthelas*)).tw,kw. (277)
70 (hyper low density lipoprotein?emia* or hyperbetalipoprotein?emia* or hyperbeta lipoprotein?emia* or hyper beta lipoprotein?emia* or (LDL receptor* adj2 (disorder* or mutat* or variant*))).tw,kw. (924)
71 ((hyperlipoprotein?emia* or hyper lipoprotein?emia* or fredrickson) adj2 (type 2 or type 2s or type 2a or type 2as or type 2b or type 2bs or type ii or type iis or type iia or type iias or type iib or type iibs)).tw,kw. (1424)
72 (HeFH or HoFH or (FH adj2 (probable or definite or diagnos* or heterozygo* or homozygo* or genetic or variant* or mutat*))).tw,kw. (5953)
73 familial hyperlipemia/ (974)
74 ((hyperlipoprotein?emia* or hyperlipid?emia*) adj2 familial combined).tw,kw. (1724)
75 apolipoprotein B/ (21567)
76 apolipoprotein B100/ (3796)
77 (apolipoprotein b or apolipoproteins b or apo b or apob or apoprotein b or apoproteins b or apolipoprotein b100 or apolipoproteins b100 or apo b100 or apob100 or apoprotein b100 or apoproteins b100).tw,kw. (50555)

78 low density lipoprotein receptor/ (25794)
79 ((LDL or LDL-C or low density lipoprotein*) adj2 (elevat* or raise or raises or raised or raising or higher or rise or rises or rising or increas*)).tw,kw. (26227)
80 proprotein convertase 9/ (6409)
81 ((proprotein convertase subtilisin* kexin adj2 9*) or kexin9* or PCSK9*).tw,kw. (11062)
82 or/67-81 (123635)
83 dna mutational analysis/ (62954)
84 dna sequencing/ (165395)
85 (DNA adj2 (variant analy* or mutation* analy* or sequenc* or diagnos*)).tw,kw,dv. (244142)
86 ((gene or genes or genetic) adj2 (variant analy* or mutation* analy*)).tw,kw,dv. (3914)
87 molecular diagnosis/ (20866)
88 molecular diagnos*.tw,kw,dv. (45129)
89 DNA microarray/ (128198)
90 (DNA microarray* or taqman*).tw,kw,dv. (70583)
91 genetic screening/ (130802)
92 ((genetic* or gene or genes) adj2 (test* or screen* or panel* or diagnos#s)).tw,kw,dv. (201857)
93 (cascade adj2 (screen* or test*)).tw,kw,dv. (2709)
94 genetic predisposition/ (202175)
95 (genetic adj2 (predisposition* or susceptibil*)).tw,kw,dv. (68125)
96 genetic counseling/ (46597)
97 (genetic adj2 counsel*).tw,kw,dv. (47818)
98 exp whole genome sequencing/ (31841)
99 (((exome or transcriptome or genom* or next gen or nextgen or sanger or panel or panels or capillary electrophoresis) adj2 sequenc*) or NGS or whole exome* or WES or parallel sequenc* or whole genom* or WGS).tw,kw,dv. (381803)
100 ((target* or next generation) adj2 (sequenc* or resequenc* or panel*)).tw,kw,dv. (154040)
101 genotyping technique/ (16936)
102 (genotype or genotypes or genotyping or polygenic risk scor*).tw,kw,dv. (692337)
103 lipidseq*.tw,kw,dv. (18)
104 or/83-103 (2052287)
105 82 and 104 (11440)
106 (FH cascade screen* or FH genetic test* or FH genetic screen*).tw,kw,dv. (98)
107 or/105-106 (11440)
108 (exp animal/ or nonhuman/) not exp human/ (10970412)
109 107 not 108 (10736)
110 Case Report/ or Comment/ or Editorial/ or (letter.pt. not (letter.pt. and randomized controlled trial/)) or conference abstract.pt. or conference review.pt. (11774903)
111 109 not 110 (8594)
112 limit 111 to english language [Limit not valid in CDSR; records were retained] (8005)
113 Economics/ (261489)
114 Health Economics/ or Pharmacoeconomics/ or Drug Cost/ or Drug Formulary/ (136753)
115 Economic Aspect/ or exp Economic Evaluation/ (490364)
116 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw,kw. (1053305)
117 exp "Cost"/ (622642)
118 (cost or costs or costing or costly).ti. (292505)
119 cost effective*.tw,kw. (388042)
120 (cost* adj2 (util* or efficac* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab,kw. (257384)
121 Monte Carlo Method/ (71852)
122 (decision adj1 (tree* or analy* or model*)).tw,kw. (54019)
123 (markov or markow or monte carlo).tw,kw. (152911)
124 Quality-Adjusted Life Years/ (45852)
125 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw,kw. (92150)
126 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw,kw. (167202)

127 or/113-126 (2456889)
128 112 and 127 (341)
129 128 use emez (182)
130 66 or 129 (338)
131 130 use medall (138)
132 130 use emez (182)
133 130 use cctr (7)
134 130 use coch (1)
135 130 use cleed (5)
136 130 use clhta (5)
137 remove duplicates from 130 (229)

Quantitative Preferences Evidence Search

Search date: February 17, 2021

Databases searched: Ovid MEDLINE, Cumulative Index to Nursing & Allied Health Literature (CINAHL)

Search filter used: Quantitative preference evidence filter, modified from Selva et al[101]

Database segment: Ovid MEDLINE(R) ALL <1946 to February 15, 2021>

Search strategy:

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1 Hyperlipoproteinemia Type II/ (6855)
2 ((hypercholesterol?emia* or hyper cholesterol?emia*) adj2 (familial or autosomal dominant or essential)).ti,ab,kf. (7251)
3 ((familial or hypercholesterol* or FH or hyperlipoprotein?emia* or dysliped?emia* or hyperlipid?emia*) adj2 (xanthomat* or xantomat* or xanthelas*)).ti,ab,kf. (197)
4 (hyper low density lipoprotein?emia* or hyperbetalipoprotein?emia* or hyperbeta lipoprotein?emia* or hyper beta lipoprotein?emia* or (LDL receptor* adj2 (disorder* or mutat* or variant*))).ti,ab,kf. (408)
5 ((hyperlipoprotein?emia* or hyper lipoprotein?emia* or fredrickson) adj2 (type 2 or type 2s or type 2a or type 2as or type 2b or type 2bs or type ii or type iis or type iia or type iias or type iib or type iibs)).ti,ab,kf. (719)
6 (HeFH or HoFH or (FH adj2 (probable or definite or diagnos* or heterozygo* or homozygo* or genetic or variant* or mutat*))).ti,ab,kf. (2090)
7 Hyperlipidemia, Familial Combined/ (754)
8 ((hyperlipoprotein?emia* or hyperlipid?emia*) adj2 familial combined).ti,ab,kf. (712)
9 Apolipoproteins B/ (9382)
10 Apolipoprotein B-100/ (2134)
11 (apolipoprotein b or apolipoproteins b or apo b or apob or apoprotein b or apoproteins b or apolipoprotein b100 or apolipoproteins b100 or apo b100 or apob100 or apoprotein b100 or apoproteins b100).ti,ab,kf. (20376)
12 Receptors, LDL/ (9948)
13 ((LDL or LDL-C or low density lipoprotein*) adj2 (elevat* or raise or raises or raised or raising or higher or rise or rises or rising or increas*)).ti,ab,kf. (9642)
14 Proprotein Convertase 9/ (2440)
15 ((proprotein convertase subtilisin* kexin adj2 9*) or kexing* or PCSK9*).ti,ab,kf. (3959)
16 or/1-15 (47790)
17 DNA Mutational Analysis/ (60799)
18 Sequence Analysis, DNA/ (161396)
19 (DNA adj2 (variant analy* or mutation* analy* or sequenc* or diagnos*)).ti,ab,kf. (114046)
20 ((gene or genes or genetic) adj2 (variant analy* or mutation* analy*)).ti,ab,kf. (1496)

21 Molecular Diagnostic Techniques/ (11670)
22 molecular diagnos*.ti,ab,kf. (17967)
23 Oligonucleotide Array Sequence Analysis/ (66148)
24 (DNA microarray* or taqman*).ti,ab,kf. (25731)
25 Genetic Testing/ (39246)
26 ((genetic* or gene or genes) adj2 (test* or screen* or panel* or diagnos#s)).ti,ab,kf. (78326)
27 (cascade adj2 (screen* or test*)).ti,ab,kf. (989)
28 Genetic Predisposition to Disease/ (141472)
29 (genetic adj2 (predisposition* or susceptibil*)).ti,ab,kf. (26745)
30 Genetic Counseling/ (14513)
31 (genetic adj2 counsel*).ti,ab,kf. (20113)
32 exp Whole Genome Sequencing/ (9797)
33 (((exome or transcriptome or genom* or next gen or nextgen or sanger or panel or panels or capillary electrophoresis) adj2 sequenc*) or NGS or whole exome* or WES or parallel sequenc* or whole genom* or WGS).ti,ab,kf. (164163)
34 ((target* or next generation) adj2 (sequenc* or resequenc* or panel*)).ti,ab,kf. (62259)
35 Genotyping Techniques/ (7412)
36 (genotype or genotypes or genotyping or polygenic risk scor*).ti,ab,kf. (289697)
37 lipidseq*.ti,ab,kf. (4)
38 or/17-37 (987551)
39 16 and 38 (4682)
40 (FH cascade screen* or FH genetic test* or FH genetic screen*).ti,ab,kf. (31)
41 or/39-40 (4682)
42 Attitude to Health/ (84338)
43 Health Knowledge, Attitudes, Practice/ (115215)
44 Patient Participation/ (26689)
45 Patient Preference/ (9099)
46 Attitude of Health Personnel/ (124338)
47 *Professional-Patient Relations/ (11943)
48 *Physician-Patient Relations/ (36155)
49 Choice Behavior/ (33114)
50 (choice or choices or value* or valuation* or knowledg*).ti. (276318)
51 (preference* or expectation* or attitude* or acceptab* or point of view).ti,ab,kf. (620860)
52 ((patient*1 or user*1 or men or women or personal or provider* or practitioner* or professional*1 or (health* adj2 worker*) or clinician* or physician* or doctor* or geneticist* or genetic counselor*) adj2 (participation or perspective* or perception* or misperception* or perceiv* or view* or understand* or misunderstand* or value*1 or knowledg*)).ti,ab,kf. (151528)
53 health perception*.ti,ab,kf. (2878)
54 *Decision Making/ (43558)
55 (patient*1 or user*1 or men or women or personal or provider* or practitioner* or professional*1 or (health* adj2 worker*) or clinician* or physician* or doctor* or geneticist* or genetic counselor*).ti. (2570948)
56 54 and 55 (8058)
57 (decision* and mak*).ti. (31015)
58 (decision mak* or decisions mak*).ti,ab,kf. (162160)
59 57 or 58 (163691)
60 (patient*1 or user*1 or men or women or personal or provider* or practitioner* or professional*1 or (health* adj2 worker*) or clinician* or physician* or doctor* or geneticist* or genetic counselor*).ti,ab,kf. (8542486)
61 59 and 60 (102743)
62 (discrete choice* or decision board* or decision analy* or decision-support or decision tool* or decision aid* or latent class* or decision* conflict* or decision* regret*).ti,ab,kf. (39545)
63 Decision Support Techniques/ (20912)
64 (health and utilit*).ti. (1578)

