ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES

Genome-Wide Sequencing for Unexplained Developmental Disabilities or Multiple Congenital Anomalies: A Health Technology Assessment

KEY MESSAGES

What Is This Health Technology Assessment About?

People with unexplained developmental disabilities or multiple congenital anomalies might have had many biochemical, metabolic, and genetic tests over a period of years without diagnosis. Genome-wide sequencing, as whole exome or whole genome sequencing, can examine the entire genetic makeup of a person in a single test, capturing genetic information that other genetic tests (such as targeted gene tests) can miss. A genetic diagnosis can help these people and their families better understand their condition and help them connect with others who have the same condition.

This health technology assessment looked at how effective and cost-effective genome-wide sequencing is for people with unexplained developmental disabilities or multiple congenital anomalies. It also looked at the budget impact of publicly funding genome-wide sequencing and at the experiences, preferences, and values of people, families, and clinicians managing people with these conditions. We examined the family perspectives and experiences of people with unexplained developmental disabilities or multiple congenital anomalies who sought genome-wide sequencing for diagnostic purposes. We conducted a quantitative evaluation on preferences in literature, engaged directly with family members of people with these conditions through interviews, and used reviews by the Canadian Agency for Drugs and Technologies in Health (CADTH) of published qualitative literature and ethical considerations.

What Did This Health Technology Assessment Find?

Compared with standard genetic testing (chromosomal microarray and targeted single-gene tests or gene panels), genome-wide sequencing has a higher diagnostic yield and, for some who are tested, prompts changes to some medications or treatments, and referrals to specialists.

When whole exome sequencing is used as a second-tier genetic test (after the current first-tier test, chromosomal microarray, fails to provide a diagnosis), it is less costly and more effective than standard testing ($6,357 vs. $8,783 per patient; 413 vs. 185 molecular diagnoses per 1,000 persons tested). When whole exome sequencing is used for patients who have no diagnosis from standard testing, we estimated it would cost an additional $13,591 to identify the genetic cause of one additional patient compared with standard testing. We estimate that publicly funding whole exome sequencing for people who have no diagnosis after standard testing would cost about $9 million yearly. If whole exome sequencing is used as a second-tier test (after chromosomal microarray testing yields no diagnosis), there would be a savings of $3.4 million per 1,000 persons tested yearly.

Participants demonstrated consistent motivations for and expectations of obtaining a diagnosis for unexplained developmental disabilities or congenital anomalies through genome-wide sequencing. Patients and families greatly value the support and information they receive through genetic counselling when considering genome-wide sequencing and learning of a diagnosis.

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ABSTRACT

Background

People with unexplained developmental disabilities or multiple congenital anomalies might have had many biochemical, metabolic, and genetic tests for a period of years without receiving a diagnosis. A genetic diagnosis can help these people and their families better understand their condition and may help them to connect with others who have the same condition. Ontario Health (Quality), in collaboration with the Canadian Agency for Drugs and Technologies in Health (CADTH) conducted a health technology assessment about the use of genome-wide sequencing for patients with unexplained developmental disabilities or multiple congenital anomalies. Ontario Health (Quality) evaluated the effectiveness, cost-effectiveness, and budget impact of publicly funding genome-wide sequencing. We also conducted interviews with patients and examined the quantitative evidence of preferences and values literature to better understand the patient preferences and values for these tests.

Methods

Ontario Health (Quality) performed a systematic literature search of the clinical evidence. We assessed the risk of bias of each included study using the Risk of Bias Assessment tool for Non-randomized Studies (RoBANS) and the quality of the body of evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. We also performed a search of the quantitative evidence and undertook direct patient engagement to ascertain patient preferences for genetic testing for unexplained developmental disabilities or multiple congenital anomalies. CADTH performed a review of qualitative literature about patient perspectives and experiences, and a review of ethical issues.

Ontario Health (Quality) performed an economic literature review of genome-wide sequencing in people with unexplained developmental disabilities or multiple congenital anomalies. Although we found eight published cost-effectiveness studies, none completely addressed our research question. Therefore, we conducted a primary economic evaluation using a discrete event simulation model. Owing to its high cost and early stage of clinical implementation, whole exome sequencing is primarily used for people who do not have a diagnosis from standard testing (referred to here as whole exome sequencing after standard testing; standard testing includes chromosomal microarray and targeted single-gene tests or gene panels). Therefore, in our first analysis, we evaluated the cost-effectiveness of whole exome sequencing after standard testing versus standard testing alone. In our second analysis, we explored the cost-effectiveness of whole exome and whole genome sequencing used at various times in the diagnostic pathway (e.g., first tier, second tier, after standard testing) versus standard testing. We also estimated the budget impact of publicly funding genome-wide sequencing in Ontario for the next 5 years.

Results

Forty-four studies were included in the clinical evidence review. The overall diagnostic yield of genome-wide sequencing for people with unexplained development disability and multiple congenital anomalies was 37%, but we are very uncertain about this estimate (GRADE: Very Low). Compared with standard genetic testing of chromosomal microarray and targeted single-gene tests or gene panels, genome-wide sequencing could have a higher diagnostic yield (GRADE: Low). As well, for some who are tested, genome-wide sequencing prompts some changes to medications, treatments, and referrals to specialists (GRADE: Very Low).

Whole exome sequencing after standard testing cost an additional $3,261 per patient but was more effective than standard testing alone. For every 1,000 persons tested, using whole exome sequencing after standard testing would lead to an additional 240 persons with a molecular diagnosis, 272 persons with any positive finding, and 46 persons with active treatment change (modifications to medications, procedures, or treatment). The resulting incremental cost-effectiveness ratios (ICERs) were $13,591 per additional molecular diagnosis. The use of genome-wide sequencing early in the diagnostic pathway (e.g., as a first- or second-tier test) can save on costs and improve diagnostic yields over those of standard testing. Results remained robust when parameters and assumptions were varied.

Our budget impact analysis showed that, if whole exome sequencing after standard testing continues to be funded through Ontario's Out-of-Country Prior Approval Program, its budget impact would range from $4 to $5 million in years 1 to 5. If whole exome sequencing becomes publicly funded in Ontario (not through the Out-of-Country Prior Approval Program), the budget impact would be about $9 million yearly. We also found that using whole exome sequencing as a second-tier test would lead to cost savings ($3.4 million per 1,000 persons tested yearly).

Participants demonstrated consistent motivations for and expectations of obtaining a diagnosis for unexplained developmental delay or congenital anomalies through genome-wide sequencing. Patients and families greatly value the support and information they receive through genetic counselling when considering genome-wide sequencing and learning of a diagnosis.

Conclusions

Genome-wide sequencing could have a higher diagnostic yield than standard testing for people with unexplained developmental disabilities or multiple congenital anomalies. Genome-wide sequencing can also prompt some changes to medications, treatments, and referrals to specialists for some people tested; however, we are very uncertain about this. Genome-wide sequencing could be a cost-effective strategy when used after standard testing to diagnose people with unexplained developmental disabilities or multiple congenital anomalies. It could also lead to cost savings when used earlier in the diagnostic pathway. Patients and families consistently noted a benefit from seeking a diagnosis through genetic testing.

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OBJECTIVE

This health technology assessment evaluates the clinical and personal utility and the cost-effectiveness of genome-wide sequencing (including whole exome and whole genome sequencing) for people with unexplained developmental disabilities or multiple congenital anomalies. It also evaluates the budget impact of publicly funding genome-wide sequencing and the experiences, preferences, and values of people with unexplained developmental disabilities or multiple congenital anomalies.

BACKGROUND

Health Condition

Developmental disability includes developmental delay and intellectual disability. Developmental delay is a term used exclusively for children younger than 5 years of age whose development is substantially behind expected development in at least two of the following: gross motor skills, fine motor/vision, speech and language, cognition, and personal/social activities of daily living.[1,2] Approximately 1% of Canadians have a developmental delay.[3] Intellectual disability, sometimes referred to as intellectual developmental disorder, denotes impaired adaptive functioning. People are said to have an intellectual disability if they have deficits in reasoning, if they fail to meet standards for independence and social responsibility, and if these deficits occurred during the developmental period.[2] Given the overlap between the terms, people with global developmental delay or intellectual disability are often grouped together in the literature. In this report we refer to the group as having developmental disability.

Congenital anomalies, also known as birth defects, can be structural or functional (e.g., metabolic) and can impair a person's development.[4] Approximately 3% of babies in the developed world are born with some congenital anomaly. Down syndrome (trisomy 21) is considered the most prevalent, with an estimated 1 case in 691 births.[5] Congenital anomalies sometimes, but not always, can occur in conjunction with developmental delay and intellectual disability.[6]

Unexplained developmental disabilities and multiple congenital anomalies are difficult to diagnose with clinical symptoms alone, given complex and overlapping presentation of symptoms across various disorders, most of which are rare. About half of all congenital anomalies (typically with developmental delay) cannot be linked to a specific cause or diagnosis on the basis of clinical presentation and examination of environmental causes alone.[7]

Clinical Need and Target Population

While Canada has no official definition of "rare" disease, under one definition, a disease is rare if it is present in fewer than 5 in 10,000 persons.[8,9] While each rare disease affects only a small number of people, an estimated 6% to 8% of the general population (1 in 12 to 16) is believed to have a rare disorder. [8,9]

Many people with unexplained developmental disabilities or multiple congenital anomalies are subjected to a multitude of diagnostic tests, venturing on what is coined the "diagnostic odyssey."[10] Lack of a diagnosis causes extreme stress for patients and their families.[10] Conversely, a genetic diagnosis can be key to understanding the cause and expected progression of disease and development, avoiding unnecessary testing, and facilitating appropriate support systems (including connecting families to disease-specific support groups).[1]

Early identification of genetic diagnoses could also help clinical decisions target potential intervention, monitoring, and optimal patient management and could establish realistic expectations for the child's development.[10]

Health Technology Under Review

The genetic makeup of our bodies (deoxyribonucleic acid, or DNA) contains the information used as building blocks for all cells in the body. An error in the genetic code can lead to a person having impaired development or function and disease or disability. Genome-wide sequencing, as whole exome or whole genome sequencing, can determine if an error is present and can help diagnose or determine the risk of diseases otherwise undetectable through clinical history, physical examination, and biochemical or metabolic tests.

Genetic Sequencing Technologies

When a genetic cause is suspected for the developmental disability and multiple congenital anomalies, a clinician sometimes orders a genetic investigation to identify the variant (historically referred to as mutation) in all of, or part of, a person's DNA code. It would take years to process a single person's entire genetic code using the traditional DNA sequencing method (using Sanger sequencing). Therefore, traditional DNA sequencing method is best suited for evaluating a single gene or a few genes. Sanger sequencing is still considered the gold standard and follows genome-wide sequencing to confirm findings. Another type of genetic examination is the microarray (also referred to as chromosomal microarray), which is quicker, but limited in that it can identify only large structural changes at the level of the chromosomes. It leads to a diagnosis in 10% to 15% of people tested.[11]

Newer methods of sequencing, sometimes referred to as next-generation sequencing, read millions of fragments of genetic information in parallel, making the process substantially faster. A recent boom in new technologies has helped to automate and improve the efficiency of the process overall.

Genome-wide sequencing includes both *whole exome* and *whole genome sequencing*. One way to speed the process of sequencing the genetic code substantially is to limit examination to only the exome, composed of the sections of the genome that are translated to proteins. A mutation in these regions is considered most likely to affect the phenotype (observable trait) and thus is where most of today's disease-related knowledge is contained. The exome makes up less than 2% of a person's entire genetic information (the genome). Whole exome sequencing can assess variants in just a few weeks.[12] As the technology for genetic sequencing is continually improving, whole genome sequencing is becoming faster as well. The time required for analysis and interpretation of the sequence still requires weeks or months of a persons' working hours. In addition to detecting variants in the exome, whole genome sequencing can detect structural variations, such as copy number variations, as well as intronic variants (non-exon). We are learning these intron (non–protein-coding) regions can affect a person's phenotype.[12]

Genome-wide sequencing is now often conducted in the proband (initial person) and their biological parents, referred to as trio testing. The parental genomic information supports identification of possible inheritance patterns and potential causal genes that could be rare or novel in the scientific field. However, it is not always feasible to test both parents (for example, if one parent is unavailable or is unknown). When testing is done on the proband alone, it is

referred to as singleton testing. Other options for testing include duo or quad testing that assesses just one parent, a non-parent relative, or even siblings.

Challenges of Genome-Wide Sequencing

Whole exome and whole genome sequencing are promising technologies, yet there are limitations and challenges for their use in clinical practice. The analysis, reporting, and sharing of data are among the primary concerns about genome-wide sequencing in clinical practice.[13] Knowledge of genetics is improving every day but is still rudimentary. While a particular variation in the genetic sequence might be found, the association between that variation of the sequence and a disease can be largely unknown. Whole genome sequencing always results in substantially longer lists of variants of unknown significance than whole exome sequencing does.[13] Interpreting and acting upon variants of unknown clinical significance is the single greatest challenge identified by clinicians.[13,14] A variant may be flagged as disease causing and, depending on what is known about that variant (i.e., published in literature) or what is found in family members, a variant can be classified as pathogenic (disease-causing), likely pathogenic, a variant of unknown significance, likely benign, or benign according to the American College of Medical Genetics and Genomics (ACMG) criteria.[15] Further, bioinformatic tools used to manage the data and to help filter and sort variants are based on imperfect databases and therefore comprise imperfect algorithms that are constantly being improved upon as new knowledge is added.[13] Analysis of an individual genome requires considerable computing power and electronic storage space that is not necessarily feasible for any single entity to support; thus networks of national and international groups are forming to share best practices and knowledge.

Atypical expressions of genetic code add to the complexity of conducting genetic sequencing for diagnosis. Some genes are imprinted and expressed from only one parent's chromosome. A person could have different genetic makeup in different cells, a phenomenon known as *mosaicism*. Some disease-associated genes have *reduced penetrance*, meaning that not all people with the mutation develop the disease or develop all features of the disorder.[14] Sometimes genetics does not cause an observed condition. For example, a condition could be due to alteration of proteins observable only with biochemical examinations to identify an anomaly with no known genetic link in an ultra-rare disease.[16] When an established target gene or multi-gene panel that covers all known genes associated with a suspected disorder is available, it is still recommended over genome-wide sequencing due to these challenges (email from various committee experts, November 2018 through June 2019).

Physical harm associated with genetic testing is considered negligible, as genetic material can be captured through a non-invasive cheek swab or a small amount of blood, which carries little risk if appropriate phlebotomy procedures are followed. There is, however, potential for unintended consequences and psychological harm from the findings of genome-wide sequencing. People can be referred for additional testing or treatment despite not displaying any symptoms if they receive a false-positive result, or even a true-positive result for a condition with low penetrance (the rate at which people with the same variant will develop symptoms). When searching the genome, findings unrelated to the symptoms being investigated might be uncovered.[17] For example, people who present with peripheral neuropathy could have a mutation of the *MLH1* gene that is unrelated to their symptoms but is associated with Lynch syndrome and carries a higher risk for certain cancers.[17] Unaffected test subjects (as in duo, trio, or quad testing) might also have findings unrelated to the proband's symptoms. For example, a parent of a child with a rare disease can submit their genetic information to support the diagnostic testing for their child but be found to have the variant for hypertrophic

cardiomyopathy. Experts recommend that the informed consent process include an opportunity to opt in or out of secondary findings, and many laboratories have adopted policies to report only medically actionable findings.[17-19] Secondary findings are the result of actively searching for specific variants that are unrelated to the primary cause of genetic testing. Incidental findings are the result of happenstance upon seeing output from a test. Canadian and international guidelines, such as those written by the Canadian College of Medical Geneticists, Clinical Sequencing Exploratory Research (CSER) consortium, and the ACMG that go into more depth about managing secondary findings.[17-19]

Ontario Context

At the time of completing this health technology assessment, no Ontario laboratory is licensed to perform genome-wide sequencing as a clinical test for use in patient care. Some large academic centres have laboratories with the capability to conduct genome-wide sequencing for research (as advised by the Ontario Ministry of Health in conversation, November 2018). Whole exome sequencing is available to Ontarians by sending samples out of the country (the Ontario Health Insurance Plan [OHIP] pays for patients who meet the Ministry's criteria for the Out-of-Country Prior Approval Program. The Genetic Testing Advisory Committee (GTAC) provided guidance to the Ministry about who should be considered eligible for sequencing, at what point in the care pathway, and after what other investigations have first been conducted.[20] A few tests (number unknown, but believed to be small) are paid for by individual patients as out-of-pocket expenses at private laboratories outside Ontario (e.g., in the United States).

Ontario has no standard protocol for assessing and managing the diagnostic testing pathway for people with developmental disabilities or multiple congenital anomalies. Typically, the diagnostic odyssey begins with the primary care practitioner (e.g., family doctor or pediatrician), who might perform some genetic testing. Once patients are referred to a developmental specialist, usually chromosomal microarray testing and Fragile X testing are ordered.[12] A geneticist might be consulted to review the patient's history, physical features, and test results. The geneticist might order a set of biochemical and metabolic tests for potential disease markers, such as plasma amino acids and venous blood gas levels. At this point people on this diagnostic odyssey would take one of three paths depending on the geneticist's suspicion of underlying disease: confirmatory single-gene or multi-gene panel testing; expanded panel (e.g., if epilepsy is suspected); or whole exome sequencing. If no diagnosis is apparent, patients are often considered for follow-up and re-analysis in 1 to 3 years. At this time, whole genome sequencing is not part of the standard practice for diagnosis (email from Ontario Genetic Advisory Committee [OGAC] experts, November 2018).

People often wait years for genetic assessment and testing, and many are subjected to a host of diagnostic tests over many years. One theory is that offering genome-wide testing earlier would improve the care and experience for patients and their families. When a test is offered also affects the diagnostic yield. Whole exome sequencing is generally used in Ontario as a third-tier test after more exhaustive genetic testing, including targeted gene or gene panel assessments, has failed to identify a molecular diagnosis. First-tier tests are offered before any other genetic testing; second-tier tests are offered after chromosomal microarray or very targeted gene panels (of one gene or only a few genes).

Equity

According to Ontario Health (Quality), "health equity allows people to reach their full health potential and receive high-quality care that is fair and appropriate to them and their needs, no

matter where they live, what they have, or who they are." One potential inequity for genome-wide sequencing in Ontario is variation in practice based on geography. Experts advise that people who fall within academic tertiary care centre referral pathways (e.g., for SickKids, CHEO, or Hamilton Health Sciences Hospital) are more likely to have whole exome and whole genome sequencing made available. Another potential equity concern is income, as some patients pay out-of-pocket for sequencing analysis. Inequities can also arise when wait times for referral to a medical geneticist are long, as wait lists sometimes do not consider individual needs and health risks.

Regulatory Information

At the time of writing, genome-wide sequencing consists of laboratory-developed tests and is therefore outside the regulatory framework of Health Canada and the US Food and Drug Administration. Test manufacturers can, however, voluntarily submit applications for approval. In the United States, certification of the performing laboratory is required under Clinical Laboratory Improvement Amendments regulations to ensure the quality and validity of the test.[21] Ontario has four legislative acts that govern the standards of Ontario licensed laboratories: the *Laboratory and Specimen Collection Centre Licensing Act; Regulated Health Professionals Act, Medical Laboratory Technology Act,* and *Public Hospitals Act*.[22]

Canadian and International Context

The Genetic Non-Discrimination Act was passed in Canada in 2017. This law prevents any person from being required to undergo a genetic test or disclose the results of a genetic test as a condition of business (e.g., to get health insurance).[23] The Chief Commissioner of the Canadian Human Rights Commission noted that it should not be a "calculated risk" to take a potentially life-saving test and that Canadians should not have to fear misuse of their genetic information.[23]

We understand that access to genome-wide sequencing is limited across Canada. Most provinces are interested in exploring access to testing for their constituents, but access might mean some of the smaller regions would need access to resources in other provinces (e.g., residents of Yukon Territory accessing services in British Columbia or Alberta; personal communication with a liaison officer from the Canadian Agency for Drugs and Technologies in Health [CADTH] about a jurisdictional scan conducted in December 2018). We are aware of a handful of (both public and private) laboratories offering next-generation sequencing for a variety of diagnostic purposes, including cancer and epilepsy (e.g., the Centre for Clinical Genomics[24]).

Internationally, more than 14 countries have invested a collective $4 billion USD since 2013 to establish genomic medicine programs.[25] These countries span the globe in nearly every continent, and programs include inter-country collaborations. Examples include collaboration between Genomics England, Australian Genomics, Japan Agency for Medical Research and Development and NHGRI Newborn Sequencing in Genomic Medicine and Public Health.[25] There are various funding and organization models; one model allows laboratories to reallocate to genome-wide sequencing funds that are offset by stopping or replacing other tests. Initiatives are focused on aligning protocols and data collection to allow for streamlining gene discovery across larger datasets and evaluation frameworks and for disseminating findings as fast as possible. New programs are also in development, such as the Hong Kong Genome Project.[26] Parallel to these government-supported programs, the private sector has seen growth in the use of genomic medicine. In jurisdictions that do not have genomic medicine as part of public health

care, private laboratories are projecting an increase in use (e.g., in segments of Latin America[27]). Some direct-to-consumer tests, such as 23andMe and Ancestry, are marketed to private citizens directly, but offer extensive health-related genomic information.[25]

Expert Consultation

We engaged with experts in the specialty areas of laboratory genetics, medical genetics, genetic counselling, neurology, pediatrics, and other laboratory specialties as needed to help inform our understanding of aspects of the health technology and our methods and to contextualize the evidence.

PROSPERO Registration

This health technology assessment has been registered in PROSPERO, the international prospective register of systematic reviews (CRD42019123619), available at https://www.crd.york.ac.uk/PROSPERO.

CLINICAL EVIDENCE

Research Question

What are the diagnostic yield and clinical utility of genome-wide sequencing (including whole exome and whole genome sequencing) compared with other genetic diagnostic tests (including combinations of genetic tests, such as chromosomal microarray and gene panels) for people with unexplained developmental disabilities or multiple congenital anomalies?

Methods

We developed the research questions in consultation with health care providers, clinical experts, and other health system stakeholders.

Clinical Literature Search

We performed a clinical literature search on January 17, 2019, to retrieve studies published from inception until the search date. We used the Ovid interface in the following databases: MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the Health Technology Assessment database, and the National Health Service's Economic Evaluation Database (NHS EED). A systematic review was identified during preliminary scoping efforts, and in consideration of the large body of primary literature in the population of interest, we limited the literature search to systematic reviews.

A medical librarian developed the search strategies using controlled vocabulary (e.g., Medical Subject Headings) and relevant keywords. A methodological filter was used to limit retrieval to systematic reviews, meta-analyses, and health technology assessments for the clinical evidence. The final search strategy was peer-reviewed using the PRESS Checklist.[28]

We created database auto-alerts in MEDLINE and Embase, and we 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. The grey literature search was updated May 3, 2019. See Appendix 1 for our literature search strategies, including all search terms.

Eligibility Criteria

Studies

Systematic reviews were considered the primary source of evidence. We sought to identify the single best review available that combined low risk of bias (assessed with the risk of bias in systematic review [ROBIS] tool), comprehensiveness, and recency. Additional primary studies identified through scoping efforts and through searching reference lists were searched for clinical utility outcomes.

Inclusion Criteria

- English-language full-text publications
- Studies published from database inception until January 17, 2019
- Systematic reviews that used diagnostic yield as a primary (or key) outcome

- Systematic search of at least one known medical database (e.g., PubMed)

Exclusion Criteria

- Animal and in vitro studies
- Nonsystematic reviews, narrative reviews, abstracts, editorials, letters, case reports, commentaries, and general discussions of genetic abnormalities or gene discovery
- Studies that primarily examined the analytical validity of a genetic test or that assessed only management of rare diseases

Participants

We included studies of people with unexplained developmental disabilities or multiple congenital anomalies. Studies were included if they assessed people with the following conditions:

- Intellectual disability
- Developmental delay
- Congenital anomalies
- Multisystem involvement or multi-differential diagnosis (several possible diagnoses)
- Rare diseases otherwise not specified

We did not limit studies by age of people included, but excluded studies in a screening or prenatal context. We also excluded studies in which genetic testing was conducted to confirm or further explore clinical diagnoses.

Interventions

We included reviews that examined genome-wide sequencing, including studies that examined any combination of whole exome sequencing and whole genome sequencing, with any comparator.