65 (gamble* or prospect theory or health utilit* or utility value* or utility score* or utility estimate* or health state or feeling thermometer* or best-worst scaling or time trade-off or TTO or probability trade-off).ti,ab,kf. (14180)
66 (preference based or preference score* or preference elicitation or multiattribute or multi attribute).ti,ab,kf. (3047)
67 or/42-53,56,61-66 (1355839)
68 41 and 67 (153)
69 Case Reports/ or Comment.pt. or Editorial.pt. or (Letter not (Letter and Randomized Controlled Trial)).pt. or Congress.pt. (3935009)
70 68 not 69 (149)
71 limit 70 to english language (138)

CINAHL

S1	(MH "Hypercholesterolemia, Familial")	1,215
S2	((hypercholesterolemia* or hypercholesterolaemia* hyper cholesterolemia* or hyper cholesterolaemia*) N2 (familial or autosomal dominant or essential))	2,057
S3	((familial or hypercholesterol* or FH or hyperlipoproteinemia* or hyperlipoproteinaemia* or dyslipedemia* or dyslipedaemia* or hyperlipidemia* or hyperlipidaemia*) N2 (xanthomat* or xantomat* or xanthelas*))	58
S4	(hyper low density lipoproteinemia* or hyper low density lipoproteinaemia* or hyperbetalipoproteinemia* or hyperbetalipoproteinaemia* or hyperbeta lipoproteinemia* or hyperbeta lipoproteinaemia* or hyper beta lipoproteinemia* or hyper beta lipoproteinaemia* or (LDL receptor* N2 (disorder* or mutat* or variant*)))	1,014
S5	((hyperlipoproteinemia* or hyperlipoproteinaemia* or hyper lipoproteinemia* or hyper lipoproteinaemia* or fredrickson) N2 (type 2 or type 2s or type 2a or type 2as or type 2b or type 2bs or type ii or type iis or type iia or type iias or type iib or type iibs))	65
S6	(HeFH or HoFH or (FH N2 (probable or definite or diagnos* or heterozygo* or homozygo* or genetic or variant* or mutat*)))	400
S7	((hyperlipoproteinemia* or hyperlipoproteinaemia* or hyperlipidemia* or hyperlipidaemia*) N2 familial combined)	71
S8	(apolipoprotein b or apolipoproteins b or apo b or apob or apoprotein b or apoproteins b or apolipoprotein b100 or apolipoproteins b100 or apo b100 or apob100 or apoprotein b100 or apoproteins b100)	4,772
S9	((LDL or LDL-C or low density lipoprotein*) N2 (elevat* or raise or raises or raised or raising or higher or rise or rises or rising or increas*))	2,658
S10	((proprotein convertase subtilisin* kexin N2 9*) or kexin9* or PCSK9*)	1,120
S11	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10	9,754
S12	(DNA N2 (variant analy* or mutation* analy* or sequenc* or diagnos*))	4,107
S13	((gene or genes or genetic) N2 (variant analy* or mutation* analy*))	2,455
S14	(MH "Sequence Analysis")	20,745
S15	(MH "Molecular Diagnostic Techniques")	2,387

S16	molecular diagnos*	4,577
S17	(MH "Oligonucleotide Array Sequence Analysis")	2,190
S18	(DNA microarray* or taqman*)	2,395
S19	(MH "Genetic Screening")	14,076
S20	((genetic* or gene or genes) N2 (test* or screen* or panel* or diagnos*))	118,260
S21	(cascade N2 (screen* or test*))	263
S22	(genetic N2 (predisposition* or susceptibil*))	5,035
S23	(MH "Genetic Counseling")	4,372
S24	(genetic N2 counsel*)	6,378
S25	(((exome or transcriptome or genom* or next gen or nextgen or sanger or panel or panels or capillary electrophoresis) N2 sequenc*) or NGS or whole exome* or WES or parallel sequenc* or whole genom* or WGS)	19,927
S26	((target* or next generation) N2 (sequenc* or resequenc* or panel*))	5,765
S27	(genotype or genotypes or genotyping or polygenic risk scor*)	45,767
S28	lipidseq*	1
S29	S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28	170,933
S30	S11 AND S29	2,459
S31	(FH cascade screen* or FH genetic test* or FH genetic screen*)	21
S32	S30 OR S31	2,459
S33	(MH "Attitude to Health")	45,429
S34	(MH "Health Knowledge")	31,428
S35	(MH "Consumer Participation")	20,898
S36	(MH "Patient Preference")	1,072
S37	(MH "Attitude of Health Personnel")	46,174
S38	(MM "Professional-Patient Relations")	13,639
S39	(MM "Physician-Patient Relations")	16,541
S40	(MM "Nurse-Patient Relations")	14,423
S41	TI (choice or choices or value* or valuation* or knowledg*)	99,907
S42	(preference* or expectation* or attitude* or acceptab* or point of view)	466,998
S43	((patient or patients or user or users or men or women or personal or provider* or practitioner* or professional or professionals or (health* N2 worker*) or clinician* or physician* or doctor* or nurse* or practitioner* or geneticist* or genetic counselor*)	836,665

	N2 (participation or perspective* or perception* or misperception* or perceiv* or view* or understand* or misunderstand* or value or values or knowledg*))	
S44	health perception*	4,498
S45	(MH "Decision Making, Shared")	1,947
S46	(MH "Decision Making, Patient")	15,232
S47	(MH "Decision Making, Family")	4,047
S48	(MM "Decision Making")	23,475
S49	TI (patient or patients or user or users or men or women or personal or provider* or practitioner* or professional or professionals or (health* N2 worker*) or clinician* or physician* or doctor* or nurse* or practitioner* or geneticist* or genetic counselor*)	1,166,488
S50	S48 AND S49	4,549
S51	TI (decision* and mak*)	18,463
S52	(decision mak* or decisions mak*)	157,819
S53	S51 OR S52	158,039
S54	(patient or patients or user or users or men or women or personal or provider* or practitioner* or professional or professionals or (health* N2 worker*) or clinician* or physician* or doctor* or nurse* or practitioner* or geneticist* or genetic counselor*)	3,372,915
S55	S53 AND S54	111,215
S56	(discrete choice* or decision board* or decision analy* or decision support or decision tool* or decision aid* or latent class* or decision* conflict* or decision* regret*)	29,542
S57	(MH "Decision Support Techniques")	6,987
S58	TI (health and utilit*)	939
S59	(gamble* or prospect theory or health utilit* or utility value* or utility score* or utility estimate* or health state or feeling thermometer* or best worst scaling or time trade off or TTO or probability trade off)	17,168
S60	(preference based or preference score* or preference elicitation or multiattribute or multi attribute)	1,543
S61	S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S50 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60	1,280,357
S62	S32 AND S61	320
S63	PT (Case Study or Commentary or Editorial or Letter or Proceedings)	1,254,661
S64	S62 NOT S63	301
S65	S62 NOT S63 Limiters - English Language	300

Grey Literature

Performed: March 4–10, 2021

Websites searched:
Alberta Health Evidence Reviews, Alberta Health Services, BC Health Technology Assessments, Canadian Agency for Drugs and Technologies in Health (CADTH), Institut national d'excellence en santé et en services sociaux (INESSS), Institute of Health Economics (IHE), McGill University Health Centre Health Technology Assessment Unit, Centre Hospitalier de l'Universite de Quebec-Universite Laval, Health Technology Assessment Database, Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers, Centers for Medicare & Medicaid Services Technology Assessments, Veterans Affairs Health Services Research and Development, Institute for Clinical and Economic Review, Oregon Health Authority Health Evidence Review Commission, Washington State Health Care Authority Health Technology Reviews, National Institute for Health and Care Excellence (NICE), Healthcare Improvement Scotland, Health Technology Wales, Ireland Health Information and Quality Authority Health Technology Assessments, Australian Government Medical Services Advisory Committee, Council of Australian Governments Health Technologies, Australian Safety and Efficacy Register of New Interventional Procedures -Surgical (ASERNIP-S), Italian National Agency for Regional Health Services (AGENAS), Belgian Health Care Knowledge Centre, Ludwig Boltzmann Institute for Health Technology Assessment, Swedish Agency for Health Technology Assessment and Assessment of Social Services, Ministry of Health Malaysia Health Technology Assessment Section, Tuft's Cost-Effectiveness Analysis Registry, Sick Kids PEDE Database, PROSPERO, EUnetHTA, clinicaltrials.gov

Keywords used:
familial hypercholesterolemia, hypercholesterolemia, hypercholesterolaemia, hyperlipoproteinemia, hyperlipoproteinaemia, hyperlipidemia, hyperlipidaemia, FH, HeFH, familial, autosomal, apolipoprotein B, apob, LDL receptor, low density lipoprotein, PCSK9, cascade screen, cascade test, genetic testing, hypercholestérolémie familial, hypercholestérolémie, apolipoprotéine B, dépistage en cascades

Clinical results (included in PRISMA): 7
Economic results (included in PRISMA): 5

Ongoing HTAs (PROSPERO/EUnetHTA/): 7

Ongoing RCTs (clinicaltrials.gov): 7

Appendix 2: Critical Appraisal of the Evidence

Table A1: Risk of Bias[a] Among Nonrandomized Trials (ROBINS-I Tool)

	Bell et al, 2015[b]	D'Erasmo et al, 2020[c]	Huijgen et al, 2010[d]	Jones et al, 2018[e]
Pre-intervention				
Confounding	No	No	No	No
Selection of participants	No	No	Yes[f]	No
Risk of bias judgment	Low for all outcomes	Low for all outcomes	Serious for all outcomes	Low for all outcomes
At intervention				
Classification of intervention	No	No	No	No
Risk of bias judgment	Low for all outcomes	Low for all outcomes	Low for all outcomes	Low for all outcomes
Post-intervention				
Deviation from intended intervention	No	No	No	No
Missing data	Yes[g]	No	No	No
Outcome measurement errors	No	No	No	No
Selective reporting	No	No	No	No
Risk of bias judgment	Serious for LDL cholesterol Low for all other outcomes	Low for all outcomes	Low for all outcomes	Low for all outcomes

Abbreviation: ROBINS-I, Risk of Bias in Non-randomized Studies—of Interventions.
[a]Possible risk-of-bias levels: low, moderate, serious, critical, and no information.
[b]Outcomes assessed were increased statin dose, adding ezetimibe to the therapy, starting statin treatment, starting ezetimibe treatment, total cholesterol, and LDL cholesterol.
[c]Outcome assessed was remain untreated with cholesterol-lowering drugs.
[d]Outcomes include using cholesterol-lowering drugs, reaching LDL cholesterol target after using cholesterol-lowering drugs, and LDL cholesterol.
[e]The outcome assessed was changing treatment regimen.
[f]281 people did not respond to the questionnaires and could not be reached by telephone. These people were notably younger, had a lower prevalence of cardiovascular disease, were more often smokers, and used less cholesterol-lowering medication at baseline than the 781 participants.
[g]Follow-up data on LDL cholesterol was available on only 77% of relatives.

Table A2: GRADE Evidence Profile for the Comparison of Genetic Testing Versus Clinical Evaluation of FH Without Genetic Testing

No. studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade consideration	Certainty
Increased statin dose							
1 (before-after)	No limitations	Cannot be evaluated	Serious limitations (−1)[a]	No limitations	None detected	None	⊕⊕⊕ Moderate
Adding ezetimibe to existing cholesterol-lowering therapy							
1 (before-after)	No limitations	Cannot be evaluated	Serious limitations (−1)[a]	No limitations	None detected	None	⊕⊕⊕ Moderate
Initiating statin treatment							
1 (before-after)	No limitations	Cannot be evaluated	Serious limitations (−1)[a]	No limitations	None detected	None	⊕⊕⊕ Moderate
Initiating ezetimibe treatment							
1 (before-after)	No limitations	Cannot be evaluated	Serious limitations (−1)[a]	Serious limitations (-2)[b]	None detected	None	⊕ Very low
Changing treatment regimen							
1 (before-after)	No limitations	Cannot be evaluated	Serious limitations (−2)[a,c]	No limitations	None detected	None	⊕⊕ Low
Using cholesterol-lowering drug treatment							
1 (before-after)	Serious limitations (−1)[d]	Cannot be evaluated	Serious limitations (−1)[a]	No limitations	None detected	None	⊕⊕ Low
Reaching LDL cholesterol target after using cholesterol-lowering drugs							
1 (before-after)	Serious limitations (−1)[d]	Cannot be evaluated	Serious limitations (−1)[a]	No limitations	None detected	None	⊕⊕ Low
Untreated with cholesterol-lowering drugs							
1 (before-after)	No limitations	Cannot be evaluated	Serious limitations (−1)[a]	No limitations	None detected	None	⊕⊕⊕ Moderate
Total cholesterol							
1 (before-after)	No limitations	Cannot be evaluated	Serious limitations (−1)[a]	No limitations	None detected	None	⊕⊕⊕ Moderate
LDL cholesterol							
2 (before-after)	Serious limitations (−1)[d]	No limitations	No limitations	No limitations	None detected	None	⊕⊕⊕ Moderate

Abbreviations: FH, familial hypercholesterolemia; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; LDL, low-density lipoprotein.

[a]Uncertain if patients will respond in a similar way across populations given that we have evidence from only one study.

[b]Confidence intervals were too imprecise.

[c]Uncertain if treatment resulted in meaningful reduction in LDL cholesterol.
[d]Subjects who did not respond to the questionnaires used less cholesterol-lowering medication at baseline.

Appendix 3: Selected Excluded Studies—Clinical Evidence

For transparency, we provide a list of studies that readers might have expected to see but that did not meet the inclusion criteria, along with the primary reason for exclusion.

Citation	Primary reason for exclusion
Kawashiri MA, Tada H, Yamagishi M. Significance of genetic diagnosis of familial hypercholesterolemia. J Atheroscler Thromb. 2016;23(5):554-6.	Wrong study design
Seed M, Roughton M, Pedersen K, Nair D, Wang T, Neil A, et al. Current statin treatment, DNA testing and cascade testing of UK patients with familial hypercholesterolaemia. Primary Care Cardiovas J. 2012;5(4):181-5.	Editorial
Ibarretxe D, Rodriguez-Borjabad C, Feliu A, Bilbao JA, Masana L, Plana N. Detecting familial hypercholesterolemia earlier in life by actively searching for affected children: the DECOPIN project. Atherosclerosis. 2018;278:210-6.	Wrong study design
Li JJ, Li S, Zhu CG, Wu NQ, Zhang Y, Guo YL, et al. Familial hypercholesterolemia phenotype in Chinese patients undergoing coronary angiography. Arterioscler Thromb Vasc Biol. 2017;37(3):570-9.	Wrong research question
Latkovskis G, Saripo V, Gilis D, Nesterovics G, Upena-Roze A, Erglis A. Latvian registry of familial hypercholesterolemia: the first report of three-year results. Atherosclerosis. 2018;277():347-54.	Wrong intervention
Chan ML, Cheung CL, Lee AC, Yeung CY, Siu CW, Leung JY, et al. Genetic variations in familial hypercholesterolemia and cascade screening in East Asians. Mol Genet Genomic Med 2019;7(2):e00520	Wrong intervention
Pang J, Abraham A, Vargas-Garcia C, Bates TR, Chan DC, Hooper AJ. An age-matched computed tomography angiographic study of coronary atherosclerotic plaques in patients with familial hypercholesterolaemia. Atherosclerosis. 2020;298:52-7.	Wrong research question
Galema-Boers JM, Versmissen J, Roeters van Lennep HW, Dusault-Wijkstra JE, Williams M, Roeters van Lennep JE. Cascade screening of familial hypercholesterolemia must go on. Atherosclerosis. 2015;242(2):415-7.	Wrong intervention
Lee S, Akioyamen LE, Aljenedil S, Riviere JB, Ruel I, Genest J. Genetic testing for familial hypercholesterolemia: impact on diagnosis, treatment and cardiovascular risk. Eur J Prev Cardiolog. 2019;26(12):1262-70.	Wrong research question
Wald DS, Wald NJ. Integration of child-parent screening and cascade testing for familial hypercholesterolaemia. J Med Screen. 2019;26(2):71-5.	Wrong study design
Raal FJ, Bahassi EM, Stevens B, Turner T A, Stein EA. Cascade screening for familial hypercholesterolemia in South Africa: the Wits FIND-FH program. Arterioscler Thromb Vasc Biol. 2020;40(11):2747-55.	Wrong study design
Stempel H, Dodge A, Marriott E, Peterson AL. Referral patterns and cascade screening for familial hypercholesterolemia in a pediatric lipid clinic. J Pediatr. 2016;178():285-7.	Wrong patient population
Kjaergaard KA, Christiansen MK, Schmidt M, Olsen MS, Jensen HK. Long-term cardiovascular risk in heterozygous familial hypercholesterolemia relatives identified by cascade screening. J Am Heart Assoc. 2017;6(6):26.	Wrong study design
Benson G, Witt DR, VanWormer JJ, Campbell SM, Sillah A, Hayes SN, et al. Medication adherence, cascade screening, and lifestyle patterns among women with hypercholesterolemia: results from the Women Heart survey. J Clin Lipidol. 2016;10(4):937-43.	Wrong patient population
Tada H, Okada H, Nomura A, Nohara A, Yamagishi M, Takamura M, et al. Prognostic impact of cascade screening for familial hypercholesterolemia on cardiovascular events. J Clin Lipidol. 2021;15(2):358-65.	Wrong patient population

Appendix 4: The Ontario Ministry of Health Funding Criteria for *PCSK9* Inhibitors

Limited Use Note(s)
ALIROCUMAB75mg/mL Inj Sol-Pref Pen

Reason for use code	Clinical criteria
555	For the treatment of Heterozygous Familial Hypercholesterolemia (HeFH) in patients 18 years of age or older who meet the following criteria: - Definite or probable diagnosis of HeFH using the Simon Broome or Dutch Lipid Network criteria or genetic testing; • AND – Unable to reach Low Density Lipoprotein Cholesterol (LDL-C) target (i.e., LDL-C less than 2.0 mmol/L for secondary prevention) or at least 50% reduction in LDL-C from untreated baseline for primary prevention despite: A) Confirmed adherence to ezetimibe for at least a total of 3 months in combination with high dose statin (e.g., atorvastatin 80 mg or rosuvastatin 40 mg); OR B) Confirmed adherence to ezetimibe for at least a total of 3 months and inability to tolerate high dose statin defined as: (i) Inability to tolerate at least 2 statins with a least one started at the lowest starting dose; (ii) For each statin (two statins in total), dose reduction is attempted for intolerable symptom (myopathy) or biomarker abnormality (creatine kinase (CK) greater than 5 times the upper limit of normal) resolution rather than discontinuation of statin altogether; (iii) For each statin (two statins in total), intolerable symptoms (myopathy) or abnormal biomarker (creatine kinase (CK) greater than 5 times the upper limit of normal) changes are reversible upon statin discontinuation but reproducible by re-challenge of statins where clinically appropriate; and (iv) One of the following: (I.) Other known determinants of intolerable symptoms or abnormal biomarkers have been ruled out; (II.) Patient developed confirmed and documented rhabdomyolysis; (III.) Patient is statin contraindicated i.e. active liver disease, unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal. • Treatment with Praluent should be discontinued if the patient does not meet all of the following: 1. Patient is adherent to therapy. 2. Patient has achieved a reduction in LDL-C of at least 40% from baseline (4-8 weeks after initiation of Praluent). 3. Patient continues to have a significant reduction in LDL-C (with continuation of Praluent) of at least 40% from baseline since initiation of PCSK9 inhibitor. LDL-C should be checked periodically with continued treatment with PCSK9 inhibitors (e.g., every 6 months). Patients prescribed Praluent 75 mg every two weeks are limited to 26 prefilled syringes (PFS) or pre-filled pens (PFP) per year. Patients prescribed Praluent 150 mg every two weeks or 300 mg every four weeks must use the 150 mg/mL dosage strength and are limited to 26 PFS or PFP per year.
	LU Authorization Period: 1 year