Outcome Measures

We included the diagnostic yield and clinical utility as outcomes of interest:

- Diagnostic yield (number of cases with positive test results as a proportion of total number tested):
    - Of each type of genome-wide sequencing technology (exome and genome)
    - When used as trio testing (versus proband alone)
    - When used at different times in the diagnostic clinical pathway
    - Of variants of unknown significance
    - Of secondary findings (proband and family)

It is not always possible to conduct trio testing (e.g., one or both parents might be unavailable). To be included as part of the trio group, studies were required to conduct trio testing for at least 75% of their study sample. We also explored if there was a difference between studies that required trio testing for 100% of the sample versus studies that incorporated results from alterative methods, such as duo and quad testing.

- Clinical utility:
    - Patient outcomes (e.g., functional outcomes)

- Impact of test result on patient care (including clinical decision making, timing)
- Impact of test results on family care (including family planning)

Literature Screening

A single reviewer conducted an initial screening of titles and abstracts using Covidence[29] 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 for any additional relevant studies not identified through the search.

Data Extraction

One reviewer extracted relevant data using a data extraction form that included the following study characteristics:

- Study population
- Inclusion and exclusion criteria
- Description of interventions, types of comparators, outcomes, and results

Systematic reviews were considered the primary source of evidence, but primary studies were to be obtained in full text to support data extraction as needed. For reviews where the scope was larger than our scope of interest, only studies that would have otherwise met our inclusion criteria were included.

Conflicts between reviews were confirmed by going to the primary studies. Occasionally we spotted a typographical error in a systematic review's reporting of the primary study. When this occurred, the data reported in the primary studies superseded the data reported in the systematic review.

Evidence Synthesis

We planned to conduct an overview of reviews for the outcomes of diagnostic yield. However, the various reviews we identified had inconsistent inclusion criteria, so we elected to perform our own quantitative synthesis of primary studies identified by the systematic reviews. Comparative studies were analyzed using Review Manager.[30] All other evidence synthesis analyses were conducted using R Studio.[31] Owing to clinical heterogeneity all analyses were conducted using inverse variance, random effects modeling.[32] We considered the I^2 statistic an inadequate reflection of the heterogeneity as a measure of sampling variability. Instead we opted to explore the τ^2 statistic as an estimate of heterogeneity for all meta-analyses conducted as a calculation of between-study effect variability.[33] Where evidence synthesis was considered unfeasible or inappropriate, results are reported narratively.

Critical Appraisal of Evidence

We assessed risk of bias using ROBIS for systematic reviews and Risk of Bias Assessment tool for Non-Randomized Studies (RoBANS) for primary studies (Appendix 2).[32,34,35]

We evaluated the quality of the body of evidence for each outcome according to the *Grading of Recommendations Assessment, Development, and Evaluation* (GRADE) *Handbook*.[36] The body

of evidence was assessed on the basis of the following considerations: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The overall rating reflects our certainty in the evidence.

Results

Clinical Literature Search

The database search yielded 288 citations published from inception until January 17, 2019. We identified 15 additional studies from other sources, for a total of 211, after removing duplicates. We obtained the full text of 40 articles for further assessment. Five systematic reviews met the inclusion criteria.[37-41] The primary reasons for exclusions are provided below. See Appendix 3 for selected studies excluded after full-text review. Figure 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram.

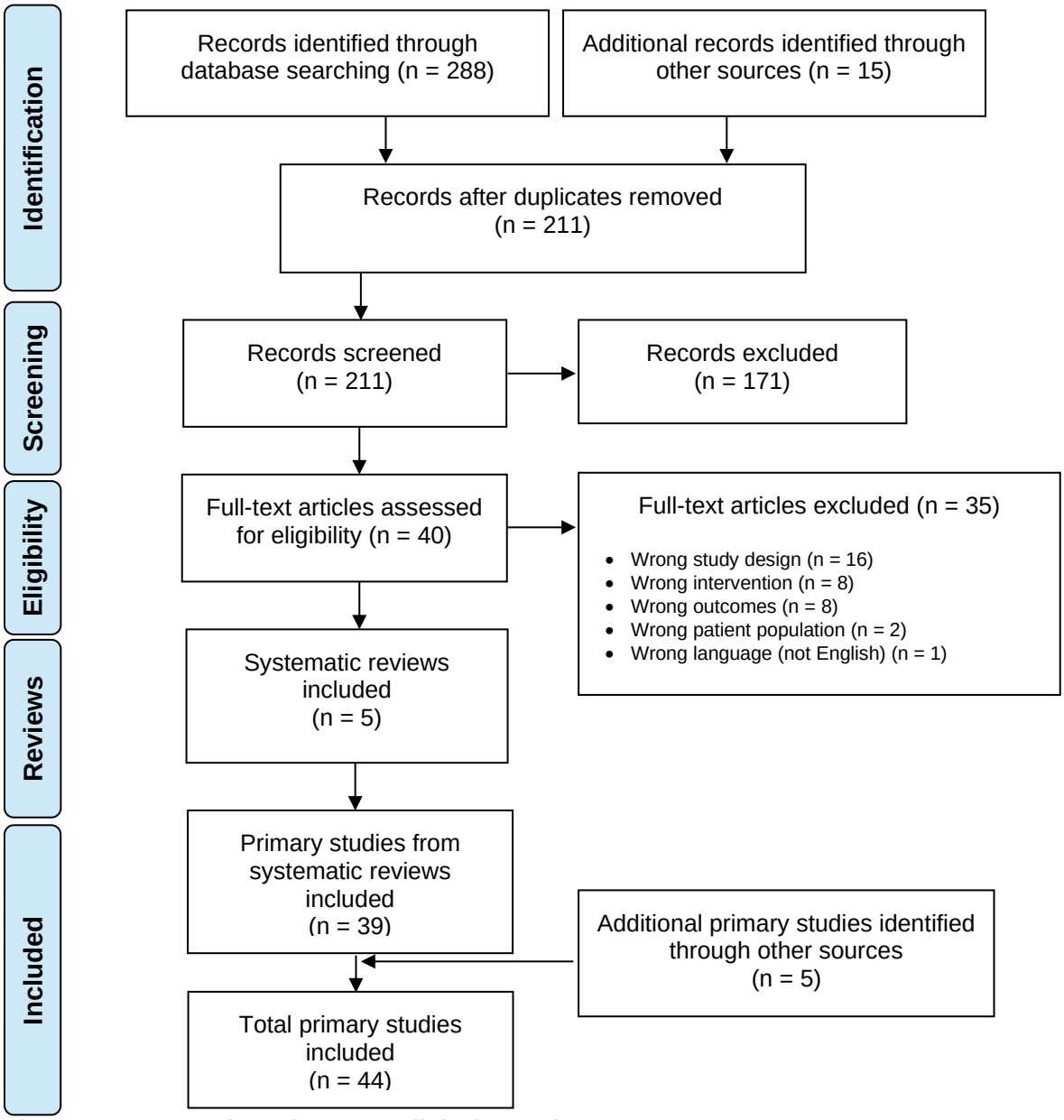

Figure 1: PRISMA Flow Diagram—Clinical Search Strategy

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.
Source: Adapted from Moher et al.[42]

Characteristics of Included Studies

Five systematic reviews met the inclusion criteria (Table 1).[37-41] Reviews were assessed using ROBIS[35] to examine their possible risk of bias.

Table 1: Characteristics of Included Systematic Reviews

Author, Year	Literature Search Dates	Population	Intervention	No. of (Relevant) Studies	ROBIS[a]
Clark et al, 2018[37]	January 2011–August 2017	Children with suspected genetic disease	Whole exome sequencing, whole genome sequencing, CMA	37 (32)	High
Schwarze et al, 2018[38]	January 2005–July 2016	Any population	Whole exome sequencing, whole genome sequencing	36 (13)	Low
Shakiba et al, 2018[39]	Up to October 2017	Patients with inborn errors of metabolism, with metabolic disorders, or with neurometabolic, neurogenetic, or genetic disorders	Whole exome sequencing	9 (9)	High
Sun et al, 2015[40]	January 2000–January 2015	People with developmental disabilities, intellectual disabilities and autism spectrum disorders	Genetic testing	426 (9)	High
WHA, 2017[41]	January 2000–September 2017	Children with developmental and intellectual disabilities, autism spectrum disorder or multiple congenital anomalies	CMA or whole exome sequencing	18 (1)	Low

Abbreviations: CMA, chromosomal microarray; ROBIS, risk of bias in systematic review; WHA, Washington Health Authority.
[a] Details about ROBIS assessment given in Appendix 4.

Risk of Bias in the Included Studies

We assessed some reviews as having a high risk of bias, largely because they drew conclusions that overemphasized their findings or did not address all limitations of primary studies identified in their respective reviews. Details about the ROBIS assessment are given in Appendix 4.

None of the systematic reviews we identified fully addressed our research question for various reasons, such as having a more focused population of interest. Overlap of the primary studies included in several of the systematic reviews—as estimated by the corrected covered area calculation—was only moderate (score = 10).[43] Therefore, we opted to use the five systematic reviews as sources to identify relevant primary studies. We conducted our own data extraction and risk of bias assessments of primary studies and calculated our own summary estimates. The systematic reviews included a total of 39 relevant and distinct primary studies between them; we identified an additional 5 studies focused on our clinical utility outcomes through scoping efforts and scanning reference lists. The 44 primary studies we included are summarized in Appendix 2.

Risk of bias was high for all included primary studies (Appendix 4). Most studies lacked a control group, and participant recruitment was subject to bias in clinical assessment of

participants' complex set of symptoms. The way diagnosis and clinical utility were determined meant that the assessor could not be blinded to the outcomes. As well, there was a learning effect as the assessor gained experience; the same assessor might assess participants later in the study differently than participants seen earlier in the same study period. For example, the assessor's skills and judgment about outcomes such as identifying a diagnosis might become more nuanced.

Diagnostic Yield

All 44 primary studies reported data on diagnostic yield, of which four[44-47] conducted analyses for both whole exome and whole genome sequencing. Of the studies that examined whole genome sequencing, three used what is known as "rapid" whole genome sequencing.[48-50] For the purposes of this report, we included these rapid tests with the other genome-sequencing studies as one group. These studies were conducted around the world, primarily in North America and Europe (countries included Canada, Australia, Argentina, Belgium, France, Germany, Hong Kong, Israel, Netherlands, Saudi Arabia, United Arab Emirates, United Kingdom, and United States of America). Studies were evenly balanced for sex (54% male) and primarily assessed children, even within studies that did not explicitly exclude participants on the basis of age. We observed consanguinity (related parents) rates of 18% across all studies (Appendix 4, Table A5).

Diagnostic yield is calculated as the number of participants diagnosed as a proportion of the total number tested. Patients were considered to be "diagnosed" as reported by the individual studies. For the most part the studies considered a diagnosis to have been made when a variant was identified that was classified as pathogenic or likely pathogenic using the ACMG guidelines.[15] Most of the populations of the included studies were based on referrals to genetic testing and were not defined by a single set of symptoms. Results were not discernable by specific population (e.g., children with a specific disorder). As such, we aligned our inclusion criteria with that in other systematic reviews and included primary studies whose populations largely included people who would have met our inclusion criteria (e.g., >70% had symptoms of developmental disability). The diagnostic yield across all studies was 37% (95% confidence interval [CI] 34%–40%) (Figure 2). More studies, with an overall larger sample size, were included in the examination on whole exome sequencing (34 studies, n = 9,142) than on whole genome sequencing (9 studies, n = 648). Results were observed to be similar between studies that used whole exome sequencing versus whole genome sequencing, as the confidence intervals overlap (37%, 95% CI 34%–40%, vs 40%, 95% CI 32%–49%).

Diagnostic yield ranged between 16% and 73%. The variation is due to several contributing factors, most notably technology used and participant selection. Some studies required participants to have had exhaustive genetic testing (e.g., chromosomal microarray and targeted gene tests) to be eligible for genome-wide sequencing, while other studies required participants to be naïve to genetic tests. We examined diagnostic yield considering various subgroups, presented in the following sections.

We rated the quality of the evidence as very low (Appendix 4, Table A5), downgrading for risk of bias, inconsistency, indirectness, and imprecision.

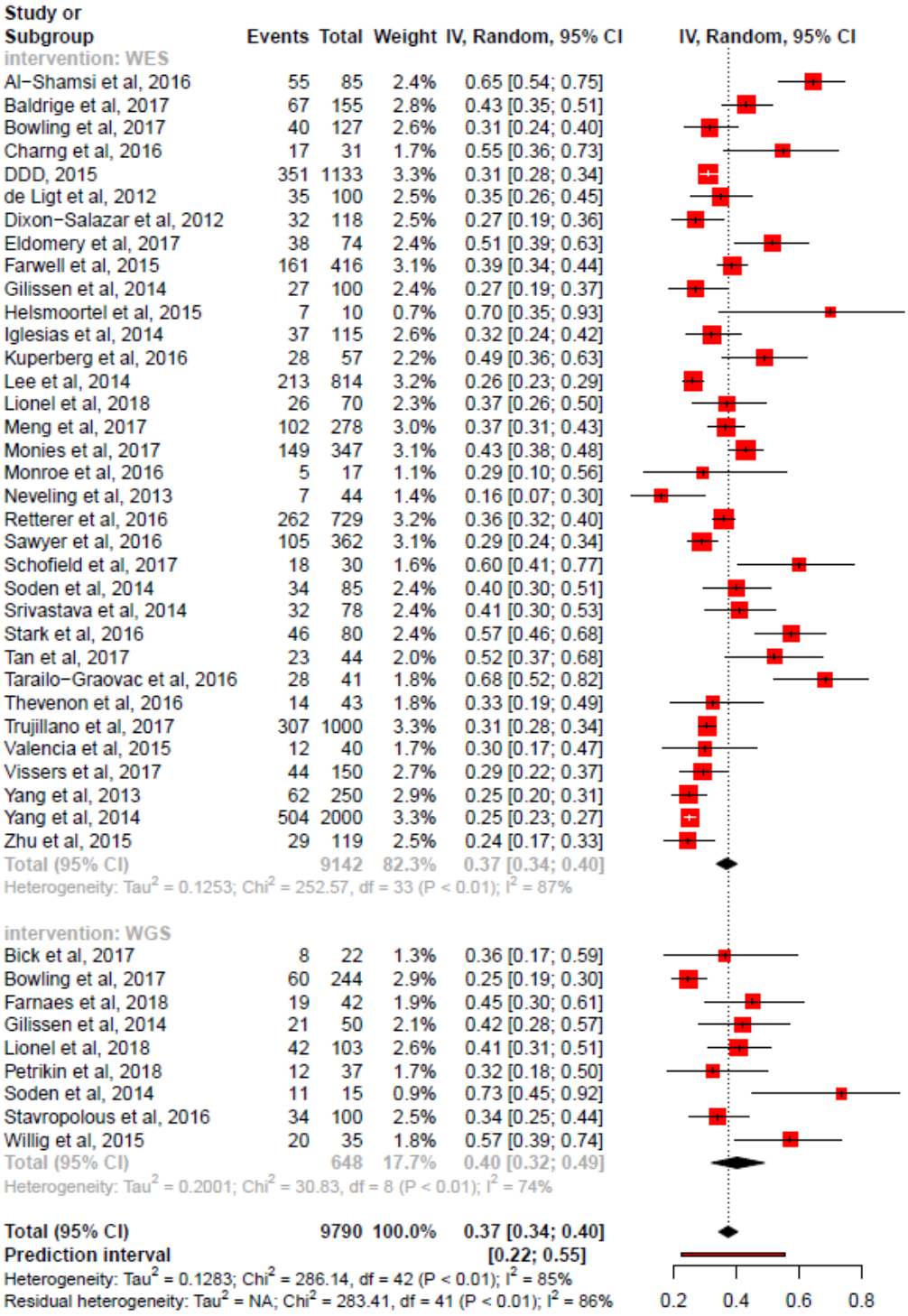

Figure 2: Diagnostic Yield by Genome-Wide Sequencing Technology

Abbreviations: CI, confidence interval; DDD, Deciphering Developmental Disorders study; df, degrees of freedom; IV, inverse variance; NA, not applicable; WES, whole exome sequencing; WGS, whole genome sequencing.

Comparative Effectiveness of Diagnostic Yield

Nine studies[45,48,50-56] were designed in such a way that we could directly compare the diagnostic yield of genome-wide sequencing versus standard genetic testing. The level of detail describing standard genetic testing was inconsistently reported, but typically it included chromosomal microarray, candidate single-gene testing, or large gene panel testing.

This subset of studies yielded a diagnostic yield of 38% for genome-wide sequencing, compared with the diagnostic yield for standard genetic testing of 21% (Table 2). The risk ratio is thus in favour of genome-wide sequencing (RR 1.76 [95% CI 1.20–2.58]), with an even larger yield among studies that used whole genome sequencing than whole exome sequencing (Figure 3).

We rated the quality of the evidence as very low (Appendix 4, Table A5), downgrading for imprecision.

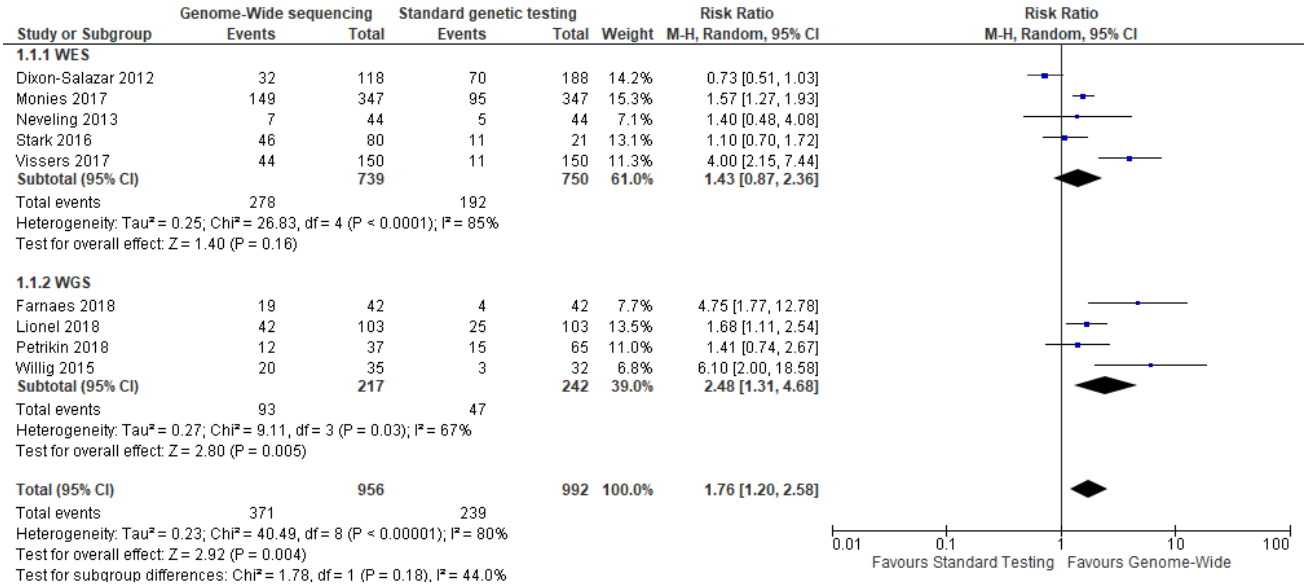

Figure 3: Comparative Diagnostic Yield of Genome-Wide Sequencing Versus Standard Genetic Testing

Abbreviations: CI, confidence interval; df, degrees of freedom; M-H, Mantel Haenszel test; WES, whole exome sequencing; WGS, whole genome sequencing.

Table 2: Diagnostic Yield from Subset of Comparative Effectiveness Studies

	WES		WGS		All
Trio Test	Sample Size	Diagnostic Yield (95% CI)[a]	Sample Size	Diagnostic Yield (95% CI)[a]	Diagnostic Yield (95% CI)[a]
Genome-wide sequencing group	739	0.34 (0.24–0.47)	217	0.43 (0.35–0.52)	0.38 (0.31–0.46)
Standard care group	750	0.24 (0.14–0.38)	242	0.18 (0.11–0.27)	0.21 (0.14–0.29)

Abbreviations: CI, confidence interval; WES, whole exome sequencing; WGS, whole genome sequencing

[a]Results are yield from each group of studies presented in Figure 3, calculated using a random effects model. See Appendix 5 for forest plot.

Given substantial advances in known genes year over year, we conducted a subgroup analysis testing the theory that including older studies could skew the results toward the null. Since the research by Dixon-Salazar et al[51] is the oldest of the group and their results appear to be inconsistent with the other studies, we conducted a sensitivity analysis in which we removed this older study from the meta-analyses. This analysis changed the results for whole exome sequencing—which becomes statistically significantly different from standard testing with a RR of 1.74 (95% CI 1.06–2.83) and an overall RR of 1.98 (95% CI 1.39–2.81) (Appendix 5).

Diagnostic Yield by Use of Trio Testing

Trio testing uses the genetic information from parents to help confirm and identify suspect genes in a proband (target person). Summary effect estimates identified no substantial differences in diagnostic yield between trio and proband-only (i.e., singleton) groups; the confidence intervals largely overlap (Table 3 and Appendix 5).

Table 3: Diagnostic Yield of Genome-Wide Sequencing by Use of Trio Testing

	WES			WGS		
Trio Use	No. of Studies	Sample Size	Diagnostic Yield (95% CI)[a]	No. of Studies	Sample Size	Diagnostic Yield (95% CI)[a]
Proband only	11	1,421	0.41 (0.33–0.50)	2	122	0.34 (0.27–0.43)
Trio	19	5,506	0.35 (0.32–0.38)	5	461	0.39 (0.27–0.51)
Uncertain	4	2,215	0.35 (0.24–0.48)	2	65	0.56 (0.26–0.82)

Abbreviations: CI, confidence interval; WES, whole exome sequencing; WGS, whole genome sequencing.
[a]Results are summary effect estimates calculated using a random effects model. See Appendix 5 for forest plot.

In Ontario although trio testing is considered the preferred method, a mix of testing is used (e.g., if one or both parents is unavailable). This sensitivity analysis explores the differences among studies that used a mix of trio testing similar to what we would expect to see in Ontario compared with studies that required trio testing in 100% of the samples (Table 4 and Appendix 5).

Table 4: Diagnostic Yield of Genome-Wide Sequencing Comparing Trio Testing and Mixed Methods

	WES			WGS		
Genetic Testing	No. of Studies	Sample Size	Diagnostic Yield (95% CI)	No. of Studies	Sample Size	Diagnostic Yield (95% CI)
100% trio: all probands received trio testing	11	4,317	0.32 (0.29–0.34)	3	180	0.46 (0.37–0.55)
Mixed method of testing[a]	8	1,968	0.39 (0.33–0.46)	2	281	0.26 (0.21–0.31)

Abbreviations: CI, confidence interval; WES, whole exome sequencing; WGS, whole genome sequencing.
[a]Mixed methods consisted mostly of trio testing, but sometimes combined proband, duo, quad, and non-parental familial tests.

Diagnostic Yield by Timing in the Testing Pathway

Where reported in the primary studies, the time from symptom onset to referral for genome-wide testing diagnosis was, on average, 6.5 years (Appendix 2). Summary effect estimates found testing earlier in the diagnostic pathway yielded higher rates of diagnoses than later as a third-tier test (Table 5 and Appendix 6). The largest body of evidence was found in third-tier testing, which reflects when testing is offered in Ontario.

Table 5: Diagnostic Yield of Genome-Wide Sequencing by Timing in Clinical Pathway

	WES			WGS		
Timing of Use[a]	No. of Studies	Sample Size	Diagnostic Yield (95% CI)[b]	No. of Studies	Sample Size	Diagnostic Yield (95% CI)[b]
First-tier test	5	706	0.37 (0.27–0.49)	5	295	0.46 (0.36–0.57)
Second-tier test	2	54	0.55 (0.42–0.68)	0	—	—
Third-tier test	19	6,091	0.33 (0.30–0.37)	4	353	0.32 (0.24–0.42)
Not specified	8	2,291	0.41 (0.35–0.48)	0	—	—

Abbreviations: CI, confidence interval, WES whole exome sequencing, WGS whole genome sequencing.
[a]First-tier (before any other genetic testing); second tier (after very limited genetic testing, such as just chromosomal microarray) or third-tier (after more exhaustive genetic testing, including targeted gene or gene panel assessments).
[b]Results are summary effect estimates calculated using a random effects model. See Appendix 5 for forest plot.

Diagnostic Yield by Condition

Given the heterogeneity of populations, we considered it inappropriate to conduct subgroup analyses according to clinical presentation of symptoms. Many studies included a mix of populations but did not report results separated by clinical presentation. We believe our decision errs on the conservative side and leans toward the likely reality in Ontario.

Yield of Variants of Unknown Significance

Five studies[44,57-60] provided data on the yield of whole exome and whole genome sequencing for variants of unknown significance aligned with the ACMG guidelines for defining pathogenic and benign variants (Figure 4). Overall there was a 17% yield for variants of unknown significance.

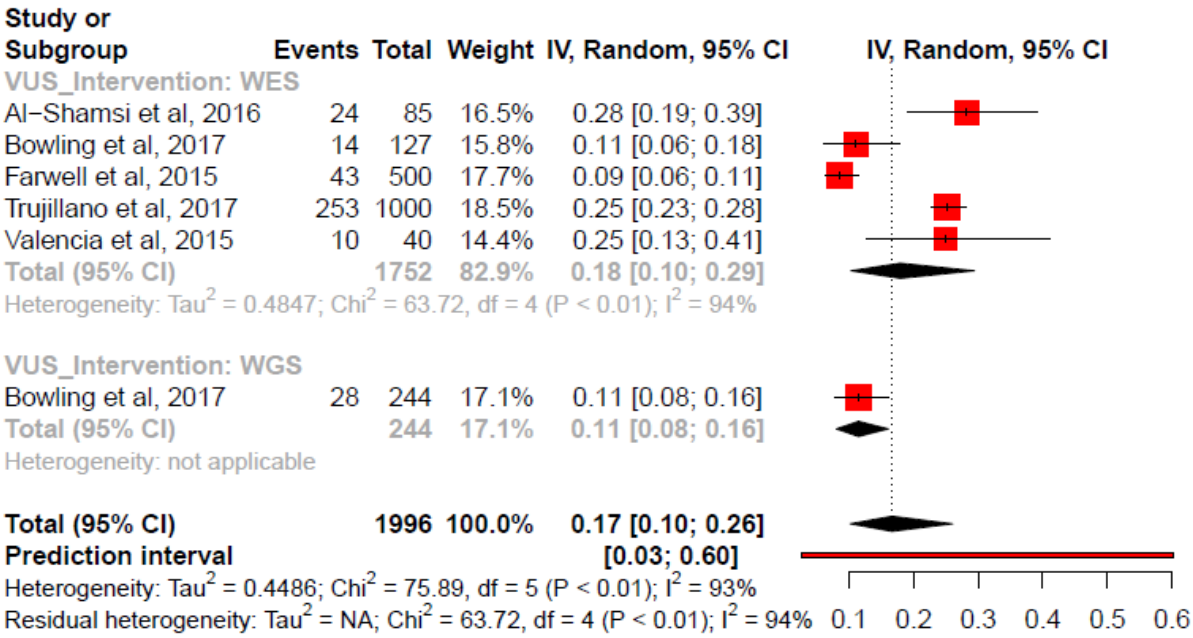

Figure 4: Variants of Unknown Significance Yield by Genome-Wide Technology

Abbreviations: CI, confidence interval; df, degrees of freedom; IV, inverse variance; VUS, variant of unknown significance; WES, whole exome sequencing; WGS, whole genome sequencing.

Two other studies reported the data of variants of unknown significance mixed with other levels of certainty, such as “probably/possible”[61] or “likely benign/benign,”[62] and one study labeled 40% of their findings as “ambiguous.”[52]

Yield of Secondary Findings

Secondary findings were reported in 14 studies. The ACMG recommends reporting a list of genes if found as secondary findings during a genetic test.[17] Rates between studies varied between 1.2% and 20% (Table 6) largely owing to how studies combined their findings and accounted for medically actionable secondary findings (summary yield 0.07 [95% CI 0.04–0.10], Appendix 5). One study examined the rate of secondary findings in family members when testing was widely done and found it to be 3.7% (see Table 6).[63]

Table 6: Diagnostic Yield of Secondary Findings From Genome-Wide Sequencing of Proband and Family Members

Study	Intervention	Sample Size	Proband			Family
			Medically Actionable[a]	Carrier Status[a]	All	
Al-Shamsi et al, 2016[57]	WES	85	9.4%	10.6%	20.0%	--
Baldridge et al, 2017[63]	WES	252[b]	--	--	--	3.7%
Bick et al, 2017[64]	WGS	66[b]	--	--	--	62% medically actionable[c] 60% carrier status[c]
Bowling et al, 2017[44]	WES and WGS	371	2.0%	4.6%	8.7%	--
Lee et al, 2014[65]	WES	814	--	--	5.0%	--
Monies et al, 2017[52]	WES	347	1.2%	--	1.2%	--
Retterer et al, 2016[61]	WES	2,091	6.2%	--	6.2%	--
Stark et al, 2016[54]	WES	80	--	--	--	26%[c]
Stavropoulos et al, 2016[66]	WGS	100	7.0%	--	7.0%	--
Tarailo-Graovac et al, 2016[67]	WES	41	--	--	2.4%	--
Thevenon et al, 2016[68]	WES	43	2.0%	--	2.0%	--
Valencia et al, 2015[60]	WES	36	8.0%	--	8.0%	--
Yang et al, 2013[69]	WES	250	12.0%	5.2%	17.2%	--
Yang et al, 2014[70]	WES	2,000	4.6%[d]	--	4.60%	--

Abbreviations: WES, whole exome sequencing; WGS, whole genome sequencing.
[a]Studies reported using criteria from American College of Medical Genetics and Genomics for medically actionable genes to report for secondary findings or carrier status.
[b]Includes proband and 2 parents conducted as part of trio testing.
[c]Limited to parents of children who received a diagnosis, from cascade testing.
[d]3% met criteria from American College of Medical Genetics and Genomics; additional findings were based on individual laboratory's policy.

Clinical Utility

No study reported how genome-wide sequencing affected long-term patient outcomes, such as functional outcomes or quality of life. However, some studies reported on intermediate activities presumed to potentially affect patient outcomes in the long term.

Clinical Impact of Diagnosis on Clinical Care

About half of the primary studies included in this review reported on how a diagnosis affected clinical care. Among these studies, the definition of what constituted a clinical utility activity and what was reported varied.

We grouped the effect of diagnosis on clinical care reported by the primary studies into the following seven categories:

- Modification to medication regimen (e.g., starting new medication or stopping unnecessary therapies)

- Procedure (e.g., heart valve repair)
- Treatment, which was a general category for therapies that were neither medication nor procedure (e.g., speech therapy)
- Additional diagnostic testing or surveillance, including status changes for monitoring known disease risks and prognoses
- Changes to specialist involvement and referrals
- Clinical trial referral, as some people could be eligible for known ongoing clinical trials for their newly identified rare disease
- Social services, impact on prognosis or lifestyle (including referral for social programs), changes to lifestyle because of the prognosis, or changes to lifestyle (such as diet) to improve patient outcomes

The first three categories were further grouped into *active clinical management*, which we defined as activities expected to have a short-term effect on patient outcomes and includes modifications to medications, procedures, or treatment. Clinical utility activities expected to have a longer-term effect on health, such as referral to specialists, surveillance, or lifestyle changes, were grouped as *monitoring and long-term clinical management* (Appendix 5).

To account for the varied sample sizes of the studies, we calculated a rate of clinical utility activity as ratio of the number of clinical utility activities to the total number of people tested (Table 7, Appendix 5).

Table 7: Rate of Clinical Utility Activities for Patients

	All Studies			Active Clinical Management[a,b]		Monitoring and Long-Term Clinical Management Activities[b,c]	
Group	No. of Studies	Sample Size	Rate (%)	No. of Clinical Utility Activities	Rate (%)	No. of Clinical Utility Activities	Rate (%)
WES	15	1,716	14.3	101	5.9	295	17.2
WGS	4	173	20.2	18	10.4	36	20.8
All groups	19	1,889	14.8	119	6.3	331	17.5
Sensitivity analysis: rate of clinical utility activity as a factor of the number of people who received a diagnosis	19	713	39.3	119	16.7	331	46.4

Abbreviations: WES, whole exome sequencing, WGS, whole genome sequencing.
[a]Includes modifications to medication, procedures, or treatment.
[b]Includes some double counting of people who received more than one clinical intervention.
[c]Monitoring and long-term activities include referrals to specialists, surveillance, or lifestyle changes.

A handful of studies commented that there is clinical utility 100% of the time among people diagnosed, as it signifies an end to the diagnostic odyssey. Once there is a diagnosis, it can describe the natural history of the disease, can connect parents and children with appropriate supports, and can improve informative genetic counselling and family planning.[60,62,71]

One study noted that 73% (11 of 15) of people whose clinical care changed would not have been identified through standard genetic testing.[54] Another study compared the clinical utility of people receiving whole exome sequencing with that of standard care and found only one person's treatment would be impacted after receiving standard care, compared with the study's 13 who were affected after whole exome sequencing (study sample size was 42).[48] Clinical utility was not affected by the timing of the test in one study that found no difference in utility when exome sequencing was offered as a first-tier versus second-tier test (P = .84) and that found whole genome sequencing had the greatest effect when conducted as trio testing in critically ill infants (23 of 32, 72%).[72]

Hayeems et al[36] explored genome-wide sequencing among people who did not receive a diagnosis through conventional microarray. A regression analysis found that additional lab activities were not actually dependent on the results of the whole genome sequencing test (P = .278) but that numbers of specialist and allied health care professional visits were higher among those who received a diagnosis than those who did not (1.73, P < .001). Treating clinicians who were interviewed commented that six of the non-diagnosed and five of the diagnosed children avoided tests as a result of their genome-sequencing.[73]

We rated the quality of the evidence as very low (Appendix 4, Table A5), downgrading for risk of bias, indirectness, and imprecision.

Clinical Impact of Diagnosis on Families

The focus of genome-wide sequencing is on people with symptoms; however, families are also affected, especially when trio testing is conducted. This impact on families was reported in seven studies (Table 8).

Table 8: Number of Clinical Utility Activities Affecting Families

Author, Year	Family Planning	Additional Screening, Testing, or Surveillance	Total Impact on Family	Ratio of Impact to Sample Size (%)
Bick et al, 2017[64]	--	8	8	36
Iglesias et al, 2014[74]	5	--	5	4
Srivastava et al, 2014[62]	27	1	28	36
Stark et al, 2016[54]	28	12	40	50
Tan et al, 2017[75]	2	--	2	5
Thevenon et al, 2016[68]	4	--	4	9
Valencia et al, 2015[60]	--	1	1	3

Ongoing Studies

We are aware of one Canadian (Ontario-based) ongoing study focused on improving diagnostics and care for rare diseases (Care4Rare study http://www.cheori.org/EN/care4rare).

We are also aware of 10 potentially relevant studies registered in clinicaltrials.gov (Table 9). As well, we are aware of one relevant systematic review that has been drafted but not yet accepted for publication at the time of writing.[76]

Table 9: Known Relevant Ongoing Studies From ClinicalTrials.gov

Study Name	ClinicalTrials.gov Identifier
Rapid Whole-Genome Sequencing Study (rWGS)	NCT03385876
Whole-Genome Sequencing in the Neonatal Intensive Care Unit	NCT03721458
Diagnostic Odyssey: Whole-Genome Sequencing (WGS)	NCT03458962
NICUSeq: A Trial to Evaluate the Clinical Utility of Human Whole-Genome Sequencing (WGS) Compared to Standard of Care in Acute Care Neonates and Infants (NICU-Seq)	NCT03290469
Adult Patients With Undiagnosed Conditions and Their Responses to Clinically Uncertain Results From Exome Sequencing	NCT03605004
Whole-Genome Sequencing in the Detection of Rare Undiagnosed Genetic Diseases in Children in China	NCT03424772
Dual Guidance Structure for Evaluation of Patients With Unclear Diagnosis in Centers for Rare Diseases (ZSE-DUO)	NCT03563677
Diagnostic Research in Patients With Rare Diseases—Solving the Unsolved Rare Diseases (DiRiP-RD)	NCT03491280
Evaluate and Understand Preferences and Representations in Families of Patients With Regard to High-Throughput Sequencing Technology for Diagnostic Purposes	NCT02814747
Next-Generation Sequencing Diagnostics—On the Road to Rapid Diagnostics for Rare Diseases (NextGen-SE)	NCT02588638
Clinical and Genetic Evaluation of Individuals With Undiagnosed Disorders Through the Undiagnosed Diseases Network	NCT02450851

All information in the table was accurate on clinicaltrials.gov as of April 10, 2019.

Discussion

Results showed that genome-wide sequencing has a higher diagnostic yield than standard genetic testing of chromosomal microarray and targeted genes or gene panels for people who have unexplained developmental disabilities or multiple congenital anomalies. The yield for whole genome sequencing was observed to be similar to that of whole exome sequencing. Most people who are tested have only modest changes to their care, for both active medical management activities as well as monitoring and long-term clinical management.

The quality of the body of evidence assessed using GRADE was very low owing to the limitations of risk of bias, indirectness, and precision. The body of evidence was downgraded because of the learning effect, whereby experiences of people seen later in a study period would differ from experiences of people seen earlier because assessors would learn from the earlier cases. We also presume that improved yield will lead to improved outcomes. However, many symptoms would already be clinically managed, and a diagnosis alone would not change the path of developmental disability. We examined clinical utility measures, such as effect on medications or treatment, but again the GRADE assessment was evaluated as very low, so we have very little confidence in the estimate, and the true effect could be different from the body of evidence as we were able to report it.

This review used other systematic reviews to identify primary studies. We could be missing some primary studies, as we relied on the search strategy and manual review conducted by others. To minimize potential bias in any single systematic review, we included all relevant primary studies across all identified systematic reviews. We also searched reference lists and undertook a grey literature search to identify additional primary studies. We conducted an update to the grey literature search and found a scoping review whose findings aligned with

ours.[77] We also consulted our clinical experts, who confirmed we have likely captured the body of evidence on this topic and have not missed any known pivotal studies likely to change our conclusions.

Subgroup analyses explored factors that might influence diagnostic yield. The way the primary studies reported their results meant we were unable to distinguish results by subpopulations based on symptoms or suspected diagnosis. Nor were we able to conduct subgroup analyses by age. While we did not exclude studies in adults, most studies were biased toward children. Even among studies that included adults, average age of participants was below 18 years of age. However, this likely represents the Ontario context, as most developmental disability appears in childhood. We did not explore the impact of consanguinity (children of related parents). Children from consanguineous relationships have a higher risk of congenital anomalies.[12] Our review included studies with a range of consanguinity rates (up to 100%); however, we did not suspect these studies skewed the overall results, given their size relative to the whole body of evidence.

The ability of a laboratory to identify a variant as pathogenic or likely pathogenic could vary by procedures and sequencing platforms used. As well, analysis of genomic data is open to interpretation. The sequencing is automated, and algorithms exist to help identify notable mutations; however, highly specialized skills are required to interpret the data. Specialists, including bioinformaticians, genome analysts, and clinicians, are sometimes required to make judgment calls in their interpretation of the data.[13] Diagnostic yield is also dependent on the field of knowledge at the time of testing. The same group of people could have a different yield a year later because of new genetic discoveries. We observed the lowest diagnostic yield of 16% in a very focused population with movement disorders in an older study from 2013.[53] The study with the highest diagnostic yield of 73% included infants who had very little or no previous testing because of their youth and degree of illness, thus the most substantial opportunity for finding a diagnosis.[46] As the technology becomes more widely known, we could see referral creep of clinicians referring a broader spectrum of patients to get tested, which could cause flattening or decreasing yield given the already very heterogenous group considered.[78]

Observed mathematical heterogeneity of a relatively high I^2 statistic was not considered a cause of concern for meta-analyses conducted in this report. The I^2 is a calculation of sampling variability among the studies, and in our analysis reflects what we know from the clinical perspective: that a heterogenous group is being selected for testing. However the τ^2, which calculates the variability in between-study effect estimates and is the preferred estimate of heterogeneity, demonstrates low between-study variability (Figure 2, $\tau^2 = 0.1$).[33] Given how diagnostic yield is calculated, it cannot be lower than 0, and so there is no inconsistency in the direction of the effect.[32] Consequently meta-analysis was conducted only as a single-arm summary estimate, and sampling heterogeneity was listed as a limitation with the reported GRADE.

Finally, experts in the field assume that increases in known causal genes will be ongoing. Some studies suggest periodic re-analysis of genome information to account for the improved bioinformatics. Studies have found that, when genome-wide sequencing was reanalyzed 1 to 2 years after initial use, it yielded an additional 10% to 15% of diagnoses.[78-80] Before widespread use of reanalysis, we would need to evaluate the optimal frequency for cost-effectiveness of gains as well as the requirements to store and analyze the mass of electronic data indefinitely. Ethical implications and expectations would need to be considered by any group undertaking re-analyses.

There are several barriers to implementing and delivering a genome-wide sequencing program, including difficulties analyzing, managing, and storing the huge amounts of data amassed, which is particularly relevant for whole genome data. However, there are additional operational considerations, such as the referral process for genetic testing and communicating the complex information to patients and families.[81] There could be delays in processing a test, and an increased chance for error among tests flagged for rapid assessment.[81] These and many other limitations must be considered as any genome-wide sequencing program is developed.

Conclusions

Genome-wide sequencing for people with unexplained developmental disabilities or multiple congenital anomalies has a diagnostic yield of 37%, but we are very uncertain about this estimate (GRADE: Very Low). The yield for whole genome sequencing was observed to be similar to that of whole exome sequencing. Compared with standard genetic testing, genome-wide sequencing could have a higher diagnostic yield (GRADE: Low).

We found no evidence on how genome-wide sequencing affects long-term patient outcomes. However, for some people, genome-wide sequencing can prompt changes to active medical management as well as monitoring and long-term clinical management, but we are very uncertain (GRADE: Very Low).

ECONOMIC EVIDENCE

Research Question

What is the cost-effectiveness of genome-wide sequencing (including whole exome and whole genome sequencing) compared with standard testing in people with unexplained developmental disabilities or multiple congenital anomalies?

Methods

Economic Literature Search

We performed an economic literature search on January 17, 2019, for studies published from January 1, 2008, until the search date. To retrieve relevant studies, we developed a search using the clinical search strategy with an economic and costing filter applied. In addition to the databases used for the clinical search, we also used the Ovid interface in the Cochrane Central Register of Controlled Trials.

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. The grey literature search was updated May 3, 2019. See Clinical Literature Search, above, for further details on methods used, and Appendix 1 for literature search strategies, including all search terms.

Eligibility Criteria

Inclusion Criteria

- English-language full-text publications
- Studies in people with unexplained developmental disabilities or multiple congenital anomalies
- Studies comparing genome-wide sequencing (both whole exome and whole genome sequencing) to any other diagnostic testing
- Studies comparing both the costs and outcomes (e.g., quality-adjusted life years [QALYs], life years, diagnostic yield, number of variants, number of diagnoses, number of people whose clinical management is changed by a diagnosis, incremental cost-effectiveness ratio [ICER])
- Cost–utility, cost-effectiveness, cost–benefit, or cost–consequence analyses

Exclusion Criteria

- Narrative reviews, letters/editorials, case reports, commentaries, conference abstracts, posters, unpublished studies
- Studies of next-generation sequencing–based broad gene panels

Literature Screening

A single reviewer conducted an initial screening of titles and abstracts using Covidence[29] and then obtained the full texts of studies that appeared eligible for review according to the inclusion criteria. This reviewer then examined the full-text articles and selected studies eligible for

inclusion. The reviewer also examined reference lists for any 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, interventions, comparators)
- Outcomes (e.g., health outcomes, costs, ICERs)

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.[82] 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 that we found to be directly applicable.

Results

Economic Literature Search

The database search yielded 464 citations published from January 1, 2008, until January 17, 2019. We identified 28 additional studies from other sources, for a total of 375 studies, after removing duplicates. We excluded a total of 338 articles on the basis of information in the title and abstract. We then obtained the full text of 37 potentially relevant articles for further assessment. Eight studies met the inclusion criteria. Figure 5 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the economic literature search.

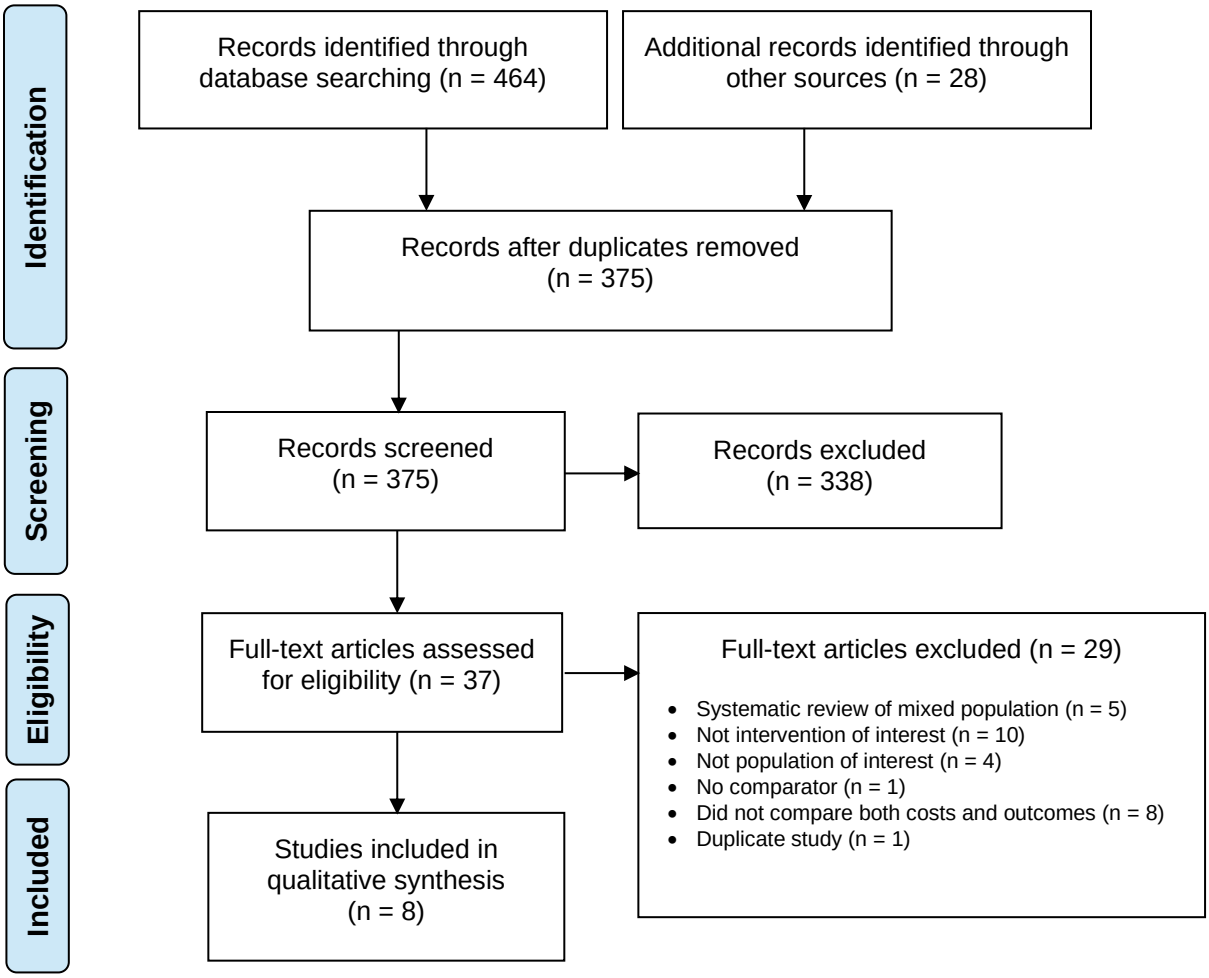

Figure 5: PRISMA Flow Diagram—Economic Search Strategy

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.
Source: Adapted from Moher et al.[42]

Overview of Included Economic Studies

We summarized the characteristics and results of the eight included studies in Table 10. The studies evaluated the use of genome-wide sequencing in people with a variety of developmental disabilities or multiple congenital anomalies, such as intellectual disability, developmental delay, muscle diseases, and neurodevelopmental disorders. Study populations were mostly children, and only one study included both children and adults.[79] Two studies were from Canada,[83,84] and the remaining six were from Australia[85-88] and the Netherlands.[55,89] One study used a hospital perspective and included the costs of genomic diagnostic tests only.[90] The other seven studies used a health care payer perspective and included broader categories of costs, such as all diagnostic tests and procedures or genetic consultation and counselling.[84-88,91,92] All eight studies were cost-effectiveness analyses, six of which were based on cost and diagnostic yield data collected directly from prospective or retrospective cohort studies.[85-88,91,92] One Ontario study used a simple decision-analytic model,[90] and another study in British Columbia used both a simple decision-analytic model and empirical estimates from a study.[84]

Only one study evaluated whole genome sequencing[90]; the others investigated whole exome sequencing.[84-88,91,92] Most whole exome sequencing studies did not evaluate the actual use of whole exome sequencing in a clinical cohort but rather estimated the cost and diagnostic yield of whole exome sequencing in hypothetical alternative diagnostic pathways.[84-88,91,92] All but one study[84] included standard testing (traditional diagnostic pathway) as a comparator, but the definition of standard testing varied across studies. One study[90] considered chromosomal microarray (the current first-tier test) as standard care, while other studies defined chromosomal microarray as prior genetic and non-genetic investigations and determined its cost via retrospective chart reviews.[84-88,91,92]

All included studies used diagnostic yield as the effectiveness outcome measure and reported the cost-effectiveness result as incremental cost per additional molecular diagnosis (diagnosis made based on genetic test results). However, it was difficult to compare the results across studies because these studies differed greatly in patient population (e.g., clinical presentations, number of prior tests, and types of prior tests), study design, analytic approach, comparator (i.e., definition of what constitutes standard testing), and interventions (e.g., how genome-wide sequencing is used, proband vs. trio testing, and at which tier). In general, genome-wide sequencing led to more diagnoses than standard testing. Diagnostic yields ranged from 28% to 79% for whole exome sequencing, 34% to 36% for whole genome sequencing, and 0 to 46% for standard testing. The per-patient cost of standard testing varied greatly across studies, ranging from $825 (2019 CAD) to $16,409 (2015 USD). This variation was caused by each study defining standard testing differently, including different cost components, and using different costing approaches. Overall, the studies found that, when using whole exome sequencing near the end of the diagnostic pathway, the per-patient cost was usually higher than standard testing. The resulting ICER ranged from $4,372 to $13,510 (2016 USD) per additional molecular diagnosis. When using whole exome sequencing early in the diagnostic pathway, the per-patient cost might be reduced or even lower than standard testing (cost-saving), depending on assumptions regarding which tests could be omitted. The cost calculations (e.g., which tests and procedures were avoided) were not clearly described in most of these studies.