Limited Use Note(s)
EVOLOCUMAB 120 mg/mL Inj Sol-Pref Cart of 3.5 mL Pk

Reason for use code	Clinical criteria
527	For the treatment of Heterozygous Familial Hypercholesterolemia (HeFH) in patients 18 years of age or older who meet the following criteria: - Definite or probable diagnosis of HeFH using the Simon Broome or Dutch Lipid Network criteria or genetic testing; AND Unable to reach Low Density Lipoprotein Cholesterol (LDL-C) target (i.e., LDL-C less than 2.0 mmol/L for secondary prevention) or at least a 50% reduction in LDL-C from untreated baseline

despite: A. Confirmed adherence to high dose statin (e.g., atorvastatin 80 mg or rosuvastatin 40 mg) in combination with ezetimibe for at least a total of 3 months;

OR

B. Confirmed adherence to ezetimibe for at least a total of 3 months and inability to tolerate high dose statin defined as: (i). Inability to tolerate at least 2 statins with at least one started at the lowest starting dose; AND (ii). For each statin (two statins in total), dose reduction is attempted for intolerable symptom (myopathy) or biomarker abnormality (creatine kinase (CK) greater than 5 times the upper limit of normal) resolution rather than discontinuation of statin altogether; AND (iii). For each statin (two statins in total), intolerable symptoms (myopathy) or abnormal biomarker (creatine kinase (CK) greater than 5 times the upper limit of normal) changes are reversible upon statin discontinuation but reproducible by re-challenge of statins where clinically appropriate; AND (iv). One of the following: I) Other known determinants of intolerable symptoms or abnormal biomarkers have been ruled out; OR II) Patient developed confirmed and documented rhabdomyolysis; OR III) Patient is statin contraindicated i.e. active liver disease, unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal

- Treatment with Repatha should be discontinued if the patient does not meet all of the following: 1. Patient is adherent to therapy. 2. Patient has achieved a reduction in LDL-C of at least 40% from baseline (4-8 weeks after initiation of Repatha). 3. Patient continues to have a significant reduction in LDL-C (with continuation of Repatha) of at least 40% from baseline since initiation of PCSK9 inhibitor. LDL-C should be checked periodically with continued treatment with PCSK9 inhibitors (e.g., every 6 months).

Patients prescribed Repatha 140 mg every two weeks are limited to 26 prefilled syringes (PFS) per year. Patients prescribed Repatha 420 mg every month must use the automated mini doser (AMD) and are limited to 12 AMD per year.

LU Authorization Period: 1 year

Appendix 5: Results of Applicability and Limitation Checklists for Studies Included in the Economic Literature Review

Table A3: Assessment of the Applicability of Studies Evaluating the Cost-Effectiveness of Genetic Testing for Familial Hypercholesterolemia

Author, year, country	Is the study population similar to the question?	Are the interventions similar to the question?	Is the health care system studied sufficiently similar to Ontario?	Were the perspectives clearly stated? If yes, what were they?	Are all direct effects included? Are all other effects included where they are material?	Are all future costs and outcomes discounted? If yes, at what rate?	Is the value of health effects expressed in terms of quality-adjusted life-years?	Are costs and outcomes from other sectors fully and appropriately measured and valued?	Overall Judgment[a]
Ademi et al, 2020[53] Australia	Yes (cascade screening question)	Partially (both genetic testing and cholesterol method, followed by statins)	Yes	Yes, publicly funded health care system	Yes	Yes, 5%	Yes	Yes	Partially applicable
Ademi et al, 2014[54] Australia	Yes (cascade screening question)	Partially (genetic screening + cholesterol measurement + statins)	Yes	Yes, publicly funded health care system	Yes	Yes, 3%	Yes	Yes	Partially applicable
Chen et al, 2014[55] United States	No (cascade screening question)	Yes	Partially	Yes, societal	Yes	Yes, 3%	Yes	Yes	Not applicable
Crosland et al, 2018[56] United Kingdom	Yes (cascade screening question)	Partially (case identification)	Yes	Yes, National Health Service	Yes	Yes, 3.5%	Yes	Yes	Partially applicable
Kerr et al, 2017[58] United Kingdom	Yes (both questions)	Partially (Simon Broome criteria, monogenic testing)	Yes	Yes, National Health Service	Yes	Yes, 3.5%	Yes	Yes	Partially applicable
Lazaro et al, 2017[59]	No	Partially (genetic testing	Yes	Yes, national health system	Yes	Yes, 3%	Yes	Yes	Not applicable

Author, year, country	Is the study population similar to the question?	Are the interventions similar to the question?	Is the health care system studied sufficiently similar to Ontario?	Were the perspectives clearly stated? If yes, what were they?	Are all direct effects included? Are all other effects included where they are material?	Are all future costs and outcomes discounted? If yes, at what rate?	Is the value of health effects expressed in terms of quality-adjusted life-years?	Are costs and outcomes from other sectors fully and appropriately measured and valued?	Overall Judgment[a]
Spain		followed by cholesterol screening)		and societal perspectives					
Marang-van de Mheen et al, 2002[60] Netherlands	Yes (cascade screening question)	Partially (DNA-based screening followed by different treatment strategies)	Yes	No	Yes	No discount	No	Yes	Not applicable
Marks et al, 2000[61] United Kingdom	Yes (cascade screening question)	Partially (clinical and genetic screening strategies)	Yes	No	Yes	Yes, 1% for costs and 6% for outcomes	No	Yes	Not applicable
McKay et al, 2018[62] United Kingdom	Partially (only children)	Partially (genetic testing followed by cholesterol screening)	Yes	Yes, National Health Service	Yes	Yes, 3.5%	Yes	Yes	Not applicable
Nherera et al, 2011[63] United Kingdom	Partially (cascade screening question, relatives aged 30 years)	Partially (Simon Broome criteria)	Yes	Yes, National Health Service	Yes	Yes, 3.5%	Yes	Yes	Partially applicable
Oliva et al, 2009[67] Spain	Yes (cascade screening)	Yes	Yes	Yes, national health system	Yes	Yes, 4%	No	Yes	Partial applicable
Pelczarska et al, 2018[64] Poland	Partially (three different populations)	No (genetic testing followed by cholesterol screening)	Yes	Yes, public payer	Yes	Yes, 5% for costs and 3.5% for outcomes	Yes	Yes	Not applicable

Author, year, country	Is the study population similar to the question?	Are the interventions similar to the question?	Is the health care system studied sufficiently similar to Ontario?	Were the perspectives clearly stated? If yes, what were they?	Are all direct effects included? Are all other effects included where they are material?	Are all future costs and outcomes discounted? If yes, at what rate?	Is the value of health effects expressed in terms of quality-adjusted life-years?	Are costs and outcomes from other sectors fully and appropriately measured and valued?	Overall Judgment[a]
Sharma et al, 2012[65] United Kingdom	Yes (cascade screening question)	No (Elucigene FH20 and LIPO chip, two specific gene panels)	Yes	Yes, National Health Service	Yes	Yes, 3.5%	Yes	Yes	Not applicable
Wonderling et al, 2004[66] Netherlands	Yes (cascade screening)	Yes	Yes	No	Yes	Yes, 4%	No	Yes	Not applicable

Note: Response options for all items were "yes," "partially," "no," "unclear," and "Not applicable."
[a]Overall judgment may be "directly applicable," "partially applicable," or "not applicable."

Table A4: Assessment of the Limitations of Studies Evaluating the Cost-Effectiveness of Genetic Testing for Familial Hypercholesterolemia

Author, year, country	Does the model structure adequately reflect the nature of the health condition under evaluation ?	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Are all important and relevant health outcomes included?	Are the clinical inputs[a] obtained from the best available sources?	Do the clinical inputs[a] match the estimates contained in the clinical sources?	Are all important and relevant (direct) costs included in the analysis?	Are the estimates of resource use obtained from the best available sources?	Are the unit costs of resources obtained from the best available sources?	Is an appropriate incremental analysis presented, or can it be calculated from the reported data?	Are all important and uncertain parameters subjected to appropriate sensitivity analysis?	Is there a potential conflict of interest?	Overall Judgment[b]
Ademi et al, 2020,[53] Australia	Yes	Yes, lifetime horizon	Partially (only coronary heart disease)	No (a single cohort, Australia life tables)	Yes	Yes	Yes	Yes	Yes	Yes	No	Potentially serious limitations
Ademi et al, 2014, [54] Australia	Yes	Partially (10 y)	Partially (only coronary heart disease)	No (95 relatives from 81 index cases)	Yes	Yes	Yes (from a model of care in Australia)	Yes	Yes	Yes	No	Potentially serious limitations
Chen et al, 2014[55] United States	Yes	Yes, lifetime horizon	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Minor limitations
Crosland et al, 2018,[56] United Kingdom	Yes	Yes, lifetime horizon	Partially (unclear model structure)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Minor limitations
Kerr et al, 2017,[58] United Kingdom	Yes	Yes, lifetime horizon	Yes	Partially (data were collected from FH cascade services)	Yes	Yes	Yes	Yes	Yes	Yes	No	Minor limitations
Lazaro et al, 2017[59] Spain	Unclear	Partially (10 y)	Partially (only coronary heart disease)	Partially (literature and UK study)	Yes	Yes	Yes	Yes	Yes	Yes	No	Potentially serious limitations
Marang-van de Mheen et al, 2002[60] Netherlands	Yes	Yes, lifetime horizon	Partially (only coronary heart disease)	Partially, (from a closed cohort screened	Yes	Yes	Yes	Yes	No	Yes	unclear	Potentially serious limitations