Three of the included studies described the diagnostic odyssey of patients with unexplained developmental disabilities or multiple congenital anomalies.[75,89,93] Mean duration of the diagnostic odyssey ranged from 6.0 to 7.7 years.[75,89] Tan et al[75] reported that patients had a mean of 19 tests and 4 clinical genetics and 4 non-genetics specialist consultations per person, and 59% (26 of 44) underwent a procedure involving general anesthetic for diagnostic

purposes. Vissers et al[55] found that, on average, patients had 23.3 physician-patient contacts, and an extensive diagnostic workup including various imaging methods (n = 4.1); neurophysiology examinations (n = 2.2); genetic testing (n = 5.4 tests); metabolic assays (n = 0.5); basic clinical chemistry tests of blood, urine, and spinal fluid (n = 54.7); and other laboratory tests (n = 2.2). The total cost of the standard diagnostic pathway was estimated to be €10,685 per patient (95% confidence interval [CI] €9,544–€11,909, 2016 Euro), 39% of which comprised genetic testing. Monroe et al[89] found that, on average, patients had 61 visits with health care professionals; most of these were visits to see a medical professional (e.g., a medical specialist, nurse, or physiotherapist), with a mean cost of $3,012 (2015 USD). Patients underwent imaging, mostly x-ray and magnetic resonance imaging (n = 16 times, mean cost = $1,439). Each patient had an average of seven genetic tests, with a mean cost of $6,588 (range $2,183–$20,476). An average of six metabolic tests were performed per patient, with a mean cost of $2,818 and mean biochemical investigation costs of $2,034. The mean total cost of the traditional diagnostic trajectory was estimated to be $16,409 per patient (range $6,343–$47,841), of which 42% was generated by genetic testing.

We also extracted cost estimates for whole exome and whole genome sequencing from the included studies (Table 11). Only two studies determined the costs using a microcosting or bottom-up approach,[83,84] while the others used commercial prices. To help compare across studies, we converted the cost estimates into Canadian dollars using exchange rates and then inflated to 2019 value using consumer price indices from Statistics Canada.[3] Cost estimates ranged from $1,568 to $3,808 per sample for whole exome sequencing of a proband; $3,143 to $6,899 per sample for whole exome sequencing in trio testing; $3,350 to $4,274 per sample for whole genome sequencing of a proband, and $6,556 to $8,096 per sample for whole genome sequencing in trio testing. Although studies were published in different years and countries, cost estimates for whole exome sequencing were similar over time and across regions.

Table 10: Summary of Economic Literature Review Results

Author, Year, Country of Publication	Analytic Technique, Study Design, Perspective, Time Horizon	Population	Interventions and Comparators	Results		
				Health Outcomes	Costs, $	ICER (Cost per Additional Molecular Diagnosis), $
Jegathisawaran et al, 2019, Canada (Ontario)[90]	• Cost-effectiveness analysis • Decision-analytic model • Hospital perspective • Time horizon: < 1 y	Children with congenital anomalies and developmental delay	• CMA • WGS-proband • WGS-trio	Diagnostic yield: • CMA: 8% • WGS-proband: 34% • WGS-trio: 36%	Cost per patient (2018 CAD):[a] • CMA: 825 • WGS-proband: 2,988 • WGS-trio: 6,435	• WGS-proband vs. CMA: 8,322 • WGS-trio vs. CMA: 20,039
Dragojlovic et al, 2018, Canada (British Columbia)[84]	• Cost-effectiveness analysis • Decision-analytic model • Health care payer perspective • Time horizon: unreported	Children suspected of having genetic disorders	WES after standard testing: • Trio, with a genomic consultation service to screen referrals for appropriateness • Trio, without a genomic consultation service • Proband only, with a genomic consultation service	Diagnostic yield: • WES-trio, with a genomic consultation service: 42.6% (49/115) • WES-trio, without a genomic consultation service: 34.0% • WES-proband only, with a genomic consultation service: 28.1%	Cost per patient (2016 CAD):[b] • WES-trio, with a genomic consultation service: 6,138 • WES-trio, without a genomic consultation service: 5,263 • WES-proband only, with a genomic consultation service: 5,125	• WES-trio, with a genomic consultation service vs. without: 10,174 • WES-trio vs. WES proband only: 6,986
Ewans et al, 2018, Australia[79]	• Cost-effectiveness analysis • Subset of a prospective cohort study (14 of 54) • Health care payer perspective • Time horizon: from initial symptom to receiving WES results	Children and adults with intellectual disability who had prior standard testing (n = 14)	Standard testing *Counterfactual pathways (mix of proband and trio)* • WES at clinical genetics review (original analysis) • WES at initial symptom (original analysis) • WES at clinical genetics review (12-mo reanalysis) • WES at initial symptom (12-mo reanalysis)	Diagnosis yield: • Standard testing: 0% (0/14) *Original analysis* • WES at clinical genetics review: 29% (4/14) • WES at initial symptom: 29% (4/14) *12-mo reanalysis* • WES at clinical genetics review: 43% (6/14) • WES at initial symptom: 43% (6/14)	Cost per patient (2017 USD):[c] • Standard testing: 6,742 *Original analysis* • WES at clinical genetics review: 6,918 • WES at initial symptom: 6,574 *12-mo reanalysis* • WES at clinical genetics review: 7,053 • WES at initial symptom: 6,709	• WES at initial symptom vs. standard testing: dominant (original analysis and 12-mo reanalysis) • WES at clinical genetics review vs. standard testing: 618 (original analysis); 726 (12-mo reanalysis)

Author, Year, Country of Publication	Analytic Technique, Study Design, Perspective, Time Horizon	Population	Interventions and Comparators	Results		
				Health Outcomes	Costs, $	ICER (Cost per Additional Molecular Diagnosis), $
Tan et al, 2017, Australia[75]	• Cost-effectiveness analysis • Prospective cohort study • Health care payer perspective • Time horizon: average of 19 mo	• Ambulatory children suspected of having monogenic conditions, who had CMA and no prior single-gene or panel sequencing (n = 44) • Age: 2–18 y • Male: 48%	WES after standard testing *Counterfactual pathways (proband only)* • Standard testing without WES • WES at first genetics appointment (i.e., as first-tier test) • WES at initial tertiary presentation	Diagnostic yield: • WES after standard testing: 52% (23/44) • Standard testing without WES: 0% (0/44) • WES at first genetics appointment (i.e., as first-tier test): 52% (23/44) • WES at initial tertiary presentation: 52% (23/44)	Cost per patient (2016 USD):[d] • WES after standard testing: 9,800 • Standard testing without WES: 7,515 • WES at first genetics appointment (i.e., as first-tier test): 5,349 • WES at initial tertiary presentation: 3,927	• WES after non-diagnostic standard testing vs. standard testing without WES: 4,372 • WES at first genetics appointment and WES at initial tertiary presentation vs. standard testing: dominant
Stark et al, 2017, Australia[94]	• Cost-effectiveness analysis • Prospective cohort study • Health care payer perspective • Time horizon: unreported	Infants with multiple congenital abnormalities and dysmorphic features (n = 40)	Standard testing *Counterfactual pathways (proband only)* • WES as last resort • WES replacing some investigations • WES as second-tier test (after CMA)	Diagnostic yield: • Standard testing: 17.5% (7/40) • WES-proband only as last resort: 62.5% (25/40) • WES-proband only replacing some investigations: 62.5% (25/40) • WES-proband only as second-tier test (after CMA): 62.5% (25/40)	Cost per patient (2015 AUD):[c] • Standard testing: 4,734 • WES-proband only as last resort: 8,384 • WES-proband only replacing some investigations: 5,914 • WES-proband only as second-tier test (after CMA): 3,752	• WES-proband only as last resort vs. standard testing: 8,112 • WES-proband only replacing some investigations vs. standard testing: 2,622 • WES-proband only as second-tier test vs. standard testing: dominant
Schofield et al, 2017, Australia[93]	• Cost-effectiveness analysis • Retrospective cohort study • Health care payer perspective • Time horizon: from patient referral to receiving WES results	• Children with suspected congenital muscular dystrophy or nemaline myopathy (n = 56) • Male: 53.6%	• Standard testing *Counterfactual pathways* • Targeted gene panel • WES-proband only	• Standard testing: 46% (26/56) • Targeted gene panel: 75% (42/56) • WES-proband only: 79% (44/56)	Cost per patient (2016 AUD)[e] • Standard testing: 10,491 • Targeted gene panel: 3,808 • WES-proband only: 6,077	• Targeted gene panel vs. standard testing: dominant • WES-proband only vs. standard testing: dominant

Author, Year, Country of Publication	Analytic Technique, Study Design, Perspective, Time Horizon	Population	Interventions and Comparators	Results		
				Health Outcomes	Costs, $	ICER (Cost per Additional Molecular Diagnosis), $
Vissers et al, 2017, Netherlands[55]	• Cost-effectiveness analysis • Prospective cohort study • Health care payer perspective • Time horizon: from patient referral to receiving WES results	• Children with neurological symptoms of suspected genetic origin (n = 150) • Age: 5.6 y (median) • Male: 53.3%	• Standard testing • WES after standard testing • WES as first-tier test	Diagnostic yield: • Standard testing: 7.3% (11/150) • WES after standard testing: 29.3% (44/150) • WES as first-tier test: 29.3% (44/150)	Cost per patient (2016 Euro):[e] • Standard testing: 10,685 • WES pathway: 9,956 • WES as first-tier test: 8,356	• WES pathway vs. standard testing: dominant • WES as first-tier test vs. standard testing: dominant
Monroe et al, 2016, Netherlands[89]	• Cost-effectiveness analysis • Prospective cohort study • Health care payer perspective • Time horizon: average of 6.6 y (from first hospital visit to WES)	• Children with intellectual disability referred to specialized multidisciplinary research centre (n = 17)	• Standard testing • WES-trio after standard testing	Diagnostic yield: • Standard testing: 0% (0/17) • WES-trio after standard testing: 29.4% (5/17)	Cost per patient (2015 USD)[f] • Standard testing: 16,409 • WES-trio after standard testing: 20,381[g]	WES after standard testing vs. standard testing without WES: 13,510[g]

Abbreviations: AUD, Australian dollars; CAD, Canadian dollars; CMA, chromosomal microarray; ICER, incremental cost-effectiveness ratio; USD, US dollars; WES, whole exome sequencing; WGS, whole genome sequencing.

Note: Costs and outcomes were not discounted in all studies.

[a]Included costs of CMA, WES, and WGS only.

[b]Included costs of genomic consultation, initial clinic visit, genome-wide test, and results discussion with family.

[c]Included costs of all diagnostic investigations and procedures, genetic consultations, and counselling.

[d]Included costs from initial presentation to tertiary services for diagnostic purposes, first clinical genetics assessment, enrollment, and WES report.

[e]Included costs of all diagnostic investigations and procedures.

[f]Included costs of all health care professional visits, hospitalizations, and all diagnostic investigations and procedures.

[g]Calculated from information presented in study.

Table 11: Unit Cost Estimates for WES and WGS in Literature

Author, Year, Location	Cost for Proband		Cost for Trio Testing		Costing Approach	Cost Components
	Original Currency	2019 CAD (Platform if Available)[a]	Original Currency	2019 CAD (Platform if Available)[a]		
WES						
Jegathisawaran et al, 2019, Canada (Ontario)[90]	--	$1,960 (HiSeq 2500) $1,981 (NextSeq 550)	--	$3,143 (HiSeq 2500) $4,072 (NextSeq 550)	Microcosting (opportunity cost[b])	Labour, large equipment, small equipment, supplies, follow-up, bioinformatics, overhead
Dragojlovic et al, 2018, Canada (British Columbia)[84]	$3,707 (2016 CAD)	$3,808	$4,706 (2016 CAD)	$4,834	Microcosting (mix of opportunity cost[b] and price)	Sample acquisition and preparation, sequencing (external vendor), bioinformatics analysis, interpretation, Sanger confirmation, and clinical laboratory report
Ewans et al, 2018, Australia[79]	$1,200 (2017 USD)	$1,568	$3,150 (2017 USD)	$4,117	Price from lab	NA
Tan et al, 2017, Australia[75]	$2,000 (2016 AUD)	$2,019	--	--	Price from lab	NA
Stark et al, 2017, Australia[94]	$2,000 (2015 AUD)	$2,103	--	--	Price from lab	NA
Schofield et al, 2017, Australia[93]	$2,600 (2016 AUD)	$2,526 (HiSeq 2000 or 2500)	$7,100 (2016 AUD)	$6,899 (HiSeq 2000 or 2500)	Price from lab	NA
Vissers et al, 2017, Netherlands	€1800 (2016 Euro)	$2,643	€3500 (2016 Euro)	$5,139	Price from lab	NA
Monroe et al, 2016, Netherlands[89]	--	--	$3,972 (2015 USD)	$5,356 (HiSeq 2500)	Estimated from previous studies	Patient registration and blood draw, DNA isolation, sample preparation, exome enrichment, sequencing, interpretation, reporting of results, data storage, and infrastructure
WGS						
Jegathisawaran et al, 2019, Canada (Ontario)[90]	--	$3,350 (HiSeq X)	--	$6,556 (HiSeq X)	Microcosting	Labour, large equipment, small equipment, supplies, follow-up, bioinformatics, overhead
Ewans et al, 2018, Australia[79]	$3,270 (2017 USD)	$4,274	$6,195 (2017 USD)	$8,096	Price from lab	NA

Abbreviations: AUD, Australian dollars; CAD, Canadian dollars; NA, not applicable; USD, US dollars; WES, whole exome sequencing; WGS, whole genome sequencing.
[a]All costs were converted to 2019 CAD using exchange rate drawn from literature ($1 USD = $1.2957 CAD,[95] €1 = $1.1032 USD,[89] $1 AUD = $0.78 USD[94]) and then adjusted for inflation using consumer price index from Statistics Canada (2019 = 128.1; 2017 = 127; 2016 = 124.7; 2015 = 123.1).[3]
[b]Hospital could have used resources for another activity.

Applicability of the Included Studies

Results of the applicability checklist for included studies are presented in Appendix 7. Only one model-based study in Ontario[83] was deemed partially applicable to our research question. Others were considered inapplicable because they were not conducted for Ontario or they included only a subset of our population of interest. In addition, these cost-effectiveness analyses were conducted alongside a cohort study with small sample size, rather than based on a decision model. Given the heterogeneity of patient populations and diagnostic pathways, the cost-effectiveness observed within these studies might not be generalizable to Ontario.

Jegathisawaran et al[83] is an update of a previously published microcosting and cost-consequence analysis.[96] It was conducted from a hospital perspective in two populations in Ontario: children with congenital anomalies and developmental delay,[90] and children with autism spectrum disorders.[83] In children with congenital anomalies and developmental delay, the ICER was $8,322 for whole genome sequencing (proband only) versus chromosomal microarray alone, and $20,039 for whole genome sequencing (trio) versus chromosomal microarray alone. We could not use this analysis directly because it was not conducted from the Ontario public payer perspective and did not include all comparators of interest. We were also unable to use the analysis in children with autism spectrum disorders because it was not our population of interest.

Discussion

Our literature review showed that the economic evidence of genome-wide sequencing is starting to emerge, as this new technology is being increasingly applied in clinical practice. Despite several recent economic studies, the current economic evidence is still very limited given the methods that have been used. There were very few model-based economic evaluations, and most studies were based on cohort studies with small sample sizes (range 14–150), which might not be representative of the target patient population. The definition of standard testing varied across studies, and genome-wide sequencing strategies also varied from one study to another, making it difficult to compare the results. Very few studies evaluated the cost-effectiveness of using genome-wide sequencing at various tiers. All studies focused on molecular diagnoses only and did not consider other important outcomes, such as secondary findings and clinical utility. Included studies also did not consider the impact of time on obtaining a diagnosis.

Included studies showed that the cost-effectiveness of genome-wide sequencing depended on how it was used in the diagnostic pathway. Given its relatively high cost, it was usually performed toward the end of the diagnostic pathway and would increase the cost per patient compared with standard testing alone. However, included studies also explored several hypothetical scenarios when whole exome sequencing is used earlier. Depending on the extent to which standard testing could be avoided, the research showed that using whole exome sequencing could reduce cost or even save on costs.

A few studies suggested that offering whole exome sequencing as a first-tier test would lead to substantial cost savings by averting unnecessary conventional tests.[85-88,91] Some of the studies defined prior investigations (which did not produce a diagnosis) as standard testing and therefore set the diagnostic yield of standard testing to be 0%. Because these analyses did not include patients who could be diagnosed with standard testing, the cost-effectiveness of genome-wide sequencing in these studies is likely overestimated.

We also identified a high-quality, model-based Ontario study by Yuen et al.[97] However, we did not include this study because it investigated a different patient population, children with autism spectrum disorders. The study evaluated the cost-effectiveness of genome-wide sequencing in Ontario using a microsimulation model. The analysis compared four genomic testing strategies: 1) chromosomal microarray as first tier; 2) whole exome sequencing as second tier (i.e., use whole exome sequencing if chromosomal microarray does not identify a diagnosis) in children with syndromic features only; 3) whole exome sequencing as first tier; and 4) whole genome sequencing as first tier. Genetic testing costs were obtained directly from the Ontario microcosting study.[96] Although this study does not address our research question, we based the model structure of our primary economic evaluation on this study.

Conclusions

Our economic literature review identified eight studies that evaluated the cost-effectiveness of genome-wide sequencing. Included studies provided widely varying estimates for the cost-effectiveness of whole exome and whole genome sequencing and had limitations that made them difficult to use for our purpose. Therefore, we were unable to determine the cost-effectiveness of whole exome and whole genome sequencing from the results of the literature review.

PRIMARY ECONOMIC EVALUATION

Despite several recent economic evaluations, the cost-effectiveness of genome-wide sequencing remains unclear. This uncertainty arises from diversity in setting, patient population, perspective, and study design. Although we identified eight published cost-effectiveness analyses in the economic literature review, only one[90] was partially applicable to our research question; the others were mostly inapplicable.[84-88,91,92] Owing to these limitations, we conducted a primary economic evaluation.

Genome-wide sequencing has been increasingly applied in the clinical setting because of advances in DNA sequencing technologies. Compared with chromosomal microarray (the current first-tier test), genome-wide sequencing provides a higher diagnostic yield but at a higher cost. Decision modelling can be used to evaluate the trade-off between costs and benefits of genome-wide sequencing versus standard testing. Currently, owing to its high cost and early stage of clinical implementation, whole exome sequencing is primarily used for patients who have no diagnosis from standard testing. However, genome-wide sequencing also could be used earlier in the diagnostic pathway, either to replace or complement chromosomal microarray. One of the current challenges facing health care providers and payers is determining the most effective way of using genome-wide sequencing in people with unexplained developmental disabilities or multiple congenital anomalies.

Research Questions

Given the above considerations, we formulated the following two research questions.

1. What is the cost-effectiveness of genome-wide sequencing, *used after standard testing*, compared with standard testing for people with unexplained developmental disabilities or multiple congenital anomalies, from the perspective of the Ontario Ministry of Health?

2. What is the cost-effectiveness of genome-wide sequencing, *used at different times in the diagnostic pathway (tiers)*, compared with standard testing for people with unexplained developmental disabilities or multiple congenital anomalies, from the perspective of the Ontario Ministry of Health?

Methods

The information presented in this report follows the reporting standards set out by the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Statement.[98]

Type of Analysis

We conducted a cost-effectiveness analysis to compare the costs and outcomes associated with different genomic testing strategies. The costs and outcomes were then used to calculate the incremental cost-effectiveness ratios (ICERs).

Several outcomes were used to measure the effectiveness of each testing strategy: number of molecular diagnoses, number of positive genetic findings, and number of people whose active clinical management is changed by a diagnosis.

Number of Molecular Diagnoses

For this outcome, we included primary findings only (i.e., a variant directly related to the patient's clinical and phenotypic symptoms). We considered number of molecular diagnoses as our primary effectiveness outcome because the main purpose of using whole exome and whole genome sequencing is to obtain a molecular diagnosis for people with unexplained developmental disabilities or multiple congenital anomalies.

We considered those with pathogenic or likely pathogenic variants as having a molecular diagnosis, and those with variants of unknown significance, likely benign variants, and benign variants as having no diagnosis. By this definition, partial diagnosis is counted as a diagnosis (i.e., clinicians could continue to pursue genetic testing to explain other aspects of the phenotype[45]).

Number of Positive Genetic Findings

For this outcome, we included both primary findings and secondary findings. Secondary findings refer to genetic variants that are unrelated to the original purpose of testing but are considered clinically significant, medically actionable, and recommended by the American College of Medical Genetics and Genomics (ACMG) for reporting.[19]

Number of People Whose Active Clinical Management Is Changed by a Diagnosis

We defined change in active clinical management as modifications to medications, procedures, or treatment. We chose this outcome to reflect the clinical utility of genome-wide sequencing. Other health care activities, such as referral to specialists or lifestyle changes, were not considered a clinical management change in the economic analysis because these activities are expected to have longer-term effects on patient outcomes.

Rationale for Not Conducting a Cost-Utility Analysis

We chose not to conduct a cost-utility analysis because quality-adjusted life-year (QALY) estimation requires data seldom available for genomic technologies. The QALY estimate combines gains in both quantity and quality of life (e.g., one QALY represents a year in perfect health).[99] Canadian guidelines for economic evaluations recommend the use of QALY when possible, because it facilitates the broad comparison of various technologies and the allocation of resources across various conditions.[99] However, QALY has several limitations and is not commonly used in economic evaluations of genomic technologies.[100] First, QALY does not capture important non-health outcomes, such as personal utility (e.g., increasing feelings of control, enhancing self-knowledge, and planning for the future) and family spillover effects (e.g., effect on family members and also future generations through reproductive planning).[101-103] Second, it is difficult to estimate QALYs gained through genome-wide sequencing because the technology does not influence long-term outcomes directly, but rather via its effect on subsequent clinical management. Because the target patient population is highly heterogenous and so is the care pathway, having an earlier diagnosis does not necessarily lead to better health-related quality of life or longer survival at the population level. There are no data to estimate QALYs from changes in management that could result from a range of possible primary and secondary findings. Last, diagnostic yield is the most common outcome measure in both clinical and economic studies of genome-wide sequencing.[37,38] Therefore, we chose to use diagnostic yield as the outcome instead of QALY.[104] Non-health benefits (such as personal utility) were captured in the qualitative and quantitative evidence on patients' preferences of this health technology assessment but not in the economic analysis. Also, the unit of our analysis

was the patient with unexplained developmental disabilities or multiple congenital anomalies. We did not include effectiveness outcomes related to parents or other family members, although standard confirmatory testing and trio testing involving biological parents were captured in the cost of whole exome and whole genome sequencing.

Population of Interest

The population of interest was people with unexplained developmental disabilities or multiple congenital anomalies (all ages). On the basis of the literature, we assumed that most of the target population has developmental disabilities (with or without multiple congenital anomalies) and 10% to 13% have multiple congenital anomalies alone.[63,105] Other than this, we did not consider specific patient characteristics (i.e., age, sex, or clinical presentation) because the target population varies greatly and none of these characteristics alone affects the diagnostic pathway.

We did not conduct subgroup analyses based on age or clinical presentation because the primary clinical studies did not report the diagnostic yield in a way that would allow subgroup analyses.

Perspective

For the reference case, we conducted the analysis from the perspective of the Ontario Ministry of Health.

Interventions and Comparators

Interventions and comparators are summarized in Table 12.

Table 12: Interventions and Comparators Considered in Research Questions

Research Question	Comparators	Interventions (Assume 90% Trio for WES/WGS)	Description of Interventions
1	Standard testing	WES after standard testing	Standard testing refers to conventional testing without genome-wide sequencing (i.e., CMA ± Fragile X ± targeted single-gene tests and multi-gene panels) WES after standard testing refers to how WES is used according to the current GTAC criteria
2	Standard testing	WES after standard testing	WES after standard testing refers to how WES is used according to the current GTAC criteria
		WES as second tier	WES as second tier refers to using WES after first-tier CMA only
		WES alone as first tier	WES alone as first tier is followed by CMA as second tier if WES did not produce a diagnosis
		WES + CMA as first tier	WES + CMA as first tier refers to using WES concurrently with CMA
		WGS after standard testing	Standard testing refers to conventional testing without genome-wide sequencing (i.e., CMA ± Fragile X ± targeted single-gene tests and multi-gene panels)
		WGS as first tier	

Abbreviations: CMA, chromosomal microarray; GTAC, Genetic Testing Advisory Committee; WES, whole exome sequencing; WGS, whole genome sequencing.

For Research Question 1, the comparator is standard testing without genome-wide sequencing (Figure 6). This is based on the current guidelines,[2,106-108] which recommend chromosomal microarray and Fragile X testing as first-tier investigations for unexplained developmental disabilities. (Fragile X testing is not recommended for people with multiple congenital anomalies alone.) If there is no diagnosis, these patients may be further tested with targeted single-gene tests or multi-gene panels when indicated (e.g., MECP2 testing for female patients with developmental regression, PTEN for patients with autism and macrocephaly, intellectual disability panel). They could also receive many other tests such as biochemical or metabolic workup and neuroimaging. Therefore, standard testing could include chromosomal microarray (first-tier test for all), Fragile X (first-tier test for developmental disabilities), targeted single-gene tests, and multi-gene panels (second-tier test) in any combination. The intervention is using whole exome sequencing *after patients have no diagnosis from standard testing* (henceforth referred to as whole exome sequencing after standard testing), which represents the status quo in Ontario. Currently whole exome sequencing is available through Ontario's Out-of-Country Prior Approval Program for some patients who meet specific criteria (see Appendix 6), including having no diagnosis after chromosomal microarray and targeted gene testing.[20] In this analysis, we considered a test *third tier* if it was used after standard testing (because chromosomal microarray and Fragile X testing are *first tier*, and targeted single-gene tests and multi-gene panels are *second tier*).

For Research Question 2, the comparator is standard testing, and the interventions are genome-wide sequencing used at various tiers. Besides using whole exome sequencing after standard testing, the following testing strategies could also be relevant for clinical practice. We included whole genome sequencing because it has the potential to identify causal variants for many conditions that can be missed with other technologies. However, whole genome sequencing is still considered experimental and unproven at this time. Also, we did not consider using whole genome sequencing as a second-tier test (after chromosomal microarray results in no diagnosis) because whole genome sequencing is able to capture copy number variations (when the number of copies of a particular gene varies from one person to the next); therefore chromosomal microarray is unnecessary.

- *Whole exome sequencing as second tier*: whole exome sequencing can be used if the first-tier test, chromosomal microarray, did not identify a diagnosis
- *Whole exome sequencing alone as first tier*: whole exome sequencing can replace chromosomal microarray as the first-tier test owing to its higher diagnostic yield; if there is no diagnosis after whole exome sequencing, chromosomal microarray can be used as second-tier testing to detect copy number variations
- *Whole exome sequencing plus chromosomal microarray as first tier*: whole exome sequencing can be used in combination with chromosomal microarray to detect both single nucleotide variations (when only one nucleotide is different from one person to the next) and copy number variations
- *Whole genome sequencing after standard testing*: as technology evolves, whole genome sequencing eventually might substitute for whole exome sequencing
- *Whole genome sequencing as first tier:* whole genome sequencing can be used *as first-tier test* because it has the potential to capture all classes of genetic variation in one test

Trio Versus Proband-Only Test

In clinical practice, trio (proband and unaffected parents) is the preferred strategy for undiagnosed patients with no family history of similarly affected members, and singleton (proband only) is preferred in the context of consanguinity.[20] However, trios are not always available depending on family configuration. Data from Ontario's Out-of-Country Prior Approval Program (Laboratories and Genetics Branch, Ontario Ministry of Health, email communication, November 19, 2018) show trio testing is used 90% of the time. Therefore, in the reference case, we assumed that trio testing was used 90% of the time and the remaining 10% was proband only. In a scenario analysis, we assumed that it was 100% trio testing.

For all testing strategies, confirmatory tests are conducted when there is a positive finding by chromosomal microarray, whole exome sequencing, and whole genome sequencing. For chromosomal microarray, real-time polymerase chain reaction (qPCR) or fluorescence in situ hybridization (FISH) is usually used to confirm the results. For whole exome and whole genome sequencing, Sanger sequencing (for sequence number variations and indels) or qPCR (for copy number variations) is usually used.[83]

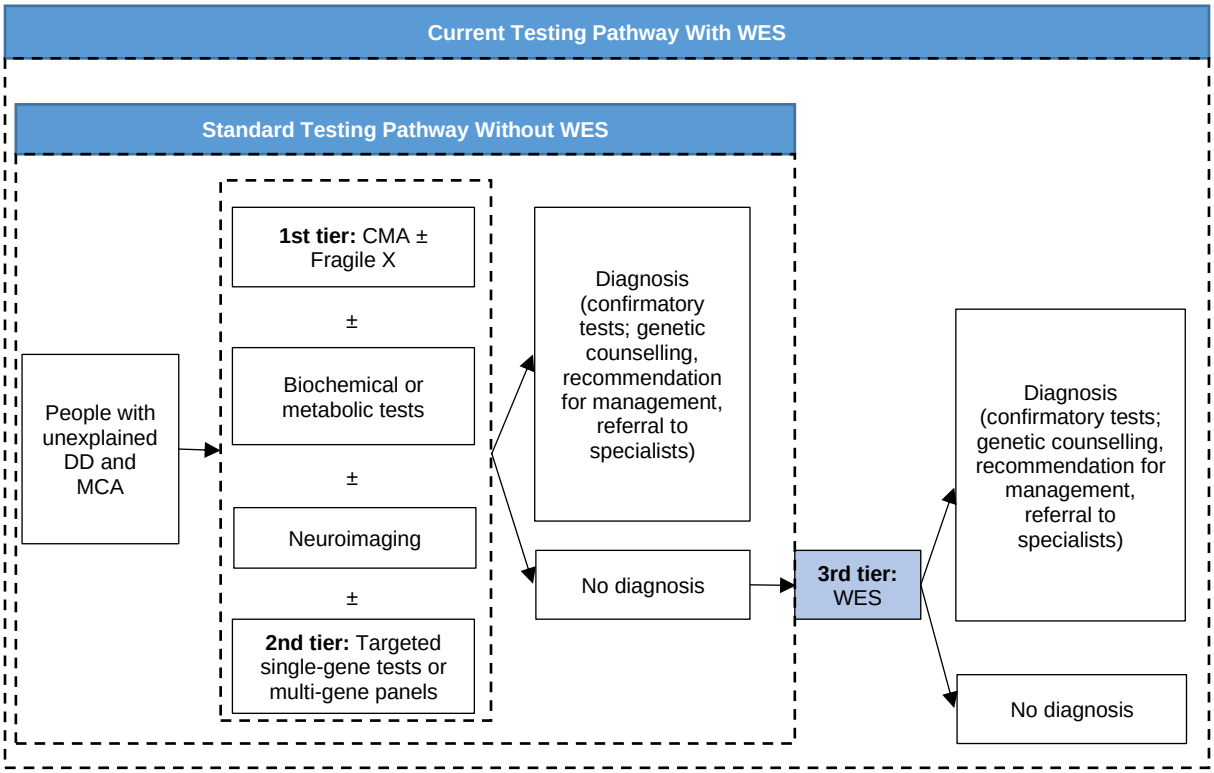

Figure 6: Standard Testing Pathway and Current Testing Pathway with WES

Abbreviations: CMA, chromosomal microarray; DD, developmental disabilities; MCA, multiple congenital anomalies; WES, whole exome sequencing.

Time Horizon

To predict the short-term effect of various testing strategies on costs and diagnostic outcomes, we used a 3-year time horizon for the reference case analysis. Patients enter the model when

they have the first appointment with a medical geneticist. We selected 3 years as a reasonable time because the wait for patients to receive positive findings from clinical genetic investigation could be long. In addition, both the wait for a medical geneticist and the turnaround time for genome-wide sequencing results are long.

One of the benefits of genome-wide sequencing is that patients might receive more timely diagnoses. Earlier diagnosis can lead to earlier intervention and potentially better long-term outcomes. Therefore, we explored how wait time and test turnaround time affect diagnostic yield by using different time horizons in scenario analyses (1 year and 4 years). The effectiveness outcome was defined as a positive finding within the model time horizon. If a positive result was not reported within the time horizon owing to delay in the health care system, it was treated as a negative finding.

Information provided by genome-wide sequencing can have long-term implications for patients. However, we did not use a long time horizon because there is limited evidence on the long-term impact of genome-wide sequencing on patient management, use of health resources, and health outcomes.

Secondary Findings

Genome-wide sequencing can generate a wide range and large volume of secondary or incidental findings. The results can reveal whether a person has medically actionable disease-causing gene variants (e.g., BRCA1, pharmacogenomic responses), higher or lower risk for common diseases, other rare genetic diseases, early onset brain diseases, or carrier status of certain genetic conditions.[109] As a result, the return of secondary findings has numerous practical and ethical implications. Currently, many laboratories conducting genome-wide sequencing have adopted policies to report only medically actionable secondary findings recommended by the ACMG (59 genes for 24 conditions).[19] The return of these secondary findings can increase downstream health care costs associated with diagnostic workup, surveillance, and prophylactic treatment while benefits to patients are uncertain. Given the lack of data, we did not include the long-term post-test costs and health consequences associated with secondary findings in this analysis, although secondary findings were included in the calculations of the number of positive genetic findings.

Discounting

In accordance with the Canadian Agency for Drugs and Technologies in Health (CADTH) guidelines,[99] we applied an annual discount rate of 1.5% to costs and outcomes that were beyond 1 year. We also explored different discount rates of 0% and 3% in sensitivity analyses.

Model Structure

We based our model structure on the diagnostic pathway in Ontario, published clinical guidelines,[2,107,108] and economic studies.[97,110] A discrete event simulation model was used to represent patients at the individual level and account for differences in wait time for genetic services and test results between testing strategies (Figure 7). We simulated a hypothetical cohort of 1,000 patients with unexplained developmental disabilities or multiple congenital anomalies. Each simulated patient was assigned to have either developmental disabilities (with or without multiple congenital anomalies) or multiple congenital anomalies only. If a patient has multiple congenital anomalies only, he or she would not receive Fragile X testing. Wait times

and test turnaround time were randomly generated from distributions estimated from published literature or in consultation with clinical experts.

In the model, the diagnostic pathway is represented by a series of sequential events. First, the patient receives the initial pre-test genetic services, which include visits with a medical geneticist and a genetic counsellor. Next, samples are taken from the patient (proband) and both parents (if available) and sent to the laboratory for genetic testing (we assumed that this happens simultaneously). The test result is returned to the ordering physician within a few weeks, depending on the turnaround time of the genetic test. Each patient can receive either a positive or negative result. For genome-wide sequencing, positive results can include primary findings only, secondary findings only, or both; negative results can include uncertain results (i.e., variants of unknown significance) or clear null findings (i.e., likely benign variants and benign variants). Results are discussed with the patient's family either in a face-to-face meeting (for positive or uncertain results) or in a telephone call (for clear null findings). If a patient has a positive result, he or she exits the model after receiving post-test genetic services. If a patient has a negative result, he or she continues with further genetic tests until the end of the testing strategy.

We developed the discrete event simulation model using TreeAge Pro 2019 (TreeAge Software, Williamstown, MA).

Main Assumptions

This model's main assumptions were as follows:

- The unit of analysis in our economic evaluation was each patient with developmental disabilities or multiple congenital anomalies. Costs of sequencing and confirmatory testing in parents were assigned to the patient for the purpose of analysis. The consequences in parents were not considered.
- We did not consider the consequences related to positive secondary findings other than post-test genetic services (genetic consultation and counselling). For example, we did not consider follow-up visits to family physicians or pediatricians generated by positive secondary findings of whole exome and whole genome sequencing.
- Fragile X syndrome is a genetic disorder caused by excessive expansion of trinucleotide repeats. Currently Fragile X syndrome is difficult to detect reliably with genome-wide sequencing.[111] Therefore, for this analysis, we assumed that at this time Fragile X syndrome cannot be detected by chromosomal microarray, whole exome sequencing, or whole genome sequencing. We included Fragile X testing as a fixed cost for people with developmental disabilities (but not for those with multiple congenital anomalies). Also, we did not count the diagnostic yield from Fragile X testing in the outcome for all testing strategies because it is very small on its own.[97]
- Biochemical and metabolic tests and neuroimaging are often conducted either for diagnosis or after diagnosis (for monitoring or for confirming the diagnosis). Given that diagnostic yields of biochemical and metabolic tests and neuroimaging alone are very small (<1%–5% and 0.2%–2.2%, respectively), their diagnostic yields were not counted in the outcome for all testing strategies and only costs of these tests were included.
- We assumed (on the basis of expert opinion) that invasive diagnostic procedures, such as muscle and skin biopsies, were likely to be averted by genome-wide sequencing.

- We assumed (on the basis of expert opinion) the following tests were unlikely to be averted by genome-wide sequencing:
  - Fragile X testing
  - Biochemical or metabolic workup
  - Neuroimaging
  - Echocardiogram
  - Electroencephalogram (EEG)
- Patients would receive in-person genetic counselling and have a clinic visit with a medical geneticist for positive primary or secondary test results (i.e., abnormal variant identified) or a proportion of negative results (e.g., variants of unknown significance).

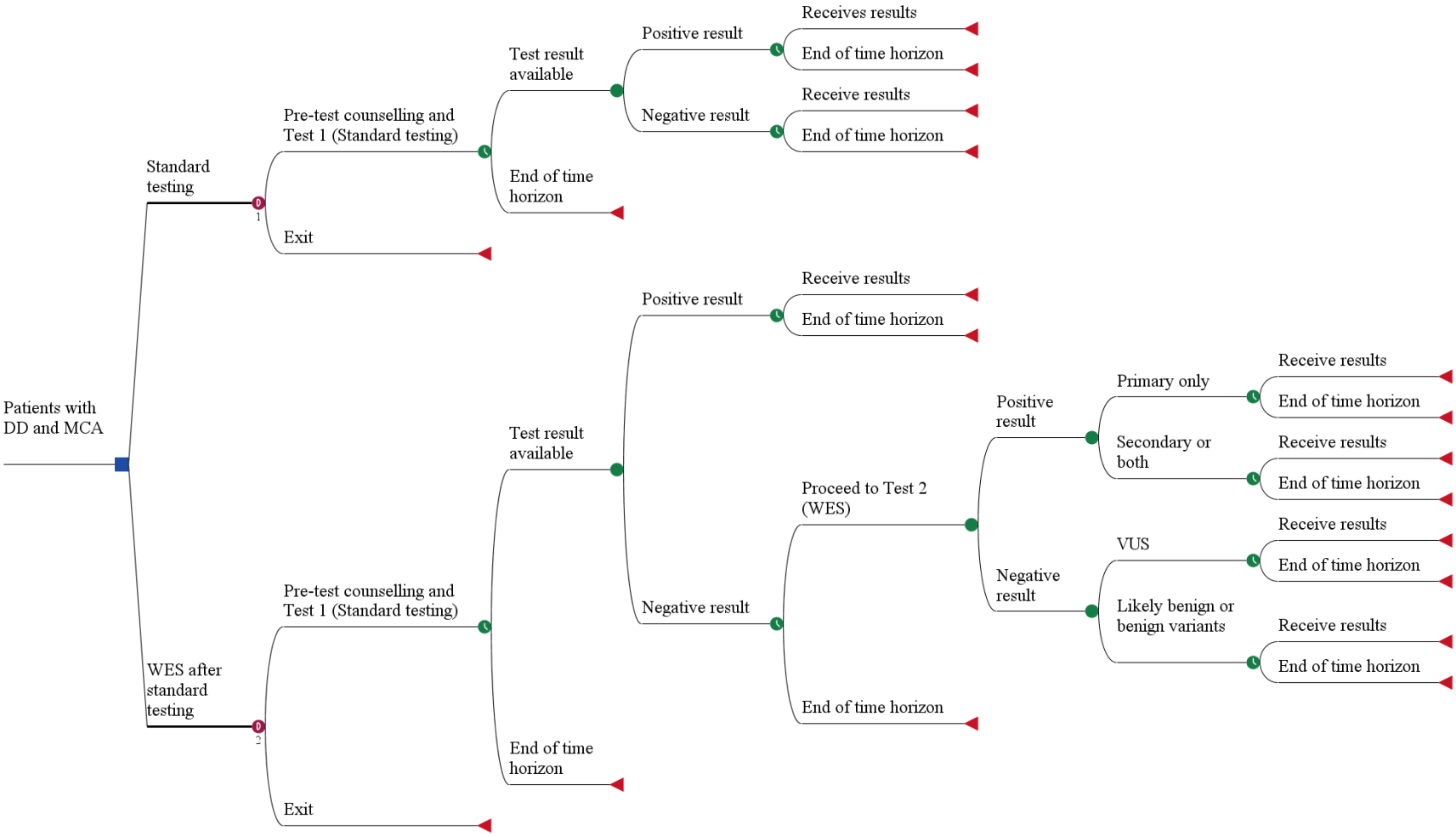

Figure 7: Model Structure

Abbreviations: DD, developmental disabilities; MCA, multiple congenital anomalies; VUS, variant of unknown significance; WES, whole exome sequencing.
Note:

- Although not explicitly shown, the sequence for other testing strategies resembles that of standard testing or WES after standard testing. We assumed that the result of one test does not influence the result of the subsequent test. We did not consider patients dropping out from testing and also did not model mortality.
- Blue squares represent a decision node, purple circles represent a discrete event simulation node, green circles represent a time node, and red triangles represent a terminal node (i.e., patient exits the model).

Clinical Parameters

Clinical input parameters were obtained from our clinical evidence review when possible (Table 13) and validated by experts to make sure that parameters reflect clinical practice (K. Boycott, April 4, 2019).

Diagnostic Yield

Because the focus of this health technology assessment was whole exome and whole genome sequencing, we did not systematically search for the diagnostic yields of chromosomal microarray and standard testing:

- To estimate the diagnostic yield of chromosomal microarray in people with developmental disabilities or multiple congenital anomalies, we conducted a summary effect estimate analysis using studies systematically identified by Miller et al[11] (Appendix 8). The weighted average yield was 0.10 (95% CI 0.09–0.12, n = 21,698, 33 studies). This is consistent with other published studies in this patient population.[2,37,66]
- Our clinical evidence review identified a total of nine studies, each of which included both genome-wide sequencing and standard testing. On the basis of these studies, we estimated the weighted average yield of standard testing to be 0.21 (95% CI 0.14–0.29, n = 992).

Diagnostic yields of genome-wide sequencing were obtained from our clinical evidence review. For whole exome sequencing, a total of 34 studies were identified and the weighted average yield was 0.37 (95% CI 0.34–0.40, n = 9,142) across various sequencing approaches and definitions for a positive result. Given the heterogeneity of included studies, we could not get reliable estimates for diagnostic yields of proband and trio testing. Many studies used a mix of proband and trio testing, and some did not report clearly whether proband or trio testing was used. For the 34 included studies of whole exome sequencing, we estimated that the proportion of trio tests was approximately 80%, which is close to the percentage of trio testing in Ontario. Clinical experts believe the diagnostic yield of trio testing is approximately 2% higher than proband-only testing for both whole exome and whole genome sequencing (W. Ungar, email communication, April 15, 2019). Because the difference in yield between proband and trio testing is relatively small, we assumed the diagnostic yield of whole exome sequencing to be the same regardless of the trio percentage, and only the cost would vary with the trio percentage. In a scenario analysis where we assumed 100% trio testing, we increased the diagnostic yield by 2%.

To address Research Question 2, we stratified the diagnostic yields of whole exome and whole genome sequencing by tiers (see the clinical evidence review). For whole exome sequencing, most studies (19 studies) evaluated whole exome sequencing as a third-tier test (after standard testing). Only five studies evaluated whole exome sequencing as a first-tier test and two studies evaluated whole exome sequencing as a second-tier test. This suggested that using whole exome sequencing late in the diagnostic pathway in the current population could lead to slightly lower yield. The same trend was observed in studies of whole genome sequencing. This is likely because, as patients undergo more tests, it results in ascertainment bias toward diagnostically more difficult cases.

- Whole exome sequencing:
  - First-tier test: 0.37 (95% CI 0.27–0.49, n = 706, 5 studies)
  - Second-tier test: 0.55 (95% CI 0.42–0.68, n = 54, 2 studies)
  - Third-tier test (i.e., after chromosomal microarray, targeted single-gene tests, or multi-gene panels): 0.33 (95% CI 0.30–0.37, n = 6,091, 19 studies)
- Whole genome sequencing:
  - First-tier test: 0.46 (95% CI 0.36–0.57, n = 295, 5 studies)
  - Third-tier test (i.e., after chromosomal microarray, targeted single-gene tests, or multi-gene panels): 0.32 (95% CI 0.24–0.42, n = 353, 4 studies)

Because the diagnostic yield of whole exome sequencing as a second-tier test was based on only two studies, it might not be representative of actual clinical practice. Therefore, for the economic model, we assumed that the yield of second-tier whole exome sequencing is between the yields of first- and third-tier whole exome sequencing (i.e., 0.35 = [0.37 + 0.33] ÷ 2).

Theoretically, whole genome sequencing can detect more genetic variation than whole exome sequencing (e.g., variants in the non-coding area). However, the current state of knowledge regarding variants outside of the exons is rather limited. Our clinical evidence review showed no overall difference in diagnostic yields between whole exome and whole genome sequencing (i.e., similar point estimates and overlapping 95% CIs) in this patient population. This finding was confirmed by clinical experts (K. Boycott, phone communication, April 4, 2019) and the literature.[37,45] However, when stratified by tiers, whole genome sequencing as first-tier test seemed to offer higher yield than whole exome sequencing as first-tier test according to five studies. This is probably because when used as first-tier test (before chromosomal microarray), whole genome sequencing is able to detect both copy number variations and sequence number variations, whereas whole exome sequencing can detect only sequence number variations. However, when used after chromosomal microarray, the diagnostic yield of whole exome and whole genome sequencing would likely be similar because chromosomal microarray would have already identified people with copy number variations. It is important to note that such comparisons must be made with caution because we lack high-quality comparative data (e.g., randomized controlled trials) and because the published studies are heterogenous (e.g., various types of clinical presentation and prior testing, proportions of trio and proband testing, proportion of consanguinity, year of publication, test platforms used). Another important consideration is that whole genome sequencing is still considered investigational.