Author, year, country	Does the model structure adequately reflect the nature of the health condition under evaluation ?	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Are all important and relevant health outcomes included?	Are the clinical inputs[a] obtained from the best available sources?	Do the clinical inputs[a] match the estimates contained in the clinical sources?	Are all important and relevant (direct) costs included in the analysis?	Are the estimates of resource use obtained from the best available sources?	Are the unit costs of resources obtained from the best available sources?	Is an appropriate incremental analysis presented, or can it be calculated from the reported data?	Are all important and uncertain parameters subjected to appropriate sensitivity analysis?	Is there a potential conflict of interest?	Overall Judgment[b]
				from 1994 to 1997)								
Marks et al, 2000[61] United Kingdom	Partially (yes for the screening, no for the long-term outcomes)	Yes. lifetime horizon	Partially (life table analysis)	Partially, (from a cohort of 1,185 participants followed prospectively since 1980)	Yes	Yes	Yes	Yes	No	Yes	No	Very serious limitations
McKay et al, 2018[62] United Kingdom	Yes	Yes, lifetime horizon	Yes	Partially (literature and expert opinion)	Yes	Yes	Yes	Yes	Yes	Yes	No	Minor limitations
Nherera et al, 2011[63] United Kingdom	Yes	Yes, lifetime horizon	Yes	Yes, systematic review	Yes	Yes	Yes	Yes	Yes	Yes	No	Minor limitations
Oliva et al, 2009[67] Spain	Yes	Yes, lifetime horizon	Yes	Partially, Simon Broome cohort	Yes	Yes	Yes	Yes	Yes	Yes	No	Potentially serious limitations
Pelczarska et al, 2018[64] Poland	Yes	Yes, lifetime horizon	Partially (only coronary heart disease)	Partially	Yes	Yes	Yes	Yes	Partially	Yes	Partially	Potentially serious limitations
Sharma et al, 2012[65] United Kingdom	Yes	Yes, lifetime horizon	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Minor limitations
Wonderling et al, 2004[66] Netherlands	Yes	Yes, lifetime horizon	Yes	Partially, national cohort in the Netherlands	Yes	Yes	Yes	Yes	Yes	Yes	No	Potentially serious limitations

Note: Response options for all items were "yes," "partially," "no," "unclear," and "not applicable."
[a]Clinical inputs include relative treatment effects, natural history, and utilities.
[b]Overall judgment may be "minor limitations," "potentially serious limitations," or "very serious limitations."

Appendix 6: Primary Economic Evaluation

Table A5: Parameters for a 43-Year-Old Female

Model parameter	Incidence rate	Probability	Reference
Probability of CVD event			
Stroke	0.0007	0.07%	PHAC, 2019[76]
Ischemic heart disease	0.00138	0.14%	PHAC, 2019[76]
Peripheral artery disease	—	0.10%	Murabito et al, 1997[77]
Total probability from pre-CVD to CVD		0.32%[a]	
Probability of death			
From pre-CVD to death	—	0.10%	Canada lifetable by sex and age
From CVD to death	—	11.10%	Smolderen et al, 2010[79]
From stroke to death	—	10.32%	Bronnum-Hansen et al, 2001[82]
From ischemic heart disease to death	—	0.74%	Crimmins et al, 2008[83]
From peripheral artery disease to death	—	0.34%	Vaartjes et al, 2009[84]
Total probability from post-CVD to death	—	2.87%[b]	
Other			
From post-CVD to CVD		1.59%[c]	Briffa et al, 2010[81]
From CVD to post-CVD		88.90%[d]	Smolderen et al, 2010[79]

Abbreviations: CVD, cardiovascular diseases; PHAC, Public Health Agency of Canada.
[a]The sum of probabilities for stroke, ischemic heart disease, and peripheral artery disease.
[b]Weighted average based on probabilities of death from ischemic heart disease, stroke, and peripheral artery disease, weighted by the probabilities of the events.
[c]Based on the probability from pre-CVD to CVD and relative risk of individuals having CVD history.
[d]1-Probability from CVD to death.

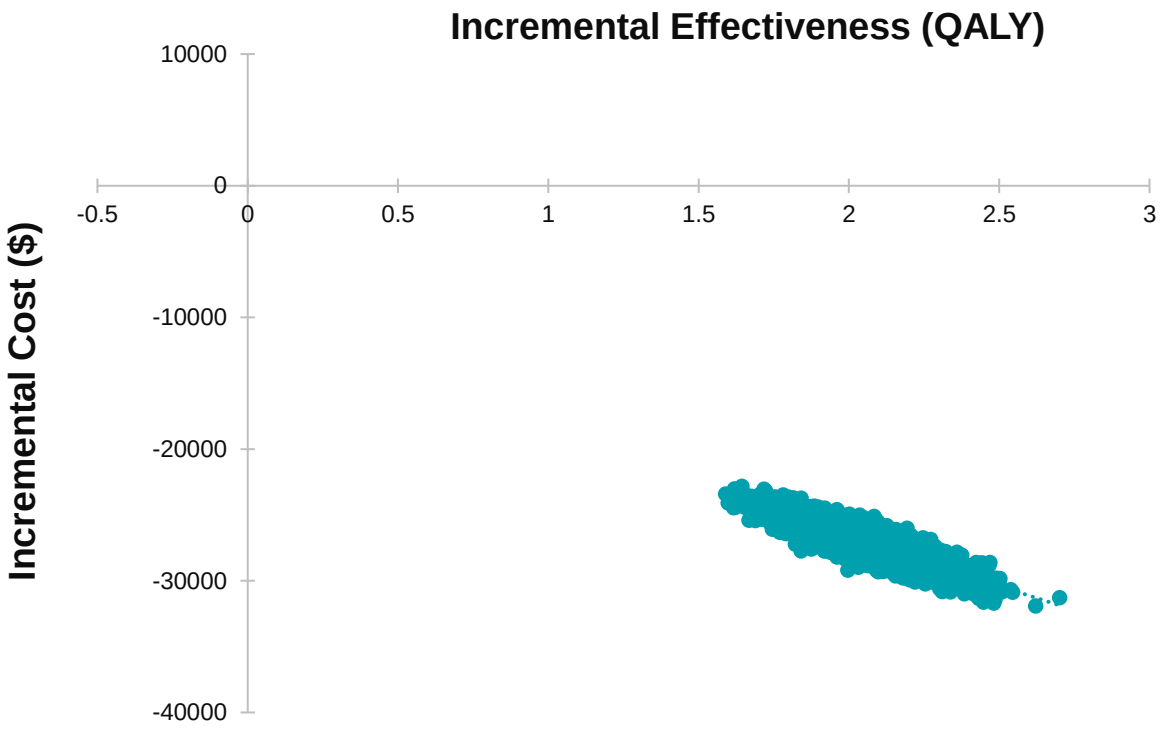

Figure A1: Scatter Plot of 5,000 Simulated Pairs of Incremental Costs and Effects in the Cost-Effectiveness Plane: Genetic Testing Versus No Genetic Testing, Reference Case

Abbreviation: QALY, quality-adjusted life year.

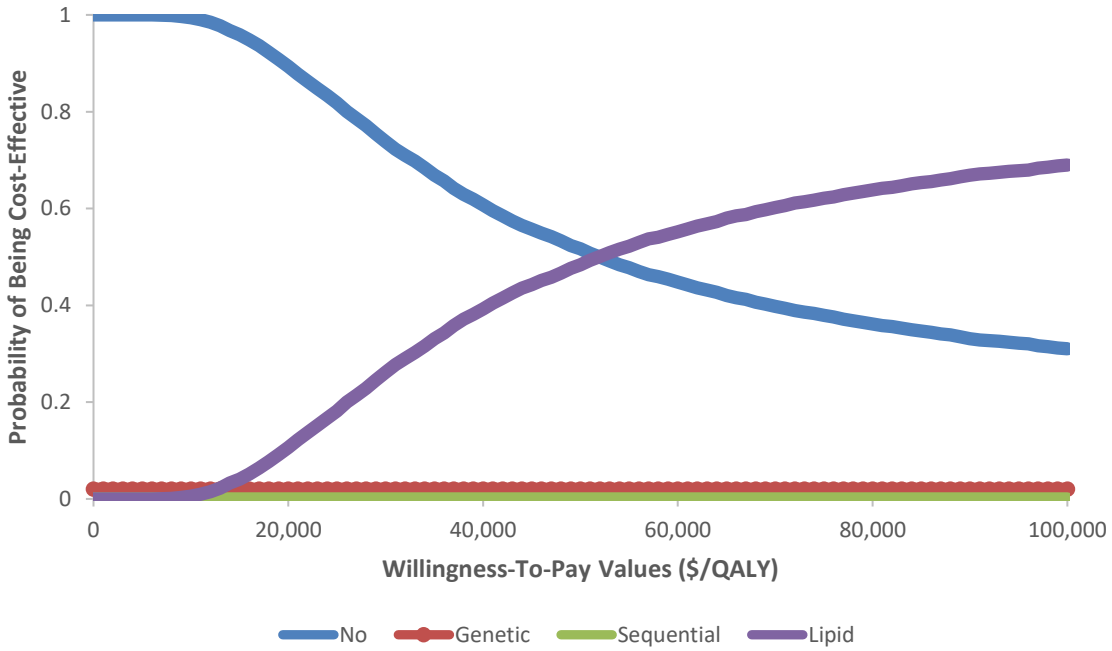

Figure A2: Cost-Effectiveness Acceptability Curve for Second-Degree Relatives of Genetically Confirmed Cases

Abbreviation: QALY, quality-adjusted life year.

Note: the probability of being cost-effective was 0 for cascade screening with genetic testing and with sequential testing.