For concurrent testing with whole exome sequencing and chromosomal microarray, we assumed the yield to be the sum of whole exome sequencing and chromosomal microarray because they detect different types of genetic variations and are considered complementary to each other (K. Boycott, phone communication, April 4, 2019).

Variant of Unknown Significance

The clinical evidence review showed variants of unknown significance were found in about 17% (95% CI 0.10–0.26, n = 1,996, 5 studies) of patients tested with genome-wide sequencing. Given limited information, we assumed that the rate would be the same for whole exome and whole genome sequencing. In a scenario analysis, we assumed that whole genome sequencing would generate more variants of unknown significance than whole exome sequencing.

Secondary Findings

Based on the clinical evidence review, the rate of medically actionable secondary findings was about 7% (95% CI 0.04–0.10, n = 4,576, 14 studies). However, according to a clinical expert (K. Boycott, phone communication, April 4, 2019), the rate of secondary findings in clinical practice might be much lower (about 2%–3%). Therefore, we conducted a scenario analysis assuming a lower rate of secondary findings.

Clinical Utility

Based on the clinical evidence review, the proportion of people whose active clinical management is changed among those who were diagnosed was 16.7%. We assumed the same rate for chromosomal microarray, whole exome sequencing, and whole genome sequencing. In a scenario analysis, we also tested different rates of clinical utility based on Clark et al.[37]

Wait Time and Test Turnaround Time

Test turnaround time and wait time for post-test genetic services were obtained from clinical experts, the Ontario Ministry of Health (Laboratories and Genetics Branch, email communication, March 26, 2019), and the websites of commercial laboratories.

Table 13: Clinical Parameters

Variables	Mean (95% CI)	Distribution	Source
Patient Characteristics			
Multiple congenital anomalies only	13%	Beta (146, 987)	Baldridge et al, 2017[63]; Wright et al, 2015[105]
Diagnostic Yield of Primary Findings			
Research Question 1			
Standard testing	0.21 (0.14–0.29)	Beta (24, 89)	Clinical evidence review (9 studies)
WES after standard testing	0.37 (0.34–0.40)	Beta (368, 626)	Clinical evidence review (34 studies)
Research Question 2			
CMA	0.10 (0.09–0.12)	Beta (154, 1,382)	Miller et al, 2010[11] (33 studies)
WES after standard testing	0.33 (0.30–0.37)	Beta (228, 464)	Clinical evidence review (19 studies)
WES as second-tier test	0.35	--	Assumed to be between WES first-tier and third-tier testing
WES alone as first-tier test	0.37 (0.27–0.49)	Beta (27, 46)	Clinical evidence review (5 studies)
WES + CMA as first-tier test	0.47	--	Assumed to be sum of yields of WES and CMA because these tests detect different genetic variations (expert opinion)
WGS after standard testing	0.32 (0.24–0.42)	Beta (33, 69)	Clinical evidence review (4 studies)
WGS as first-tier test	0.46 (0.36–0.57)	Beta (39, 46)	Clinical evidence review (5 studies)
Variant of Unknown Significance			
WES or WGS	0.17 (0.10-0.26)	Beta (14, 69)	Clinical evidence review (5 studies)
Secondary Findings			
WES or WGS	0.07 (0.04-0.10)	Beta (19, 257)	Clinical evidence review (14 studies)
Rate of Clinical Utility (Among Diagnosed Patients)[a]			
CMA, WES, or WGS	16.7%	Beta (20, 99)	OH(Q) clinical evidence review (assumed same rate for CMA, WES, and WGS)
Wait Time or Turnaround Time (weeks)			
Standard testing	120	Normal (120, 24)	Oei et al, 2017[112]
CMA test result (as first-tier testing)[b]	0	--	CMA and testing for Fragile X are usually done before referral to medical geneticist; results will be explained in the first appointment (expert opinion[d])
CMA test result (as second-tier testing)	5	Uniform (3, 7)	Yuen et al, 2018[97]
WES Test Result[b]			
• In Ontario	8	Uniform (6, 10)	Expert opinion[d]

Variables	Mean (95% CI)	Distribution	Source
• Commercial lab	8	Uniform (6, 10)	GeneDx[113]; Baylor Genetics[114]
WGS Test Result[b]			
• In Ontario	12	Uniform (10, 14)	Expert opinion[d]
• Commercial lab	12	Uniform (10, 14)	GeneDx[113]; Baylor Genetics[114]
Post-test Genetic Services[c]			
• Positive finding	3	Uniform (1, 6)	Expert opinion[d]
• Negative finding or VUS	18	Uniform (12, 24)	Expert opinion[d]

Abbreviations: CI, confidence interval; CMA, chromosomal microarray; OH(Q), Ontario Health (Quality); VUS, variant of unknown significance; WES, whole exome sequencing; WGS, whole genome sequencing.
[a]Defined as percentage of patients with a change in active clinical management (among those who have a diagnosis).
[b]Defined as time from blood draw to having lab report ready.
[c]Defined as time from receiving lab report in clinic to disclosure to family.
[d]*Source: R. Hayeems, email communication, March 22, 2019.*
Normal (μ, σ) denotes normal distribution where μ is the mean and σ is the standard deviation.
Beta (α, β) denotes beta distribution where α and β are shape parameters.
Uniform (a, b) denotes uniform distribution where a is minimum value and b is maximum value.

Cost Parameters

Cost parameters (unit prices) were obtained from standard Ontario sources and the published literature (Tables 14 and 15). All costs were reported in 2019 Canadian dollars. Where 2019 prices were unavailable, the health care component of the Canadian Consumer Price Index (CPI) was used to adjust all prices to 2019 dollars.

We included the following types of costs in our model:

- Pre- and post-test genetic consultation and genetic counselling
- Cost of chromosomal microarray, whole exome sequencing, and whole genome sequencing
- Cost of other genetic tests (e.g., Fragile X testing, targeted single-gene tests and multi-gene panels) and non-genetic diagnostic tests (e.g., biochemical and metabolic workup, neuroimaging, invasive tests and procedures, echocardiogram, electroencephalogram)

Cost of Pre- and Post-Test Genetic Services

The costs of pre-test and post-test genetic consultations (with a medical geneticist) and counselling sessions (with a genetic counsellor) were based on expert opinion (E. Goh, email communication, January 30, 2019) and the literature,[97] respectively. We assumed that patients undergoing whole exome and whole genome sequencing would receive longer pre-test and post-test genetic counselling than those undergoing chromosomal microarray because the new tests are more complex and potentially return more results. For positive or uncertain results (variants of unknown significance), we assumed that patients would receive in-person post-test consultation and counselling. For clear negative test results (i.e., no diagnosis and no variant of unknown significance), we assumed a medical geneticist would make a telephone call.

Cost of Standard Testing Pathway

We estimated the cost of the standard testing pathway with the unit prices and resource use frequencies obtained from the literature and clinical experts. The cost of the standard testing pathway was calculated as the sum of the costs of conventional genetic testing, non-genetic testing, and medical geneticist visits.

We estimated the cost of conventional genetic testing on the basis of findings from Oei et al.[112] They conducted a retrospective analysis of 420 children enrolled in complex care programs at Toronto's SickKids Hospital. Among those who underwent genetic testing (n = 319), a random sample of 20% was further analyzed. The mean cost of standard genetic testing was estimated to be $6,953 in 2015 Canadian dollars (standard deviation $8,368, range $200–$44,892) (W. Ungar, email communication, March 28, 2019). The median number of genetic tests was four (interquartile range [IQR] 2.5–7) and the median length of testing was 2.31 years (IQR 0.33–6.08). This is consistent with estimates from two other Ontario studies also conducted at the SickKids Hospital. Lionel et al[45] prospectively recruited 103 patients suspected of having genetic disorders from pediatric non-genetic subspecialty clinics. In this patient population, the median cost of conventional genetic tests was $5,173 USD (range $585–$18,361) and the median number of genetic tests was three (range 1–12). Given the study design, all patients had targeted gene sequencing and 43% had chromosomal microarray. In another prospective study, Stavropoulos et al[62] recruited 100 patients referred to a pediatric

genetics service who met the criteria for chromosomal microarray.[66] The number of genetic investigations received by patients before chromosomal microarray ranged between three and six tests at a total cost of $3,325 to $5,280.

We also estimated the costs of non-genetic testing. Resource use frequencies were obtained from clinical experts (E. Goh, email communication, January 30, 2019; K. Boycott, phone communication, May 27, 2019). We estimated that 55% of patients would receive biochemical or metabolic workup, 40% would receive neuroimaging, 35% would receive an electroencephalogram, 2.5% would receive invasive procedures (such as skin and muscle biopsies), and 3% would receive an echocardiogram.

Last, we estimated the cost of physician visits associated with conventional genetic testing. According to clinical experts, conventional genetic tests are usually ordered sequentially and approximately three medical geneticist visits are needed to order these tests and go over the results with patients (E. Goh, email communication, March 6, 2019; K. Boycott, phone communication, May 27, 2019). Biochemical and metabolic tests are usually ordered along with the genetic tests and therefore no separate physician visits are needed.

Whole Exome Sequencing Costs to Out-of-Country Prior Approval Program

The current cost of whole exome sequencing to the Ontario Ministry of Health (by commercial laboratories) was obtained from Ontario's Out-of-Country Prior Approval Program, and this cost was used in the reference case analysis (Laboratories and Genetics Branch, Ontario Ministry of Health, email communication, November 19, 2018). The average per-person cost across all types of whole exome sequencing (proband, duo, trio) was $5,200 USD in fiscal year (FY) 2015/16 and decreased to $3,500 USD in FY 2017/18, although the cost of test per person ranged up to $11,600 in FY 2015/16 and up to $9,000 in FY 2017/18. It is important to note that these were charges, typically with an embedded mark-up, rather than the commercial laboratory's true opportunity cost. The per-test costs were trending downward, likely reflecting the decreased costs of sequencing in general and greater competition due to greater volumes of whole exome sequencing. According to the Ontario Ministry of Health, the pricing structure for FY 2017/18 is anticipated to remain valid through FY 2018/19, although the overall reimbursement amount can be expected to increase as clinical demand increases. The full cost of testing is currently covered by the Ontario Ministry of Health, while the cost of sample shipping, processing, storage, and handling is paid by the sending institution or laboratory.

Whole Exome and Whole Genome Sequencing Costs in Ontario Laboratories

The unit costs for chromosomal microarray, whole exome sequencing, and whole genome sequencing in Ontario were obtained from a recently published Ontario microcosting study by Jegathisawaran et al.[90] The opportunity costs (costs foregone when an alternative is chosen) of testing were based on laboratory practices at the SickKids Hospital. The study included the full array of laboratory-related costs from blood draw to reporting laboratory results to the ordering physician. Major cost categories for all three tests included labour (e.g., DNA sample preparation and processing, clinical interpretation, and report writing), equipment (e.g., array or sequencing machine, service contract), supplies (e.g., reagents, shipping and handling of DNA samples), and confirmatory testing (i.e., for positive and inconclusive results in the proband and parents). Bioinformatics-related costs (e.g., labour, maintenance, file storage, and computation) are included for whole exome and whole genome sequencing. The study did not include training and start-up costs or costs of validation testing (which are usually performed by laboratories periodically for calibration and quality control). It is important to note that the analytic, computation,

bioinformatics, and interpretation costs associated with secondary genetic targets are already built into the cost of whole exome and whole genome sequencing in the microcosting models developed at SickKids,[83] even if secondary findings are not disclosed to patients.

The test cost was expected to vary by institution (e.g., various laboratory practices, various microarray or sequencing platforms and reagents, various number of sequencers procured, various volumes of tests for all indications, and for the target indication conducted per year). Therefore, we conducted extensive sensitivity analyses over a range of plausible values recommended by experts. The local costs of whole exome sequencing (using the HiSeq 2500 and NextSeq 550 platforms) were used in scenario analyses.

Post-test Costs

We also explored post-test costs in a scenario analysis. Very few studies have reported the costs of downstream clinical activities after genome-wide sequencing. A recent Ontario study by Hayeems et al[36] found that, in children with developmental delay, within 1 year of disclosure of chromosomal microarray and whole genome sequencing results, the distribution of cost was highly skewed. The mean post-test cost (in 2016 Canadian dollars) was $136 (median $0, range $0–$3,595) for chromosomal microarray if there is no diagnosis, $77 for whole genome sequencing if there is no diagnosis (median $0, range $0–$4,826), and $180 for diagnostic whole genome sequencing (median $0, range $0–$1,212).[36] Ongoing care accounted for 88.6% of post-test activities. The type of health care activities differed by test: chromosomal microarray promoted additional diagnostic investigations while whole genome sequencing promoted tailored care guided by genotypic variants.

Table 14: Cost per Test for CMA, WES, and WGS (in 2019 Canadian Dollars)

Cost Category	CMA	WES-HiSeq 2500 (Proband)	WES-NextSeq 550 (Proband)	WES-HiSeq 2500 (Trio Testing)	WES-NextSeq 550 (Trio Testing)	WGS-Proband HiSeq X	WGS-Trio HiSeq X
	In Ontario: Used in Scenario Analysis, $[a]						
Labour	151.3	506.3	499.8	688.5	656.4	464.7	473.7
Large equipment	50.1	385.5	115.1	128.5	38.4	583.6	194.6
Small equipment	NA	8.8	8.8	2.9	2.9	8.8	2.9
Supplies	501.2	643.2	1,002.7	1,929.6	3,008	1,367.5	4,099.9
Confirmatory genetic testing[b]	76.9	155.4	155.3	31.1	31.1	177	96.2
Bioinformatics	NA	49.1	49	147.1	147.2	419.4	1,258.3
Overhead	44.9	211.8	150	215.7	188.4	329.3	430.3
Total (95% CI)	825 (789, 859)	1,960 (1,899, 2,020)	1,981 (1,909, 2,054)	3,143.4 (3,052.9, 3,233.9)	4,072.3 (3,922.6, 4,222.5)	3,350 (3,234, 3,467)	6,556 (6,278, 6,832)
	Out of Country[c]: Used in Reference Case Analysis, $[d]						
	WES (90% trio)						
Cost of testing	4,535.0 (3,500 USD)						
Cost of sample shipping, processing, storage, handling[e]	54.4 (42 USD)						
Total cost per sample	**4,589.4 (3,542 USD)**						

Abbreviations: CI, confidence interval; CMA, chromosomal microarray; WES, whole exome sequencing; WGS, whole genome sequencing.

[a]*Source: J. Jegathisawaran, email communication, April 16, 2019*.

[b]Refer to confirmatory testing of positive and inconclusive results in the proband and in parents (or fluorescence in situ hybridization and real-time polymerase chain reaction (qPCR) for CMA; Sanger sequencing and qPCR for WES and WGS).

[c]*Source: Ministry of Health; Purolator (personal communication, November 19, 2018).*

[d]Exchange rate: $1 USD = $1.2957 CAD (Bank of Canada[95]).

[e]Cost based on estimates provided by Trillium Health Partners (E. Goh, MD, email communication, March 7, 2019).

Table 15: Resource Use and Cost Parameters (Costs in 2019 Canadian Dollars)

Parameters	Mean	Distribution	Source and Assumptions
Standard Testing: Patients Receiving Non-genetic Investigations or Procedures			
Biochemical/metabolic workup	55%	Fixed	Expert opinion: 20%–90%
Neuroimaging (brain MRI)	40%	Fixed	Expert opinion: 30%–50%
Invasive tests (muscle biopsy)	2.5%	Fixed	Expert opinion: 0–5%
Echocardiogram	3%	Fixed	Expert opinion: 1%–5%
Electroencephalogram	35%	Fixed	Expert opinion: 20%–50%
Cost of Genetic and Non-genetic Diagnostic Tests			
CMA	$825	Gamma (2,010, 2.44)	Jegathisawaran et al, 2019[90]
WES (90% trio)	$4,589.4	Normal (4,589.4, 45)	Based on average price paid by OOC Prior Approval Program
WGS (90% trio)	$6,235.4	--	Weighted average based on Jegathisawaran et al, 2019[90]
• WGS proband	$3,350	Gamma (3,202, 0.96)	Jegathisawaran et al, 2019[90]
• WGS trio	$6,556	Gamma (1,992, 0.30)	Jegathisawaran et al, 2019[90]
Standard genetic testing			
• Test cost	$7,235.4	Lognormal (8.40, 0.95)	Oei et al, 2017[112]
• Physician cost	$448.2	Fixed	Cost per visit based on OHIP SOB (K222); assumed 6 medical geneticist visits on average based on clinical expert opinion
Fragile X testing	$333.9	Normal (333.9, 2.6)	Yuen et al, 2018[97] (for patients with developmental disabilities only)
Biochemical or metabolic workup	$528.0	Normal (528, 53)	Bélanger and Caron, 2018[2]
Neuroimaging (brain MRI)			
• Test cost	$771.6	Normal (771.6, 77)	Ontario Case Costing Initiative 2017
• Physician fees	$73.35	Fixed	OHIP SOB (X421)
Invasive procedures			
• Muscle biopsy	$748.2	Normal (748.2, 75)	Rosenberg et al, 1993[115]
• Physician fees	$48.65	Fixed	OHIP SOB (L864)
• Skin biopsy	$404.6	Normal (404.6, 41)	Joshi et al, 2016 ($379)[116]
• Physician fees	$48.65	Fixed	OHIP SOB (L864)
Echocardiogram			
• Test cost	$412.9	Normal (412.9, 41)	Medical Advisory Secretariat 2010[117]

Parameters	Mean	Distribution	Source and Assumptions
• Physician fees	$204.05	Fixed	OHIP SOB (G570, G571, G572)
Electroencephalogram			
• Test cost	$831.1	Normal (831.1, 83)	Green et al, 1985[118]
• Physician fees	$47.55	Fixed	OHIP SOB (G414, G415)
Pre-test Genetic Services			
Medical geneticist (cost per session)			OHIP SOB (A225 for 1st session; K222 x 2 for 2nd session); Yuen et al, 2018 (CMA: 1 session only; WES/WGS: 90% have 1 session, and 10% have 2 sessions)[97]
• 1st session (assume 1 h)	$165.0	Fixed	
• 2nd session (assume 1 h)	$149.4	Fixed	
Genetic counsellor (cost per session; assume 1 h)	$41.2	Fixed	Yuen et al, 2018 (CMA: 1 session only; WES/WGS: 90% have 1 session, and 10% have 2 sessions)[97]
Post-test Genetic Services			
Positive finding or VUS (cost per session)			
• Medical geneticist (assume 1 h)	$149.4	Fixed	OHIP SOB (K222 x 2 for 1-h session)
• Genetic counsellor (assume 1 h)	$41.2	Fixed	Yuen et al, 2018 (if secondary finding is identified)[97]
Negative finding	--	--	Expert opinion: negative results are usually communicated by phone with medical geneticist; no clinical visit is needed

Abbreviations: CMA, chromosomal microarray; MRI, magnetic resonance imaging; OHIP SOB, Ontario Health Insurance Program Schedule of Benefit; ON, Ontario; OOC, Out-of-Country; VUS, variant of unknown significance; WES, whole exome sequencing; WGS, whole genome sequencing.
Normal (μ, σ) denotes the normal distribution where μ is the mean and σ is the standard deviation.
Gamma (α, λ) denotes the Gamma distribution where α is the shape parameter and λ is the scale parameter.
Lognormal (μ, σ) denotes the lognormal distribution where μ is the mean of logs and σ is the standard deviation of logs.

Analysis and Uncertainty

For the reference case analyses (Research Questions 1 and 2), we conducted probabilistic analyses to capture parameter uncertainty. When possible, we specified distributions around input parameters using the mean and standard deviation. Selected cost parameters were characterized by lognormal or normal distributions, and probabilities were characterized by beta distributions. We ran a total of 1,000,000 simulations and calculated the expected values of costs and outcomes for each testing strategy. We presented the probability of each testing strategy being cost-effective over a range of thresholds on a cost-effectiveness acceptability curve. We also addressed structural and parameter uncertainty by conducting several scenario analyses (Table 16).

Table 16: Summary of Scenario Analyses

Aspects of Scenarios	Parameters/Assumptions Used in Reference Case	Parameters/Assumptions Used in Scenario Analysis
Time horizon	3 y	1 y (assume standard testing is CMA ± Fragile X testing); 4 y
Discount rate	1.5%	0%; 3%
Proportion of trio for WES/WGS	Weighted average (90% trio)	80% of trio (diagnostic yield remains constant); 100% trio (diagnostic yield increases by 2%)
Rate of clinical utility among those who have diagnosis	Same rate for all testing strategies based on values from clinical evidence review	Various rates based on Clark et al[37]: • CMA: 0.06 (95% CI 0.05–0.07; n = 4,271) • WES: 0.47 (95% CI 0.12–0.24; n = 992) • WGS: 0.66 (95% CI 0.17–0.40; n = 136)
Rate of secondary findings	7% based on clinical evidence review	2%–3% according to expert opinion
Non-genetic tests/procedures averted by WES/WGS	Invasive procedures only (muscle and skin biopsy)	10%, 30%, or 50% of non-genetic tests/procedures (biochemical workup, neuroimaging, invasive procedures, echocardiogram, electroencephalogram)
TAT for WES/WGS result	Ideal TAT (see Table 13)	Real-world TAT = Ideal TAT with delays (additional 8 wk)
VUS of WGS	Same as WES	Higher than WES (10% more)
Diagnostic yield of WES/WGS	Based on clinical evidence review	Low yield: lower 95% CI High yield: upper 95% CI
Diagnostic yield of standard testing	Based on clinical evidence review	Low yield: lower 95% CI High yield: upper 95% CI
Cost of standard testing	Based on Oei et al[112]	Assume less (or more) extensively tested population and cost 50% lower (or higher)
Cost of WES/WGS	Based on average price charged to Out-of-Country Prior Approval Program	Based on Ontario microcosting study[90] Based on higher cost estimates from literature: $6,899 for WES trio, $8,090 for WGS trio
Cost of post-test genetic services for negative results	None (assume results communicated over phone)	Assume medical geneticist visit is needed
Cost of post-test genetic services for incidental findings	Assume 1 h with medical geneticist, 1 h with genetic counsellor	Assume 6 h with medical geneticist, 6 h with genetic counsellor
Cost of post-test activities	None	Include post-test cost within 1 y after disclosure of results, based on Hayeems et al[36]

Abbreviations: CI, confidence interval; CMA, chromosomal microarray; TAT, turnaround time; VUS, variant of unknown significance; WES, whole exome sequencing; WGS, whole genome sequencing.

Internal Validation: Cost-Effectiveness Analysis

Formal internal validation was conducted by the secondary health economist. This included testing the mathematical logic of the model and checking for errors and accuracy of parameter inputs and equations.[99]

Results

Research Question 1: Genome-Wide Sequencing After Standard Testing Versus Standard Testing

Table 17 presents the results of the reference case analysis for whole exome sequencing after standard testing compared with standard testing. For standard testing, we estimated the total mean cost to be $8,783 per patient. For every 1,000 persons tested, 185 persons had a molecular diagnosis, 185 persons had any positive finding, and 31 persons had active treatment change. When whole exome sequencing is used after standard testing, we estimated the total cost of the diagnostic pathway including standard testing to be $12,044 per patient. For every 1,000 persons tested, 425 persons had a molecular diagnosis, 457 persons had any positive finding, and 77 persons had active treatment change. The incremental cost between the two testing strategies was $3,261 per patient ($3,077 of which was attributable to the whole exome sequencing test itself, $205 of which was related to additional genetic services, and $21 savings came from non-genetic tests avoided). The resulting ICERs were $13,591 per additional molecular diagnosis, $12,005 per additional positive finding, and $71,459 per active treatment change.

Table 17: Reference Case Analysis—Cost-Effectiveness of WES After Standard Testing Versus Standard Testing

	WES After Standard Testing Mean (95% CrI)	Standard Testing Mean (95% CrI)
Total cost per patient ($)	12,044 (5,520–34,494)	8,783 (2,309–31,123)
• Cost of genome-wide sequencing	3,077	--
• Cost of other genetic tests	7,116	7,116
• Cost of genetic services	887	682
• Cost of non-genetic tests	964	985
Number of molecular diagnoses (per 1,000 persons tested)	425 (370–483)	185 (119–267)
Number of positive findings (per 1,000 persons tested)	457 (402–514)	185 (119–267)
Number of active treatment change (per 1,000 persons tested)	77 (47–111)	31 (17–51)
Incremental cost per patient ($)	3,261	
Incremental molecular diagnoses (per 1,000 persons tested)	240	
Incremental positive findings (per 1,000 persons tested)	272	
Incremental active treatment change (per 1,000 persons tested)	46	
ICER (cost per additional molecular diagnosis)	**13,591**	
ICER (cost per additional positive finding)	**12,005**	
ICER (cost per additional active treatment change)	**71,459**	

Abbreviations: CrI, credible interval; ICER, incremental cost-effectiveness ratio; WES, whole exome sequencing.

Results of the scenario analyses are shown in Table 18. Results remained robust when parameters and assumptions were varied. The ICER increased when the turnaround time for whole exome sequencing was increased by 8 weeks to account for potential delays, the diagnostic yield of whole exome sequencing was lowered, the cost of whole exome sequencing was higher, a medical geneticist visit was assumed for communicating negative results, more hours of genetic counselling was assumed for communicating incidental findings, and the cost of post-test activities over 1 year was included. The ICER decreased substantially when local costs of whole exome sequencing were used (i.e., cost estimates from the Ontario microcosting study). The ICER also decreased when we assumed that the proportion of trio testing was lower, more non-genetic tests and procedures could be averted by whole exome sequencing, and the diagnostic yield of whole exome sequencing was higher.

Table 18: Scenario Analysis Results—Cost-Effectiveness of WES After Standard Testing Versus Standard Testing

Scenarios	Total Cost for WES After Standard Testing	Total Cost for Standard Testing	Incremental Cost	Incremental No. of Molecular Diagnosis	ICER ($ per Additional Molecular Diagnosis)	Incremental No. of Positive Findings	ICER ($ per Additional Positive Findings)	Incremental No. of Active Treatment Change	ICER ($ per Additional Active Treatment Change)
Reference case[a]	12,042	8,783	3,259	0.239	13,636	0.271	12,021	0.046	71,556
Time horizon of 1 y	7,143	2,767	4,376	0.332	13,189	0.376	11,641	0.063	69,294
Time horizon of 4 y	12,496	8,785	3,711	0.281	13,211	0.318	11,666	0.053	69,441
Discount rate of 0%	12,159	8,784	3,375	0.248	13,631	0.281	12,015	0.047	71,518
Discount rate of 3%	11,931	8,782	3,149	0.231	13,644	0.262	12,028	0.044	71,597
Proportion of trio testing: 80%	11,880	8,783	3,097	0.239	12,958	0.271	11,424	0.046	67,999
Proportion of trio testing: 100%	12,205	8,783	3,422	0.252	13,579	0.285	12,028	0.048	71,596
Rate of clinical utility from Clark et al[37]	12,042	8,783	3,259	0.239	13,636	0.271	12,021	0.203	16,027
Rate of secondary finding from expert opinion	12,039	8,783	3,256	0.239	13,623	0.250	13,003	0.042	77,400
Non-genetic tests or procedures averted by WES or WGS: 10%	11,997	8,783	3,214	0.239	13,448	0.271	11,855	0.046	70,568
Non-genetic tests or procedures averted by WES or WGS: 30%	11,865	8,783	3,082	0.239	12,895	0.271	11,368	0.046	67,670
Non-genetic tests or procedures averted by WES or WGS: 50%	11,733	8,783	2,950	0.239	12,343	0.271	10,882	0.046	64,771
Turnaround time for WES or WGS: additional 8 wk of potential delays	11,734	8,783	2,951	0.213	13,867	0.242	12,209	0.041	72,675
Diagnostic yield of WES or WGS: low (lower 95% CI)	12,040	8,783	3,257	0.220	14,811	0.252	12,935	0.042	76,993
Diagnostic yield of WES or WGS: high (upper 95% CI)	12,045	8,783	3,262	0.259	12,580	0.292	11,190	0.049	66,609
Diagnostic yield of standard testing: low (lower 95% CI)	12,320	8,774	3,546	0.260	13,633	0.295	12,004	0.050	71,453
Diagnostic yield of standard testing: high (upper 95% CI)	11,718	8,794	2,924	0.215	13,613	0.244	12,008	0.041	71,477
Cost of standard testing (50% less)	8,463	5,203	3,260	0.239	13,640	0.271	12,025	0.046	71,578
Cost of standard testing (50% more)	15,622	12,363	3,259	0.239	13,636	0.271	12,021	0.046	71,556
Cost of WES from Ontario microcosting study (HiSeq 2500)[90]	10,994	8,783	2,211	0.239	9,251	0.271	8,156	0.046	48,546

Scenarios	Total Cost for WES After Standard Testing	Total Cost for Standard Testing	Incremental Cost	Incremental No. of Molecular Diagnosis	ICER ($ per Additional Molecular Diagnosis)	Incremental No. of Positive Findings	ICER ($ per Additional Positive Findings)	Incremental No. of Active Treatment Change	ICER ($ per Additional Active Treatment Change)
Cost of WES from Ontario microcosting study (NextSeq 550)[90]	11,556	8,783	2,773	0.239	11,603	0.271	10,229	0.046	60,885
Cost of WES: based on higher cost from literature ($6,899)	13,590	8,783	4,807	0.239	20,113	0.271	17,731	0.046	105,544
Cost of post-test genetic services for negative results	12,174	8,870	3,304	0.239	13,824	0.271	12,187	0.046	72,544
Cost of post-test genetic services for incidental findings (6 h with medical geneticist, 6 h with genetic counsellor)	12,085	8,783	3,302	0.239	13,816	0.271	12,180	0.046	72,500
Cost of post-test activities from Hayeems et al[36]	12,116	8,783	3,333	0.239	13,946	0.271	12,294	0.046	73,181

Abbreviations: CI, confidence interval; ICER, incremental cost-effectiveness ratio; WES, whole exome sequencing; WGS, whole genome sequencing.
[a]Reference case result is calculated on basis of 100,000 simulations instead of 1,000,000.

Research Question 2: Genome-Wide Sequencing Used at Various Tiers Compared With Standard Testing

Tables 19 and 20 present the results of the reference case analysis for genome-wide sequencing used at various tiers compared with standard testing. Early use of genome-wide sequencing in the diagnostic pathway could save on costs and improve diagnostic yield over those of standard testing. Four genome-wide testing strategies had lower cost and higher diagnostic yield than standard testing ($8,783 per patient). Whole exome sequencing as second-tier (after patients have no diagnosis from chromosomal microarray alone) was the least costly testing strategy ($6,357 per patient), followed by whole exome sequencing alone as first tier ($6,755 per patient), whole exome sequencing plus chromosomal microarray as first tier ($6,985 per patient), and whole genome sequencing as first-tier ($7,811 per patient) test. Using whole exome or whole genome sequencing after standard testing were the most costly strategies: $12,041 and $12,958 per patient, respectively. For every 1,000 persons tested, whole exome sequencing plus chromosomal microarray as first tier led to the highest number of molecular diagnoses (466), positive findings (515), and active treatment change (87) within the model time horizon (3 years). Standard testing resulted in the lowest number of molecular diagnoses (185), positive findings (185), and active treatment change (31). Whole exome sequencing plus chromosomal microarray as first tier was considered to have absolute dominance over several strategies (i.e., whole genome sequencing as first-tier, standard testing, whole exome sequencing after standard testing, and whole genome sequencing after standard testing) because it was less costly and more effective. Whole exome sequencing alone as first tier was extendedly dominated because it was less effective and had a higher ICER than whole exome sequencing plus chromosomal microarray as first tier. The resulting ICER of whole exome sequencing plus chromosomal microarray as first tier compared with whole exome sequencing as second tier after chromosomal microarray alone was $11,831 per additional molecular diagnosis, $10,848 per additional positive finding, and $64,082 per active treatment change.

Results of the scenario analyses remained robust when key parameters and assumptions were changed (Table 21).

Table 19: Reference Case Results—Total Costs and Outcomes of WES/WGS at Various Tiers Versus Standard Testing

	WES After Standard Testing[a]	WES as 2nd Tier (After CMA Alone)	WES Alone as 1st Tier	WES+CMA as 1st Tier	WGS After Standard Testing	WGS as 1st Tier	Standard Testing
Total cost per patient, $[b]	12,041 (5,517–34,491)	6,357 (6,179–6,520)	6,755 (6,597–6,907)	6,985 (6,851–7,116)	12,958 (6,425–35,444)	7,811 (7,533–8,092)	8,783 (2,309–31,123)
• Cost of genome-wide sequencing, $	3,077	4,120	4,590	4,590	4,003	6,240	0
• Cost of other genetic tests, $	7,116	780	769	1,114	7,116	290	7,116
• Cost of genetic services, $	884	500	442	328	873	327	682
• Cost of non-genetic tests, $	964	957	954	954	965	954	985
No. of molecular diagnoses (per 1,000 persons tested)[b]	399 (342–462)	413 (354–475)	429 (331–536)	466 (357–584)	382 (302–462)	460 (352–570)	185 (119–267)
No. of positive findings (per 1,000 persons tested)[b]	431 (375–492)	457 (393–521)	473 (378–578)	515 (404–636)	412 (333–491)	509 (398–617)	185 (119–267)
No. of active treatment changes (per 1,000 persons tested)[b]	72 (45–105)	77 (48–112)	80 (48–122)	87 (51–133)	69 (43–103)	86 (51–131)	31 (17–51)

Abbreviations: CMA, chromosomal microarray; WES, whole exome sequencing; WGS, whole genome sequencing.
[a]Current pathway in Ontario.
[b]Values presented are the mean and the 95% credible interval.

Table 20: Reference Case Results—Cost-Effectiveness of WES/WGS at Various Tiers Versus Standard Testing

Testing Strategy	Total Cost ($)	Incremental Cost ($)	No. of Molecular Diagnoses	Incremental No. of Molecular Diagnoses	ICER ($ per Additional Molecular Diagnosis)	Incremental No. of Positive Findings	ICER ($ per Additional Positive Finding)	Incremental No. of Active Treatment Changes	ICER ($ per Additional Active Treatment Change)
WES as 2nd-tier test (after CMA alone)	6,357	--	0.413	--	--	--	--	--	--
WES alone as 1st-tier test	6,755	398	0.429	0.017	23,960 (ExtDom)	0.017	23,820 (ExtDom)	0.003	139,908 (ExtDom)
WES + CMA as 1st-tier test	6,985	628	0.466	0.053	11,831	0.058	10,848	0.010	64,082
WGS as 1st-tier test	7,811	1,455	0.460	0.047	Dominated	0.052	Dominated	0.009	Dominated
Standard testing	8,783	2,427	0.185	−0.228	Dominated	−0.272	Dominated	−0.046	Dominated
WES after standard testing	12,041	5,684	0.399	−0.014	Dominated	−0.026	Dominated	−0.004	Dominated
WGS after standard testing	12,958	6,601	0.382	−0.031	Dominated	−0.045	Dominated	−0.008	Dominated

Abbreviations: CMA, chromosomal microarray; ExtDom, extendedly dominated; ICER, incremental cost-effectiveness ratio; WES, whole exome sequencing; WGS, whole genome sequencing.
Note: Incremental cost and effectiveness are calculated against common baseline strategy (the one with the lowest cost). If a strategy is dominated, it means that it has a higher cost but lower effectiveness compared with other strategies. If a strategy is extendedly dominated, it means that it has a higher ICER than the next, more effective, alternative.

Table 21: Scenario Analysis Results—Cost-Effectiveness of WES and WGS at Various Tiers Versus Standard Testing

	Cost and Effectiveness of Undominated Strategies; ICER ($/Molecular Diagnosis)	Cost and Effectiveness of Dominated Strategies
Reference case[a]	WES as second tier: $6,358, 0.413 WES + CMA as first tier: $6,985, 0.467; **ICER:** $11,421	WES alone as first tier (ExtDom): $6,754, 0.430 WGS as first tier: $7,811, 0.462 Standard testing: $8,783, 0.185 WES after standard testing: $12,039, 0.399 WGS after standard testing: $12,953, 0.381
Time horizon 1 y	Standard testing: $2,767, 0.100 WES as second tier: $6,358, 0.413 WES + CMA as first tier: $6,985, 0.467; **ICER** WES as second tier vs. standard testing: $11,484 WES + CMA as first tier vs. standard testing: $11,474	WES alone as first tier (ExtDom): $6,754, 0.430 WES after standard testing: $7,138, 0.396 WGS as first tier: $7,811, 0.462 WGS after standard testing: $8,612, 0.386
Time horizon 4 y	WES as second tier: $6,358, 0.413 WES + CMA as first tier: $6,985, 0.467 **ICER:** $11,421	WES alone as first tier (ExtDom): $6,754, 0.430 WGS as first tier: $7,811, 0.462 Standard testing: $8,785, 0.202 WES after standard testing: $12,492, 0.453 WGS after standard testing: $13,740, 0.445
Discount rate 0%	WES as second tier: $6,369, 0.414 WES + CMA as first tier: $6,985, 0.469; **ICER:** $11,159	WES alone as first tier (ExtDom): $6,756, 0.432 WGS as first tier: $7,812, 0.463 Standard testing: $8,784, 0.192 WES after standard testing: $12,155, 0.413 WGS after standard testing: $13,106, 0.394
Discount rate 3%	WES as second tier: $6,348, 0.412 WES + CMA as first tier: $6,984, 0.466; **ICER:** $11,691	WES alone as first tier (ExtDom): $6,751, 0.429 WGS as first tier: $7,811, 0.460 Standard testing: $8,782, 0.179 WES after standard testing: $11,928, 0.385 WGS after standard testing: $12,808, 0.368
Proportion of trio testing 80%	WES as second tier: $6,140, 0.413 WES + CMA as first tier: $6,742, 0.467; **ICER:** $11,148	WES alone as first tier (ExtDom): $6,511, 0.430 WGS as first tier: $7,490, 0.462 Standard testing: $8,783, 0.185 WES after standard testing: $11,876, 0.399 WGS after standard testing: $12,747, 0.381
Proportion of trio 100%	WES as second tier: $6,577, 0.431 WES + CMA as first tier: $7,228, 0.487; **ICER:** $12,056	WES alone as first tier (ExtDom): $6,975, 0.448 WGS as first tier: $8,135, 0.481 Standard testing: $8,783, 0.185 WES after standard testing: $12,202, 0.412 WGS after standard testing: $13,161, 0.393
Rate of clinical utility, based on Clark et al[37]	WES as second tier: $6,358, 0.413 WES + CMA as first tier: $6,985, 0.467; **ICER:** $11,421	WES alone as first tier (ExtDom): $6,754, 0.430 WGS as first tier: $7,811, 0.462 Standard testing: $8,783, 0.185 WES after standard testing: $12,039, 0.399 WGS after standard testing: $12,953, 0.381

	Cost and Effectiveness of Undominated Strategies; ICER ($/Molecular Diagnosis)	Cost and Effectiveness of Dominated Strategies
Rate of secondary finding, based on expert opinion	WES as second tier: $6,354, 0.413 WES + CMA as first tier: $6,980, 0.467; **ICER:** $11,593	WES alone as first tier (ExtDom): $6,782, 0.430 WGS as first tier: $7,806, 0.462 Standard testing: $8,783, 0.185 WES after standard testing: $12,035, 0.399 WGS after standard testing: $12,950, 0.381
Non-genetic tests or procedures averted by WES/WGS: 10%	WES as second tier: $6,298, 0.413 WES + CMA as first tier: $6,918, 0.467; **ICER:** $11,481	WES alone as first tier (ExtDom): $6,687, 0.430 WGS as first tier: $7,744, 0.462 Standard testing: $8,783, 0.185 WES after standard testing: $11,994, 0.399 WGS after standard testing: $12,910, 0.381
Non-genetic tests or procedures averted by WES/WGS: 30%	WES as second tier: $6,121, 0.413 WES + CMA as first tier: $6,721, 0.467; **ICER:** $11,111	WES alone as first tier (ExtDom): $6,489, 0.430 WGS as first tier: $7,547, 0.462 Standard testing: $8,783, 0.185 WES after standard testing: $11,862, 0.399 WGS after standard testing: $12,784, 0.381
Non-genetic tests or procedures averted by WES/WGS: 50%	WES as second tier: $5,944, 0.413 WES + CMA as first tier: $6,524, 0.467 **ICER:** $10,741	WES alone as first tier (ExtDom): $6,292, 0.430 WGS as first tier: $7,350, 0.462 Standard testing: $8,783, 0.185 WES after standard testing: $11,730, 0.399 WGS after standard testing: $12,658, 0.381
Turnaround time for WES/WGS: additional 8 wk due to potential delays	WES as second tier: $6,348, 0.412 WES + CMA as first tier: $6,985, 0.466; **ICER:** $11,796	WES alone as first tier (ExtDom): $6,752, 0.429 WGS as first tier: $7,811, 0.460 Standard testing: $8,783, 0.185 WES after standard testing: $11,730, 0.375 WGS after standard testing: $12,478, 0.356
VUS of WGS higher than WES	WES as second tier: $6,358, 0.413 WES + CMA as first tier: $6,985, 0.467 **ICER:** $11,421	WES alone as first tier (ExtDom): $6,754, 0.430 WGS as first tier: $7,825, 0.462 Standard testing: $8,783, 0.185 WES after standard testing: $12,039, 0.399 WGS after standard testing: $12,960, 0.381
Diagnostic yield of WES/WGS: low yield (lower 95% CI)	WES as second tier: $6,350, 0.356 WES + CMA as first tier: $6,971, 0.371; **ICER:** $41,400	WES alone as first tier (ExtDom): $6,840, 0.344 WGS as first tier: $7,796, 0.360 Standard testing: $8,783, 0.185 WES after standard testing: $12,036, 0.380 WGS after standard testing: $12,946, 0.332
Diagnostic yield of WES/WGS: high yield (upper 95% CI)	WES as second tier: $6,369, 0.487 WES + CMA as first tier: $7,002, 0.589; **ICER:** $6,206	WES alone as first tier (ExtDom): $6,643, 0.542 WGS as first tier: $7,826, 0.569 Standard testing: $8,783, 0.185 WES after standard testing: $12,043, 0.424 WGS after standard testing: $12,963, 0.444

	Cost and Effectiveness of Undominated Strategies; ICER ($/Molecular Diagnosis)	Cost and Effectiveness of Dominated Strategies
Diagnostic yield of standard testing: low yield (lower 95% CI)	WES as second tier: $6,358, 0.413 WES + CMA as first tier: $6,985, 0.467; **ICER:** $11,421	WES alone as first tier (ExtDom): $6,754, 0.430 WGS as first tier: $7,811, 0.462 Standard testing: $8,774, 0.124 WES after standard testing: $12,316, 0.356 WGS after standard testing: $12,312, 0.337
Diagnostic yield of standard testing: high yield (upper 95% CI)	WES as second tier: $6,358, 0.413 WES + CMA as first tier: $6,985, 0.467; **ICER:** $11,421	WES alone as first tier (ExtDom): $6,754, 0.430 WGS as first tier: $7,811, 0.462 Standard testing: $8,794, 0.257 WES after standard testing: $11,715, 0.449 WGS after standard testing: $12,535, 0.433
Cost of standard testing (50% less)	Standard testing: $5,203, 0.185 WES as second tier: $6,358, 0.413 WES + CMA as first tier: $6,985, 0.467; **ICER** WES as second tier vs. standard testing: $5,066 WES + CMA as first tier vs. standard testing: $6,319	WES alone as first tier (ExtDom): $6,754, 0.430 WGS as first tier: $7,811, 0.462 WES after standard testing: $8,459, 0.399 WGS after standard testing: $9,373, 0.381
Cost of standard testing (50% more)	WES as second tier: $6,358, 0.413 WES + CMA as first tier: $6,985, 0.467; **ICER:** $11,421	WES alone as first tier (ExtDom): $6,754, 0.430 WGS as first tier: $7,811, 0.462 Standard testing: $12,363, 0.185 WES after standard testing: $15,619, 0.399 WGS after standard testing: $16,533, 0.381
Cost of WES, based on Ontario microcosting study (HiSeq 2500)[90]	WES as second tier: $4,953, 0.413 WES + CMA as first tier: $5,420, 0.467; **ICER:** $8,648	WES alone as first tier (ExtDom): $5,189, 0.430 WGS as first tier: $7,811, 0.462 Standard testing: $8,783, 0.185 WES after standard testing: $10,990, 0.399 WGS after standard testing: $12,953, 0.381
Cost of WES, based on Ontario microcosting study (NextSeq 550)[90]	WES as second tier: $5,706, 0.413 WES + CMA as first tier: $6,258, 0.467; **ICER:** $10,222	WES alone as first tier (ExtDom): $6,027, 0.430 WGS as first tier: $7,811, 0.462 Standard testing: $8,783, 0.185 WES after standard testing: $11,552, 0.399 WGS after standard testing: $12,953, 0.381
Cost of WES/WGS, based on higher cost from literature ($6,899 for WES trio and $8,090 for WGS trio)	WES as second tier: $8,432, 0.413 WES + CMA as first tier: $9,294, 0.467; **ICER:** $15,963	Standard testing: $8,783, 0.185 WES alone as first tier (ExtDom): $9,063, 0.430 WGS as first tier: $9,667, 0.462 WES after standard testing: $13,586, 0.399 WGS after standard testing: $14,143, 0.381
Cost of post-test genetic services for negative results	WES as second tier: $6,552, 0.413 WES + CMA as first tier: $7,033, 0.467; **ICER:** $8,907	WES alone as first tier (ExtDom): $6,895, 0.430 WGS as first tier: $7,860, 0.462 Standard testing: $8,870, 0.185 WES after standard testing: $12,173, 0.399 WGS after standard testing: $13,081, 0.381

	Cost and Effectiveness of Undominated Strategies; ICER ($/Molecular Diagnosis)	Cost and Effectiveness of Dominated Strategies
Cost of post-test genetic services for incidental findings (6 h with medical geneticist, 6 h with genetic counsellor)	WES as second tier: $6,419, 0.413 WES + CMA as first tier: $7,052, 0.467; **ICER:** $11,722	WES alone as first tier (ExtDom): $6,821, 0.430 WGS as first tier: $7,879, 0.462 Standard testing: $8,783, 0.185 WES after standard testing: $12,082, 0.399 WGS after standard testing: $12,994, 0.381
Cost of post-test activities, based on Hayeems et al[36]	WES as second tier: $6,467, 0.413 WES + CMA as first tier: $7,116, 0.467; **ICER:** $12,019	WES alone as first tier (ExtDom): $6,828, 0.430 WGS as first tier: $7,942, 0.462 Standard testing: $8,783, 0.185 WES after standard testing: $12,109, 0.399 WGS after standard testing: $13,018, 0.381

Abbreviations: CI, confidence interval; CMA, chromosomal microarray; ICER, incremental cost-effectiveness ratio; VUS, variant of unknown significance; WES, whole exome sequencing; WGS, whole genome sequencing.

[a]Reference case result is calculated based on 100,000 simulations instead of 1,000,000.

Discussion

In our first analysis, we found that using whole exome sequencing after standard testing led to an average cost increase of $3,261 per patient and an additional 240 molecular diagnoses, 272 positive findings, and 46 active treatment changes in every 1,000 persons tested. The resulting ICERs were $13,591 per additional molecular diagnosis, $12,005 per additional positive finding, and $71,459 per active treatment change. In a scenario analysis where we used whole exome sequencing costs from Ontario, the ICER was lower ($9,251 and $11,603 per additional molecular diagnosis using the HiSeq 2500 and NextSeq 550 platforms, respectively).

In our second analysis, we explored the cost-effectiveness of using genome-wide sequencing at various tiers in the diagnostic testing pathway. The costs of whole exome and whole genome sequencing are high relative to chromosomal microarray, the current first-tier test, in part owing to the volume of sequencing and the requirement to perform follow-up testing (e.g., Sanger sequencing) to confirm the results. However, we found that in this patient population standard testing actually had a high cumulative cost and a prolonged time to diagnosis because of iterative testing, while the yield was low. All strategies involving early use of genome-wide sequencing were found to be less costly and more effective than standard testing. Whole exome sequencing as second tier (used after chromosomal microarray) was the least costly testing strategy and should be implemented instead of standard testing, regardless of the willingness-to-pay value. Whole exome sequencing plus chromosomal microarray as first tier had the highest diagnostic yield among all strategies. The ICER of whole exome sequencing plus chromosomal microarray as first tier compared with whole exome sequencing as second-tier test is $11,831 per additional molecular diagnosis.