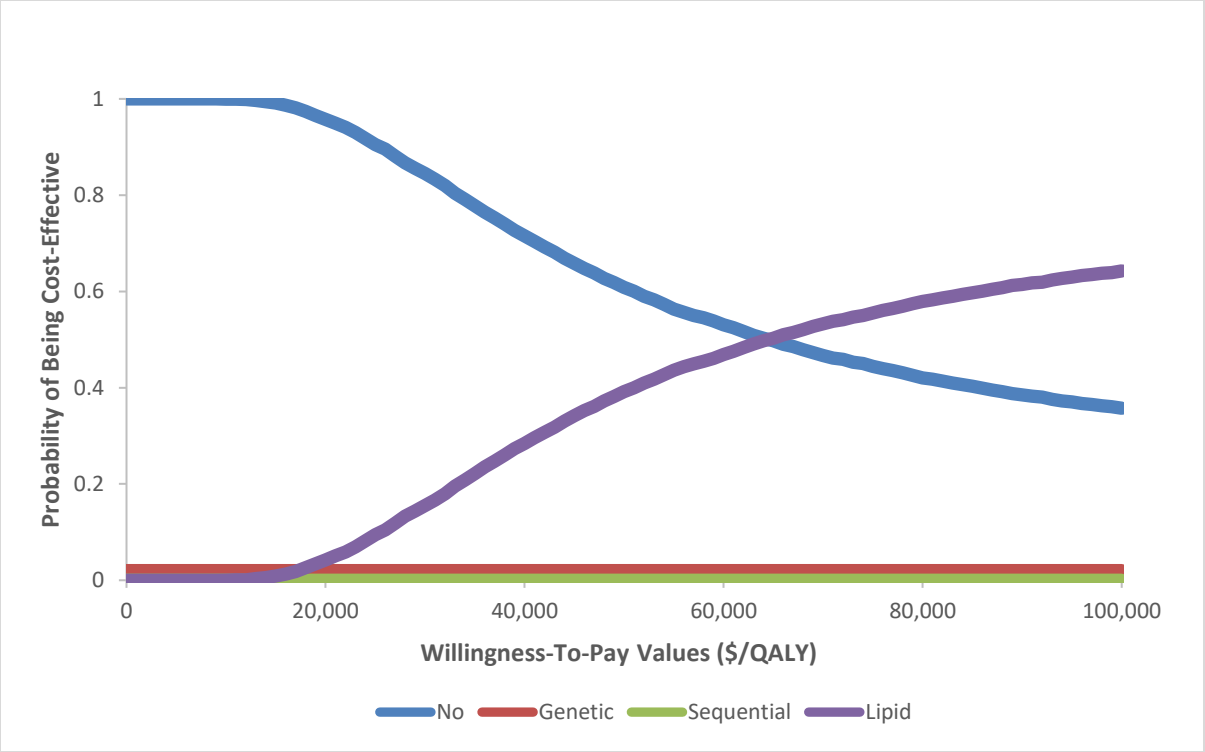

Figure A3: Cost-Effectiveness Acceptability Curve for Third-Degree Relatives of Genetically Confirmed Cases

Abbreviation: QALY, quality-adjusted life year.

Note: The probability of being cost-effective was 0 for cascade screening with genetic testing and with sequential testing.

Table A6: Scenario/Sensitivity Analyses Results for Genetic Testing of Index Cases

Scenario	Total costs, mean (95% CrI), $	No. FH diagnoses, mean (95% CrI)	No. CVD events, mean (95% CrI)	QALYs, mean (95% CrI)	ICER, $/QALY
Improved adherence					
No genetic testing	154,245 (148,976–159,302)	0.53 (0.49–0.56)	1.55 (1.43–1.66)	15.39 (14.95–15.81)	
Genetic testing	155,493 (150,584–60,654)	0.16 (0.15–0.17)	1.40 (1.29–1.50)	16.66 (16.27–17.05)	
Incremental	−12,600 (−15,008 to −10,371)	−0.37 (−0.40 to −0.33)	−0.15 (−0.16 to −0.13)	1.27 (1.04–1.51)	Dominant[a]
LLT dose increase					
No genetic testing	168,5807 (163,176–174,253)	0.89 (0.83–0.94)	1.58 (1.45–1.69)	14.63 (14.11–15.11)	
Genetic testing	143,503 (139,187–148,08)	0.17 (0.17–0.18)	1.40 (1.28–1.50)	16.68 (16.29–17.06)	
Incremental	−25,078 (−27,640 to −22,503)	−0.72 (−0.77 to −0.65)	−0.18 (−0.20 to −0.17)	2.05 (1.77–2.34)	Dominant[a]
Add-on therapy of ezetimbe					
No genetic testing	167,672 (162,379–173,364)	0.89 (0.83–0.94)	1.58 (1.46–1.70)	14.74 (14.23–15.25)	
Genetic testing	141,633 (137,107–146,080)	0.17 (0.17–0.18)	1.40 (1.29–1.50)	16.70 (16.28–17.08)	
Incremental	−26,040.00 (−28,891 to −23,092)	−0.72 (−0.77 to −0.65)	−0.18 (−0.20 to −0.17)	1.96 (1.61–2.27)	Dominant[a]
Add-on therapy of evolocumab					
No genetic testing	168,768 (163,615–173,620)	0.89 (0.83–0.94)	1.58 (1.46–1.70)	14.62 (14.12–15.08)	
Genetic testing	146,196 (141,257–151,831)	0.17 (0.17–0.18)	1.40 (1.29–1.50)	16.67 (16.29–17.07)	
Incremental	−25,572 (−25,893 to −18,417)	−0.72 (−0.77 to −0.65)	−0.18 (−0.20 to −0.17)	2.05 (1.77–2.33)	Dominant[a]
Probable FH tested					
No genetic testing	163,927 (156,961–170,670)	0.60 (0.52–0.68)	1.57 (1.45–1.68)	15.18 (14.55–15.82)	
Genetic testing	143,469 (138,816–148,301)	0.16 (0.14–0.18)	1.41 (1.31–1.52)	16.57 (16.16–16.96)	
Incremental	−20,458 (−24,222 to −16,595)	−−0.45 (−0.52 to −0.37)	−0.15 (−0.17 to −0.13)	1.40 (1.02–1.78)	Dominant[a]

Scenario	Total costs, mean (95% CrI), $	No. FH diagnoses, mean (95% CrI)	No. CVD events, mean (95% CrI)	QALYs, mean (95% CrI)	ICER, $/QALY
All individuals suspected of having FH tested					
No genetic testing	157,501 (149,098–165,005)	0.89 (0.82–0.94)	1.52 (1.41––1.64)	15.34 (14.75–15.94)	
Genetic testing	135,691 (130,685–141,117)	0.18 (0.17–0.18)	1.36 (1.26–1.46)	16.97 (16.55–17.35)	
Incremental	−21,811 (−25,653 to −17,645)	−0.71 (−0.76 to −0.65)	−0.17 (−0.18 to −0.15)	1.63 (1.25–2.00)	Dominant[a]

Abbreviations: CrI, credible interval; FH, familial hypercholesterolemia; ICER, incremental cost-effectiveness ratio; LLT, lipid-lowering therapy; QALY, quality-adjusted life-year.
[a]Dominant indicates genetic testing is less costly and more effective than no genetic testing.

Table A7: Sensitivity Analyses Results for Genetic Testing of Index Cases by Age (5–60 Years)

Scenario[a]	Total costs, mean (95% CrI), $	No. FH diagnoses, mean (95% CrI)	No. CVD events, mean (95% CrI)	QALYs, mean (95% CrI)	ICER, $/QALY
Age: 8 years					
No genetic testing	187,558 (181,785–193,934)	0.89 (0.83–0.94)	1.47 (1.37–1.58)	25.48 (24.75–26.14)	
Genetic testing	153,947 (149,162–158,218)	0.17 (0.17–0.18)	1.34 (1.24–1.44)	28.13 (27.59–28.61)	
Incremental	−33,611 (−37,405 to −29,614)	−0.72 (−0.77 to −0.66)	−0.24 (−0.26 to −0.22)	2.65 (2.17–3.14)	Dominant[b]
Age: 18 years					
No genetic testing	181,761 (175,898–187,551)	0.89 (0.83–0.94)	1.50 (1.39–1.61)	23.08 (22.42–23.66)	
Genetic testing	150,491 (146,119–154,763)	0.17 (0.17–0.18)	1.36 (1.25–1.46)	25.49 (25.01–25.95)	
Incremental	−31,270 (−34,778 to −27,811)	−0.72 (−0.77 to −0.65)	−0.15 (−0.16 to −0.14)	2.41 (1.98–2.84)	Dominant[b]
Age: 28 years					
No genetic testing	177,007 (171,771–182,2112)	0.89 (0.83–0.94)	1.53 (1.42–1.64)	20.02 (19.43–20.62)	
Genetic testing	147,684 (143,469–151,921)	0.17 (0.17–0.18)	1.37 (1.27–1.47)	22.27 (21.83–22.71)	
Incremental	−29,323 (−32,489 to −25,810)	−0.72 (−0.77 to −0.65)	−0.21 (−0.23 to −0.19)	2.25 (1.82–2.64)	Dominant[b]
Age: 38 years					
No genetic testing	168,881 (163,6356–174,345)	0.89 (0.83–0.94)	1.57 (1.45–1.69)	15.66 (15.15–16.17)	
Genetic testing	144,028 (139,680–148,822)	0.17 (0.17–0.18)	1.39 (1.28–1.50)	18.62 (18.20–19.02)	
Incremental	−24,853 (−27,701 to −22,054)	−0.72 (−0.77 to −0.65)	−0.18 (−0.20 to −0.17)	2.96 (2.63–3.30)	Dominant[b]
Age: 48 years					
No genetic testing	165,229 (159,931–171,109)	0.89 (0.82–0.94)	1.60 (1.48–1.72)	12.74 (12.23–13.20)	
Genetic testing	139,834 (135,243–144,385)	0.17 (0.17–0.18)	1.41 (1.31–1.52)	14.63 (14.22–15.01)	
Incremental	−25,395 (−28,155 to −22,903)	−0.72 (−0.77 to −0.65)	−0.19 (−0.20 to −0.17)	1.89 (1.59–2.20)	Dominant[b]

Scenario[a]	Total costs, mean (95% CrI), $	No. FH diagnoses, mean (95% CrI)	No. CVD events, mean (95% CrI)	QALYs, mean (95% CrI)	ICER, $/QALY
Age: 58 years					
No genetic testing	150,837 (145,494–156,046)	0.89 (0.83–0.94)	1.60 (1.48–1.72)	9.82 (9.52–10.31)	
Genetic testing	128,372 (123,981–132,8645)	0.17 (0.17–0.18)	1.39 (1.28–1.50)	11.38 (11.05–11.68)	
Incremental	−22,465 (−24,768 to −20,318)	−0.72 (−0.77 to −0.66)	−0.21 (−0.23 to −0.19)	1.46 (1.23–1.69)	Dominant[b]

Abbreviations: CrI, credible interval; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.
[a]Ages listed represent the median of the relevant group; e.g., 8 includes children aged 5–12, 18 includes people aged 13–22.
[b]Dominant indicates genetic testing is less costly and more effective than no genetic testing.

Table A8: Sensitivity Analyses Results for Genetic Testing of Index Cases by Genetic Testing Cost ($200–$1,600)

Scenario	Total costs, mean (95% CrI), $	QALYs, mean (95% CrI)[a]	ICER, $/QALY
$200			
No genetic testing	167,523 (162,091–172,844)	14.74 (14.24–15.24)	
Genetic testing	141,114 (136,817–145,274)	16.70 (16.31–17.10)	
Incremental	−26,409 (−28,944 to −23,770)	1.95 (1.63–2.27)	Dominant[b]
$400			
No genetic testing	167,559 (162,658–173,000)	14.75 (14.27–15.24)	
Genetic testing	141,372 (137,036–145,785)	16.70 (16.31–17.11)	
Incremental	−26,187 (−28,814 to −23,525)	1.95 (1.65–2.25)	Dominant[b]
$600			
No genetic testing	167,722 (162,838–173,108)	14.73 (14.23–15.25)	
Genetic testing	141,704 (137,565–146,282)	16.69 (16.28–17.10)	
Incremental	−26,018 (−28,675 to −23,440)	1.95 (1.62–2.26)	Dominant[b]
$800			
No genetic testing	167,594 (162,201–173,109)	14.77 (14.25–15.23)	
Genetic testing	141,834 (137,481–146,714)	16.71 (16.31–17.08)	
Incremental	−25,760 (−28,213 to −23,136)	1.94 (1.63–2.25)	Dominant[b]
$1,000			
No genetic testing	167,518 (162,688–173,012)	14.75 (14.24–15.22)	
Genetic testing	141,991 (137,856–146,547)	16.71 (16.31–17.08)	
Incremental	−25,527 (−28,365 to −22,591)	1.94 (1.63–2.25)	Dominant[b]
$1,200			
No genetic testing	167,617 (162,693–173,009)	14.76 (14.25–15.24)	
Genetic testing	142,209 (137,954–146,580)	16.70 (16.28–17.12)	
Incremental	−25,407 (−28,289 to −22,735)	1.95 (1.63–2.25)	Dominant[b]
$1,400			
No genetic testing	167,506 (162,115–172,226)	14.75 (14.24–15.22)	
Genetic testing	142,283 (137,734–146,268)	16.69 (16.28–17.09)	
Incremental	−25,223 (−27,964 to −22,632)	1.96 (1.64–2.27)	Dominant[b]
$1,600			
No genetic testing	167,595 (161,993–173,137)	14.76 (14.25–15.24)	
Genetic testing	142,631 (138,162–147,162)	16.70 (16.28–17.12)	
Incremental	−24,964 (−27,748 to −22,253)	1.95 (1.63–2.25)	Dominant[b]

Abbreviations: CrI, credible interval; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.
[a]All scenarios had the same effectiveness outcomes as the reference case because the cost would not influence the treatment outcomes, see Table 15 for diagnosis and cardiovascular outcomes.
[b]Dominant indicates genetic testing is less costly and more effective than no genetic testing.

Table A9: Sensitivity Analyses Results for Genetic Testing of Index Cases by Lipid-Lowering Therapy Costs (±50%)

Scenario	Total costs, mean (95% CrI), $	QALYs, mean (95% CrI)[a]	ICER, $/QALY
50%			
No genetic testing	161,019 (155,765–166,320)	14.76 (14.25–15.24)	
Genetic testing	135,120 (130,811–139,840)	16.70 (16.28–17.12)	
Incremental	−25,899 (−29,065 to −22,616)	1.94 (1.63–2.25)	Dominant[b]
70%			
No genetic testing	163,688 (158,517–169,263)	14.76 (14.28–15.25)	
Genetic testing	137,638 (133,370–142,225)	16.71 (16.31–17.07)	
Incremental	−26,049 (−29,130 to −23,004)	1.94 (1.59–2.27)	Dominant[b]
90%			
No genetic testing	166,274 (161,411–171,639)	14.75 (14.21–15.24)	
Genetic testing	140,189 (135,836–144,721)	16.70 (16.28–17.10)	
Incremental	−26,086 (−28,890 to −23,381)	1.95 (1.63–2.25)	Dominant[b]
110%			
No genetic testing	168,079 (163,007–173,213)	15.49 (14.98–15.98)	
Genetic testing	141,380 (137,364–145,508)	17.52 (17.12–17.89)	
Incremental	−26,699 (−29,321 to −24,313)	2.03 (1.70–2.39)	Dominant[b]
130%			
No genetic testing	171,665 (166,436–176,516)	14.75 (14.22–15.24)	
Genetic testing	145,487 (141,463–149,651)	16.70 (16.30–17.09)	
Incremental	−26,178 (−28,480 to −23,772)	1.95 (1.64–2.25)	Dominant[b]
150%			
No genetic testing	174,232 (168,949–179,630)	14.75 (14.23–15.24)	
Genetic testing	147,971 (143,724–152,200)	16.71 (16.31–17.10)	
Incremental	−26,261 (−28,700 to −23,779)	1.95 (1.63–2.27)	Dominant[b]

Abbreviations: CrI, credible interval; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.
[a]All scenarios had the same effectiveness outcomes as the reference case because the cost would not influence the treatment outcomes, see Table 15 for diagnosis and cardiovascular outcomes.
[b]Dominant indicates genetic testing is less costly and more effective than no genetic testing.

Table A10: Sensitivity Analyses Results for Cascade Screening of First-Degree Relatives by Age (5–60)

Scenario[a]	Total costs, mean (95% CrI), $	No. FH diagnoses, mean (95% CrI)	No. CVD events, mean (95% CrI)	QALYs, mean (95% CrI)	ICER, $/QALY versus no screening
Age: 18 years					
No screening	97,007 (92,322–101,711)	0.00 (0.00–0.00)	1.36 (1.26–1.45)	28.23 (27.80–28.66)	—
Lipid screening	105,173 (101,213–109,091)	0.38 (0.34–0.43)	1.36 (1.26–1.45)	28.40 (28.02–28.75)	48,542
Sequential screening	106,062 (102,065–109,893)	0.28 (0.25–0.32)	1.36 (1.26–1.45)	28.40 (28.02–28.75)	53,829
Genetic screening	107,513 (103,709–111,200)	0.50 (0.50–0.50)	1.36 (1.26–1.45)	28.40 (28.02–28.75)	62,453
Age: 28 years					
No screening	100,476 (96,090–105,378)	0.00 (0.00–0.00)	1.37 (1.28–1.46)	24.68 (24.26–25.09)	—
Lipid screening	107,122 (103,588–111,231)	0.38 (0.33–0.43)	1.37 (1.27–1.46)	24.85 (24.46–25.22)	40,507
Sequential screening	108,003 (104,431–112,045)	0.28 (0.25–0.32)	1.37 (1.27–1.46)	24.85 (24.46–25.22)	45,870
Genetic screening	109,229 (105,674–113,210)	0.50 (0.50–0.50)	1.37 (1.27–1.46)	24.85 (24.46–25.22)	53,346
Age: 38 years					
No screening	104,062 (99,420–108,493)	0.00 (0.00–0.00)	1.38 (1.29–1.46)	20.69 (20.31–21.09)	—
Lipid screening	109,128 (105,464–112,801)	0.38 (0.34–0.43)	1.37 (1.28–1.46)	20.84 (20.49–21.17)	35,061
Sequential screening	110,016 (106,268–113,649)	0.28 (0.25–0.32)	1.37 (1.28–1.46)	20.84 (20.49–21.17)	41,204
Genetic screening	110,988 (107,338–114,536)	0.50 (0.50–0.50)	1.37 (1.28–1.46)	20.84 (20.49–21.17)	47,932
Age: 48 years					
No screening	107,475 (103,280–112,108)	0.00 (0.00–0.00)	1.38 (1.29–1.47)	16.35 (15.98–16.68)	—
Lipid screening	110,739 (106,880–114,688)	0.38 (0.34–0.43)	1.37 (1.28–1.46)	16.47 (16.14–16.78)	25,432
Sequential screening	111,628 (107,737–115,579)	0.28 (0.25–0.32)	1.37 (1.28–1.46)	16.47 (16.14–16.78)	32,357
Genetic screening	112,321 (108,488–116,228)	0.50 (0.50–0.50)	1.37 (1.28–1.46)	16.47 (16.14–16.78)	37,761

Scenario[a]	Total costs, mean (95% CrI), $	No. FH diagnoses, mean (95% CrI)	No. CVD events, mean (95% CrI)	QALYs, mean (95% CrI)	ICER, $/QALY versus no screening
Age: 58 years					
No screening	101,415 (97,536–105,302)	0.00 (0.00–0.00)	1.34 (1.24–1.43)	12.69 (12.40–12.96)	—
Lipid screening	103,830 (100,228–107,509)	0.38 (0.34–0.43)	1.34 (1.24–1.43)	12.78 (12.52–13.03)	25,450
Sequential screening	104,721 (101,109–108,471)	0.28 (0.25–0.32)	1.34 (1.24–1.43)	12.78 (12.52–13.03)	34,837
Genetic screening	105,264 (101,588–108,986)	0.50 (0.50–0.50)	1.34 (1.24–1.43)	12.78 (12.52–13.03)	40,551

Abbreviations: CrI, credible interval; CVD, cardiovascular disease; FH, familial hypercholesterolemia; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

[a]Ages listed represent the median of the relevant groupings; e.g., 8 includes children aged 5–12, 18 includes people aged 13–22.

Table A11: Sensitivity Analyses Results for Cascade Screening of First-Degree Relatives by Genetic Testing Cost

Scenario	Total costs, mean (95% CrI), $	QALYs, mean (95% CrI)[a]	ICER, $/QALY versus no screening
$200			
No screening	95,924 (91,316–100,918)	31.13 (30.63–31.60)	—
Lipid screening	110,255 (106,310–114,229)	31.33 (30.91–31.74)	44,203
Sequential screening	110,995 (106,965–115,062)	31.33 (30.91–31.74)	47,241
Genetic screening	112,611 (108,684–116,613)	31.33 (30.91–31.74)	55,057
$400			
No screening	96,041 (90,744–101,401)	31.13 (30.63–31.60)	—
Lipid screening	105,062 (100,900–108,911)	31.33 (30.91–31.74)	45,850
Sequential screening	105,857 (101,614–109,712)	31.33 (30.91–31.74)	49,890
Genetic screening	107,470 (103,317–111,300)	31.33 (30.91–31.74)	58,088
$600			
No screening	96,072 (90,735–101,174)	31.13 (30.63–31.60)	—
Lipid screening	105,029 (100,850–109,186)	31.33 (30.91–31.74)	44,206
Sequential screening	106,013 (101,814–110,158)	31.33 (30.91–31.74)	49,064
Genetic screening	107,640 (103,604–111,708)	31.33 (30.91–31.74)	57,093
$800			
No screening	96,111 (90,853–101,683)	31.13 (30.63–31.60)	—
Lipid screening	105,101 (101,177–109,171)	31.33 (30.91–31.74)	45,167
Sequential screening	106,264 (102,335–110,268)	31.33 (30.91–31.74)	51,014
Genetic screening	107,908 (104,161–111,846)	31.33 (30.91–31.74)	59,273
$1,000			
No screening	95,968 (90,983–101,351)	31.13 (30.63–31.60)	—
Lipid screening	105,022 (101,128–109,126)	31.33 (30.91–31.74)	46,045
Sequential screening	106,374 (102,498–110,503)	31.33 (30.91–31.74)	52,921
Genetic screening	108,025 (104,238–112,007)	31.33 (30.91–31.74)	61,315
$1,200			
No screening	95,945 (91,135–101,514)	31.13 (30.63–31.60)	—
Lipid screening	104,999 (100,748–109,140)	31.33 (30.91–31.74)	45,505
Sequential screening	106,537 (102,275–110,787)	31.33 (30.91–31.74)	53,233
Genetic screening	108,206 (104,133–112,255)	31.33 (30.91–31.74)	61,623

Scenario	Total costs, mean (95% CrI), $	QALYs, mean (95% CrI)[a]	ICER, $/QALY versus no screening
$1,400			
No screening	96,019 (91,103–101,114)	31.13 (30.63–31.60)	—
Lipid screening	105,039 (101,040–109,031)	31.33 (30.91–31.74)	45,209
Sequential screening	106,851 (102,906–110,916)	31.33 (30.91–31.74)	54,295
Genetic screening	108,542 (104,599–112,581)	31.33 (30.91–31.74)	62,768
$1,600			
No screening	95,997 (90,883–101,037)	31.13 (30.63–31.60)	—
Lipid screening	105,033 (101,011–109,199)	31.33 (30.91–31.74)	45,735
Sequential screening	106,939 (102,958–111,105)	31.33 (30.91–31.74)	55,382
Genetic screening	108,639 (104,782–112,622)	31.33 (30.91–31.74)	63,987

Abbreviations: CrI, credible interval; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.
[a]All scenarios had the same effectiveness outcomes as the reference case because the cost would not influence the treatment outcomes, see Table 15 for diagnosis and cardiovascular outcomes.

Appendix 7: Parameters and Results of Budget Impact Analysis

Table A12: Breakdown Costs Used in Budget Impact Analyses: Reference Case

Scenario	Year 1	Year 2	Year 3	Year 4	Year 5
Index Cases					
No Genetic Testing					
Testing costs	0	0	0	0	0
Treatment costs	1,433	1,374	1,318	1,264	1,213
Health state costs	5,552	3,434	3,695	3,895	4,076
Total	6,984	4,808	5,013	5,160	5,289
Genetic Testing					
Testing costs	1,215	0	0	0	0
Treatment costs	1,448	1,417	1,038	1,011	985
Health state costs	3,960	2,085	2,233	2,340	2,439
Total	6,623	3,502	3,271	3,351	3,424

Table A13: Sensitivity Analysis by Genetic Testing Cost for Index Cases

		Budget impact, $ million[a,b]					
Scenario		**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total[c]**
Reference case	Testing-related costs	6.74	9.28	12.26	15.70	19.59	63.57
	Total	−2.00	−10.00	−23.28	−41.18	−64.42	−140.89
$200	Testing-related costs	5.13	7.07	9.34	11.96	14.93	48.42
	Total	−3.61	−12.21	−26.20	−44.92	−69.09	−156.04
$400	Testing-related costs	6.24	8.60	11.36	14.54	18.15	58.88
	Total	−2.50	−10.69	−24.18	−42.33	−65.87	−145.57
$600	Testing-related costs	7.35	10.12	13.38	17.12	21.38	69.35
	Total	−1.39	−9.16	−22.16	−39.75	−62.64	−135.11
$800	Testing-related costs	8.46	11.65	15.39	19.71	24.60	79.81
	Total	−0.28	−7.63	−20.15	−37.17	−59.42	−124.65
$1,000	Testing-related costs	9.57	13.18	17.41	22.29	27.82	90.27
	Total	0.83	−6.11	−18.13	−34.58	−56.19	−114.19
$1,200	Testing-related costs	10.68	14.71	19.43	24.87	31.05	100.74
	Total	1.93	−4.58	−16.11	−32.00	−52.97	−103.72
$1,400	Testing-related costs	11.79	16.23	21.45	27.46	34.27	111.20
	Total	3.04	−3.05	−14.09	−29.42	−49.74	−93.26
$1,600	Testing-related costs	12.90	17.76	23.47	30.04	37.50	121.66
	Total	4.15	−1.52	−12.07	−26.83	−46.52	−82.80

[a]In 2021 CAD. All costs were calculated using the mean cost from the Primary Economic Evaluation's probabilistic results.
[b]Negative costs indicate savings.
[c]Results may appear inexact due to rounding.

Table A14: Sensitivity Analysis by Lipid Lowering Therapy Costs for Index Cases

Scenario		Budget impact, $ million[a,b]					
		Year 1	Year 2	Year 3	Year 4	Year 5	Total[c]
Reference case	Testing-related costs	4.01	6.45	9.74	14.03	19.46	53.69
	Total	4.23	6.98	10.96	16.27	23.15	61.58
Add-on therapy of ezetimbe	Testing-related costs	6.73	9.27	12.25	15.69	19.58	63.53
	Total	4.51	1.46	−5.16	−14.75	−27.82	−41.76
Add-on therapy of evolocumab	Testing-related costs	6.74	9.28	12.26	15.70	19.59	63.57
	Total	9.01	12.61	12.56	11.20	8.17	53.55

[a]In 2021 CAD. All costs were calculated using the mean cost from the primary economic evaluation's probabilistic results.
[b]Negative costs indicate savings.
[c]Results may appear inexact due to rounding.

Table A15: Sensitivity Analysis by Genetic Testing Cost for Relatives of Genetically Confirmed Index Cases

Scenario		Budget impact, $ million[a,b]					
		Year 1	Year 2	Year 3	Year 4	Year 5	Total[c]
Reference case	Testing costs only	4.01	6.45	9.74	14.03	19.46	53.69
	Total	4.23	6.98	10.96	16.27	23.15	61.58
$200	Testing costs only	3.49	5.61	8.48	12.21	16.94	46.73
	Total	3.71	6.14	9.70	14.45	20.62	54.62
$400	Testing costs only	3.85	6.19	9.35	13.47	18.68	51.54
	Total	4.06	6.72	10.57	15.71	22.37	59.43
$600	Testing costs only	4.21	6.77	10.22	14.72	20.42	56.35
	Total	4.42	7.29	11.44	16.96	24.11	64.23
$800	Testing costs only	4.57	7.35	11.09	15.98	22.16	61.15
	Total	4.78	7.87	12.31	18.22	25.85	69.04
$1,000	Testing costs only	4.93	7.92	11.97	17.23	23.90	65.96
	Total	5.14	8.45	13.19	19.48	27.59	73.84
$1,200	Testing costs only	5.29	8.50	12.84	18.49	25.64	70.76
	Total	5.50	9.03	14.06	20.73	29.33	78.65
$1,400	Testing costs only	5.65	9.08	13.71	19.74	27.39	75.57
	Total	5.86	9.60	14.93	21.99	31.07	83.46
$1,600	Testing costs only	6.01	9.66	14.58	21.00	29.13	80.37
	Total	6.22	10.18	15.80	23.24	32.82	88.26

[a]In 2021 CAD. All costs were calculated using the mean cost from the Primary Economic Evaluation's probabilistic results.
[b]Negative costs indicate savings.
[c]Results may appear inexact due to rounding.

Appendix 8: Letter of Information

Ontario Health

LETTER OF INFORMATION

Ontario Health is conducting a review of **molecular testing for Familial Hypercholesterolemia (FH)**. The purpose is to understand whether this testing should be more broadly funded in Ontario.

An important part of this review involves speaking to patients and family members of those who may have experience with high cholesterol and molecular testing, or who may have attempted to access it. Our goal is always to make sure the lived-experience of individuals and families are considered in the funding recommendations for this test.

WHAT DO YOU NEED FROM PARTICIPANTS?

- ✓ 20-30 minutes of time for a phone or in-person interview to hear about their experiences
- ✓ Permission to audio- (not video-) record the interview

WHAT PARTICIPATION INVOLVES

If a participant agrees to share their experiences, they will be asked to have an interview with Ontario Health staff. The interview will likely last 20-30 minutes. It will be held in a private location or over the telephone. With consent, the interview will be audio-recorded. The interviewer will ask questions about perspectives of cholesterol testing, treatments, decision-making and more general thoughts about molecular testing and cholesterol treatment options in Ontario.

Participation is voluntary. Those who volunteer may decide not to participate, refuse to answer any questions or withdraw before the interview. Withdrawal will in no way affect the care received.

CONFIDENTIALITY

All information collected for the review will be kept confidential and privacy will be protected except as required by law. The results of this review will be published, however no identifying information will be released or published. Any records containing information from the interview will be stored securely.

RISKS TO PARTICIPATION:

There are no known physical risks to participating. Some participants may experience discomfort or anxiety after speaking about their lived experience. If this is the case, participants can speak to our staff.

If you have any questions, please contact Ontario Health staff:

Appendix 9: Interview Guide

Interview for Familial Hypercholesterolemia HTA

What are the preferences and values of patients who may seek out genetic testing for Familial Hypercholesterolemia? What are their preferences and values in considering this test and its impact on the care of themselves or their loved ones?

Intro
Explain HQO purpose, HTA process, and purpose of interview

Lived- Experience
What led to testing?
Medical journey to receiving diagnosis
Access to diagnosis and specialists – any barriers?

Treatments and Decision-Making
What kind of info was provided about FH?
Where did this info come from (doc, friends, research, etc)
Decision-making surrounding different treatment options – what factors were important to you?
- Family planning?
- Change in treatment management? (new drug eligibility?)

Genetic Testing
Would information from genetic testing be valuable to you?
What (if anything) would make you hesitate about getting genetic testing?
Procedure? Cost?
Genetic testing and decision-making – would it influence it?
Family impact of testing for FH?

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