Another benefit of using genome-wide sequencing earlier in the diagnostic pathway is that patients can get more timely diagnoses. Based on the literature, due to iterative testing, standard testing could take years to reach a diagnosis. Oei et al[112] found that most children undergoing standard testing in Ontario used a high volume of genetic tests (median of four) over a median of more than 2 years, and most remained undiagnosed.[112] Children with no genetic diagnosis pursued a greater proportion of sequence-level testing. Sequence-level testing is usually conducted in a stepwise manner and requires clinicians to make diagnostic hypotheses regarding putative candidate genes based on the patient's clinical symptoms. Genome-wide sequencing, on the other hand, is a high-resolution but hypothesis-free approach. If it is used earlier in the diagnostic pathway, time to diagnosis could be shortened in some patients (months instead of years). Our analysis showed that, when the time horizon was shortened to 1 year, fewer people undergoing standard testing would receive a molecular diagnosis (85 fewer molecular diagnoses in every 1,000 persons tested compared with the reference case). However, for testing strategies involving early use of whole exome or whole genome sequencing, the number of people who received a molecular diagnosis remained the same.

Overall, our findings were consistent with results from published economic studies. When genome-wide sequencing is applied to appropriate candidates and is ordered and interpreted by medical specialists, it can save both time and resources for patients and their families if there is sufficient sequencing capacity. Because whole exome sequencing is not currently used as a first-tier diagnostic test, averted testing is less relevant as a measure of clinical utility because most of the clinical investigations have already occurred. Also, metabolic and imaging tests are usually used together with genetic testing to fully understand the disease. Compared with some published studies that assumed a significant portion of non-genetic tests would be averted by whole exome or whole genome sequencing, our reference case analysis was very conservative

and assumed that only invasive procedures, such as skin or muscle biopsy (in 2.5% of the target population), could be averted.

The ICER results were most sensitive to the cost of genome-wide sequencing. The cost of genome-wide sequencing varies with many factors, such as where the test is conducted (Ontario vs. out of the country), sequencing platforms, and total test volume[90]:

- We estimated the cost-effectiveness of genome-wide sequencing using both commercial prices charged by out-of-country laboratories and opportunity costs estimated from local laboratories. Because the cost per test is lower in Ontario, conducting genome-wide sequencing in Ontario is likely more cost-effective.
- In scenario analyses, we also tested the impact of different sequencing platforms on the cost-effectiveness results. According to Jegathisawaran et al[83] (the Ontario microcosting study), the cost per test was lower with the HiSeq 2500 platform compared with the NextSeq 550 platform.
- In addition, the unit cost of whole exome and whole genome sequencing could be potentially reduced by achieving an economy of scale that maximizes patient throughput. However, Jegathisawaran et al[83] found that, while there was considerable cost reduction for proband testing when the total test volume doubled (13.3% for whole exome sequencing on the HiSeq 2500 platform and 12% for whole genome sequencing on the HiSeq X platform), there was minimal cost reduction for trio tests at increasing test volumes (1.6% for whole genome sequencing on the HiSeq X platform).[83] This is because trio testing already increased the number of tests by three factors (from proband only to proband plus two parents). The relatively minimal cost reduction for trio testing was attributable to its equipment and follow-up costs constituting a smaller part of total costs compared with the three-factor increase in the cost of supplies and computation for singleton testing.
- Over the last two decades, advances in sequencing technology have reduced the cost of genome-wide sequencing dramatically from extremely high initial costs of $100 million USD in 2001 (i.e., switching from Sanger sequencing to massively parallel throughput technologies).[119] It is unclear whether the cost of genome-wide sequencing will continue to drop in the next few years. Our economic literature review showed that the recent cost estimates for whole exome and whole genome sequencing were similar over time (2015–2019) and across regions (Canada, Australia, the Netherlands).

Strengths and Limitations

Our analysis has several strengths:

- First, our analysis was based on high-quality Ontario costing data. The precise costs associated with chromosomal microarray, whole exome sequencing, and whole genome sequencing (proband and trio) in Ontario were obtained from a recently updated microcosting study in our target population. Using a bottom-up approach, the microcosting study captured all relevant cost components from taking the blood draw to returning laboratory results to the ordering physician. We also estimated the cost of standard testing from several Ontario costing studies and inputs from clinical experts.

- Second, we included a comprehensive list of possible testing strategies involving genome-wide sequencing, in order to help decision-makers determine the most optimal way of using genome-wide sequencing in clinical practice.
- Last, compared with most published economic studies that considered proband testing only, our analysis evaluated trio testing, which reflects recent clinical practice. Traditionally, whole exome and whole genome sequencing have been conducted with probands only because of the high cost of genome-wide sequencing. However, the use of trio testing (including the two biological parents) is on the rise because this sequencing method enhances both the speed and likelihood of accurate diagnosis.[83,105]

There were some limitations to our analysis:

- First, we did not measure effectiveness using QALY (a universal outcome measure), but instead used indirect outcomes, such as the number of molecular diagnoses, positive findings, and active treatment change. Without a common willingness-to-pay threshold for these outcomes, interpreting the cost-effectiveness results can be difficult.
- Second, we did not model the long-term costs and consequences related to primary or secondary findings due to a lack of data (e.g., resource implications for health care and social support services). It is uncertain what effect these omissions may have on the ICER. Future research in this area is warranted. A recent Ontario study by Hayeems et al[36] described the type and cost of health care activities in a cohort of children with developmental delay 1 year after receiving results from chromosomal microarray and whole genome sequencing.[36] They found that, in complex pediatric care, post-test activities were mainly driven by the child's ongoing care (88.6%), rather than by results from chromosomal microarray or whole genome sequencing. In a scenario analysis, we included the cost of post-test activities within 1 year after receiving whole exome or whole genome sequencing results. For patients undergoing whole exome sequencing after standard testing, the total cost per patient increased by only $74 ($12,116 vs. $12,042 per patient in the reference case). The resulting ICER was $13,946 per additional molecular diagnosis (2.3% increase compared with the reference case).
- Third, we defined clinical utility as a change in active clinical management (e.g., modifications to medications, procedures, or treatment) as a result of having a diagnosis. This captures clinical utility for diagnosed patients only, but not for undiagnosed people (e.g., further testing avoided because of whole exome or whole genome sequencing).
- Fourth, diagnostic yield is an indirect outcome. Data on health outcomes related to genome-wide sequencing are limited. Improvement in diagnostic yield does not necessarily mean improvement in health outcomes.
- Last, since the current knowledge about genetics is still rudimentary, the positive findings from genome-wide sequencing could include both true- and false-positive results, and the negative findings could include both true- and false-negative results. We could not assess the effect of true or false results given the lack of data.

Re-analysis

According to the GTAC document,[109] clinicians may request data re-analysis in 1 year if whole exome sequencing is unrevealing (i.e., the patient's clinical presentation is still unexplained after whole exome sequencing).[20] However, re-analysis was considered out of scope for this health technology assessment, as it is not done routinely and therefore was not addressed in the economic analysis. Including re-analysis will likely make whole exome and whole genome sequencing more costly than standard testing but potentially cost-effective compared with single-analysis whole exome or whole genome sequencing. The cost of re-analysis is lower and more variants will likely be identified as more is learned about causal variants in this patient population.

Implementation

Introducing whole exome and whole genome sequencing in more clinical laboratories in Ontario will require substantial capital investment, laboratory retooling, and training in procedures and bioinformatics. It will also increase demand on clinical geneticists and genetic counselors for whom wait times can be prolonged. These factors were not considered in the current analysis, which assumed sufficient capacity and ideal turnaround times for results.

Generalizability

The findings of this economic analysis cannot be generalized to patients with other types of developmental disabilities (e.g., autism spectrum disorders), mild developmental disabilities, or multiple congenital anomalies. They can, however, be used to guide decision-making about the specific patient populations addressed in this health technology assessment.

Conclusions

Our economic model showed that, compared with standard testing alone, incorporating whole exome sequencing after standard testing increased diagnostic yield at an additional cost. Using whole exome sequencing as first- or second-tier test yielded more diagnoses at a lower cost than using whole exome sequencing after standard testing or using standard testing alone. Early use of genome-wide sequencing could enable more timely diagnosis for patients with unexplained developmental disabilities or multiple congenital anomalies.

BUDGET IMPACT ANALYSIS

Research Questions

From the perspective of the Ontario Ministry of Health, for people with unexplained developmental disabilities or multiple congenital anomalies, what is the 5-year budget impact of:

1. Providing whole exome sequencing after standard testing through the Out-of-Country Prior Approval Program?
2. Publicly funding whole exome sequencing after standard testing in Ontario?
3. Publicly funding whole exome or whole genome sequencing at various tiers in Ontario?

Methods

Analytic Framework

We estimated the budget impact of genome-wide sequencing as the cost difference between the *Current Scenario* (standard testing without genome-wide sequencing) and the *New Scenario* (Figure 8).

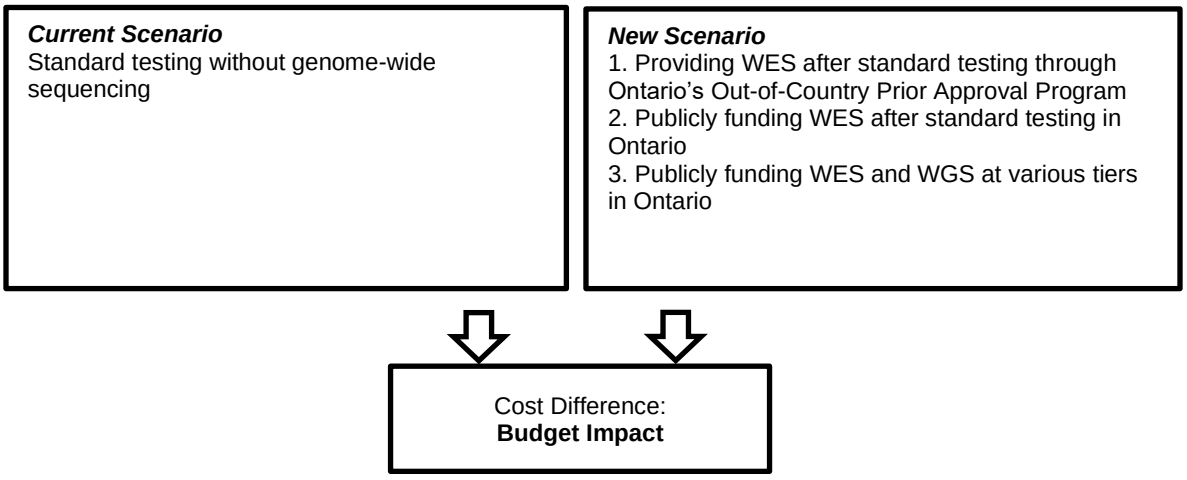

Figure 8: Analytic Framework of Budget Impact Analysis

Abbreviations: WES, whole exome sequencing; WGS, whole genome sequencing.

Key Assumptions

- Per-test costs of whole exome and whole genome sequencing were assumed to stay constant over the next 5 years
- Start-up and implementation costs, such as training, lab renovation, and credentialing, were not included
- If whole exome and whole genome sequencing is conducted in Ontario, sequencing would likely be centralized to a few locations with existing equipment and personnel

Target Population

The size of the population of interest was estimated using prevalence and incidence data (Figure 9). According to Statistics Canada, about 14,322,757 persons (all ages) lived in Ontario in 2018. Based on a prevalence rate of 1.5% (1%–3%),[120-122] the number of persons living with developmental disabilities in Ontario was approximately 214,841 (all ages). If we assume that 40% of those cases have an unexplained cause,[123] we can estimate the number of cases where developmental disabilities in Ontario are unexplained to be 85,937 (all ages). We then assume that 35% of those cases were moderate to severe (30,078 for all ages) on the basis of expert opinion (E. Goh, email communication, January 30, 2019). In addition, there were about 139,999 live births each year in Ontario.[124] Using an incidence rate of 2.5% (2%–3%)[125] and assuming that 40% have an unexplained origin,[123] we estimate that about 1,400 newborns have unexplained multiple congenital anomalies each year. All these patients (both prevalence and incidence cases) are potentially eligible for genetic testing.

Although many patients are potentially eligible for genetic testing, the number who have received whole exome sequencing in Ontario is much smaller. Currently, all clinical whole exome sequencing samples are sent outside of Canada for testing. The cost of testing is covered by Ontario's Out-of-Country Prior Approval Program. Applications for whole exome sequencing are reviewed on a case-by-case basis. Data from the Ontario Ministry of Health (Laboratories and Genetics Branch, email communication, November 19, 2018) show the numbers of people approved for out-of-country whole exome sequencing were 340, 690, and 780 in the past 3 fiscal years (FY). Given poor data quality and use of non-standardized data fields, accurate estimation of the various whole exome sequencing subgroups (i.e., trio, duo, or proband) was not feasible. However, an estimated 90% of the tests were conducted in trio.

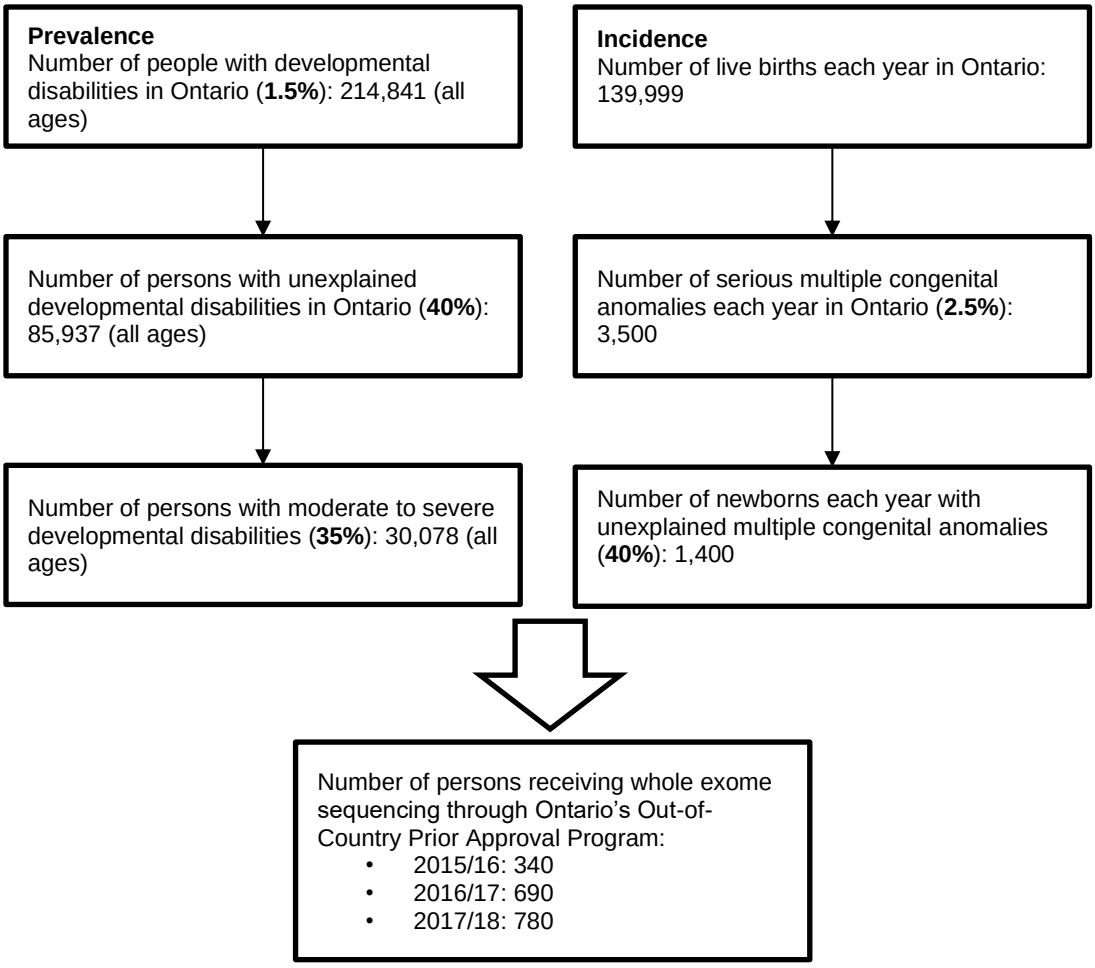

Figure 9: Estimation of the Size of the Target Population

Current Scenario: Standard Testing

Because clinical whole exome sequencing is not yet conducted in Ontario laboratories, the *Current Scenario* is considered standard testing without whole exome and whole genome sequencing.

New Scenario: Whole Exome and Whole Genome Sequencing

1. Providing Whole Exome Sequencing After Standard Testing Through Out-of-Country Prior Approval Program

Data provided by the Ontario Ministry of Health show that, under Out-of-Country Prior Approval Program, the number of whole exome sequencing assessments doubled from FY2015/16 to FY2016/17 (340 to 690), but the increase slowed to 13% from FY2016/17 to FY2017/18 (690 to 780). Given this historical trend, we estimated the volumes of whole exome sequencing would increase steadily at a rate of 5% per year in the next 5 years, if it continues to be funded through the Out-of-Country Prior Approval Program (Table 22). In sensitivity analyses, we also tested a

range of 0 to 10% increase per year. As a result, the number of persons expected to receive whole exome sequencing was estimated to range from 819 to 995 yearly in the next 5 years.

2. Publicly Funding Whole Exome Sequencing After Standard Testing in Ontario

Based on clinical expert feedback, if whole exome sequencing is publicly funded more patients would be able to have access to the test and the volume of whole exome sequencing conducted per year would triple compared to the current level (K. Boycott, phone communication, April 4, 2019). Therefore, we assumed that about 2,400 persons per year would receive whole exome sequencing (see Table 22) and the tests would be conducted in Ontario laboratories. In a scenario analysis, we also assumed a slower, more controlled uptake. In this scenario, the number of people expected to receive whole exome sequencing (conducted in Ontario laboratories) would be similar to the current level.

Table 22: Persons Expected to Receive Whole Exome Sequencing After Standard Testing

	No. of Persons Expected to Receive WES After Standard Testing				
Scenario	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Continue through OOC Health Services	819	860	903	948	995
With positive funding recommendation and tests conducted in Ontario laboratories					
• Increased access: triple current level (reference case)	2,400	2,400	2,400	2,400	2,400
• Controlled access: similar to current level (scenario)	819	860	903	948	995

Abbreviations: OOC, out of country; WES, whole exome sequencing.

3. Publicly Funding Whole Exome and Whole Genome Sequencing At Various Tiers in Ontario

We also compared the budget impact of using whole exome and whole genome sequencing as various tiers. Given whole exome sequencing is currently used only after standard testing, this analysis is for exploratory purposes only. Also, a different testing strategy would lead to different numbers of people receiving whole exome and whole genome sequencing. Therefore, we estimated the budget impact for a hypothetical cohort of 1,000 patients with developmental disabilities or multiple congenital anomalies instead. The budget impact is calculated as the cost difference between the *New Scenario* (public funding of a testing strategy involving whole exome and whole genome sequencing) and the *Current Scenario* (standard testing only).

Resources and Costs

The annual per-person costs (undiscounted) for each testing strategy were obtained from the Primary Economic Evaluation section (Tables 23 and 24). Costs included the cost of genome-wide sequencing, other genetic tests, non-genetic tests, and pre-test and post-test genetic services. All costs were reported in 2019 Canadian dollars.

Table 23: Cost Per Patient of Using WES After Standard Testing (2019 Canadian Dollars)

Cost per Patient	WES Through OOC Health Services	WES in Ontario[a]
Total Costs ($)	**4,874**	**3,729**
Cost of WES	4,589	3,444
Cost of pre-test genetic services	225	225
Cost of post-test genetic services	91	91
Cost of non-genetic tests and procedures averted	−31	−31

Abbreviations: OOC, out of country; WES, whole exome sequencing.
[a]Assume 90% trio testing and average cost using both the HiSeq 2500 and NextSeq 550 platforms.

Table 24: Cost Per Patient of Using WES or WGS at Various Tiers in Ontario (2019 Canadian Dollars)

Cost per Patient	WES[a] After Standard Testing	WES[a] as 2nd Tier (After CMA Alone)	WES[a] Alone as 1st Tier	WES[a] + CMA as 1st Tier	WGS After Standard Testing	WGS as 1st Tier	Standard Testing
Total Costs ($)	11,360	5,337	5,610	5,839	13,106	7,812	8,784
Cost of genome-wide sequencing	2,390	3,100	3,444	3,444	4,145	6,240	0
Cost of other genetic tests	7,116	779	770	1,113	7,116	290	7,116
Cost of genetic services	892	501	443	328	881	328	683
Cost of non-genetic tests	963	957	954	954	964	954	985

Abbreviations: CMA, chromosomal microarray; WES, whole exome sequencing; WGS, whole genome sequencing.
[a]Cost of WES is calculated on basis of Ontario microcosting study (assume 90% trio testing).

Analysis

We conducted reference case analyses and sensitivity analyses. Reference case analyses represent the analysis with the most likely set of input parameters and model assumptions. In sensitivity analyses we explored how results are affected by varying input parameters and model assumptions.

Sensitivity analyses were conducted to explore the impact of the following:

- Varying the cost of whole exome and whole genome sequencing
- Varying the diagnostic yield of whole exome and whole genome sequencing
- Varying the number of people expected to receive whole exome and whole genome sequencing
- Varying the assumption of which tests can be averted by whole exome and whole genome sequencing

Internal Validation: Budget Impact Analysis

The secondary health economist conducted formal internal validation. This process included checking for errors and accuracy of parameter inputs and equations in the budget impact analysis.[99]

Results

Reference Case

1. Providing Whole Exome Sequencing After Standard Testing Through Out-of-Country Prior Approval Program

Results of the budget impact analysis are shown in Table 25. Since we assumed that no whole exome sequencing is used in the *Current Scenario*, the budget impact reflects costs associated with whole exome sequencing alone (costs associated with standard testing would be incurred in both the *Current Scenario* and the *New Scenario* and therefore would cancel out). We estimated that, if whole exome sequencing continues to be funded through Ontario's Out-of-Country Prior Approval Program, the budget impact would range from $3.99 million to $4.85 million yearly in the next 5 years. More than 90% of the budget impact is from the test itself, and the rest is related to providing genetic services. There is also a small cost offset from non-genetic tests and procedures averted by whole exome sequencing (i.e., invasive skin and muscle biopsies).

Table 25: Reference Case Results—Budget Impact of Funding WES Through Out-of-Country Prior Approval Program (2019 $ Million CAD)

	Budget Impact of Using WES After Standard Testing ($ Million)				
Out-of-Country Laboratories	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Total Costs	3.99	4.19	4.40	4.62	4.85
Cost of genome-wide sequencing	3.76	3.95	4.14	4.35	4.57
Cost of pre-test genetic services	0.18	0.19	0.20	0.21	0.22
Cost of post-test genetic services	0.07	0.07	0.08	0.08	0.08
Cost of non-genetic tests and procedures averted	−0.03	−0.03	−0.03	−0.03	−0.03

Abbreviation: WES, whole exome sequencing.

2. Publicly Funding Whole Exome Sequencing After Standard Testing in Ontario

Table 26 shows that, if whole exome sequencing after standard testing is publicly funded in Ontario, the budget impact would be about $8.95 million yearly in the next 5 years. Although the number of persons receiving whole exome sequencing was expected to triple compared with the current level, the budget impact did not increase as quickly because the cost per test in Ontario is expected to be lower than that in out-of-country laboratories.

If we assume a slower, more controlled uptake of whole exome sequencing, the budget impact was estimated to range from $3.05 million to $3.71 million in Years 1 to 5. Although the number of people receiving whole exome sequencing remained the same, savings would be substantial because the cost per test in Ontario would be lower than in out-of-country laboratories (roughly 23% lower than the Out-of-Country Prior Approval Program).

Table 26: Reference Case Results—Budget Impact of Funding Whole Exome Sequencing After Standard Testing in Ontario

	Budget Impact (2019 $ Million)				
	Year 1	Year 2	Year 3	Year 4	Year 5
Rapid Uptake in Ontario: Triple Current Level					
Total Costs	8.95	8.95	8.95	8.95	8.95
Cost of genome-wide sequencing	8.27	8.27	8.27	8.27	8.27
Cost of pre-test genetic services	0.54	0.54	0.54	0.54	0.54
Cost of post-test genetic services	0.22	0.22	0.22	0.22	0.22
Cost of non-genetic tests and procedures averted	−0.08	−0.08	−0.08	−0.08	−0.08
Controlled Uptake in Ontario: Similar to Current Level					
Total Costs	3.05	3.20	3.36	3.53	3.71
Cost of genome-wide sequencing	2.82	2.96	3.11	3.27	3.43
Cost of pre-test genetic services	0.18	0.19	0.20	0.21	0.22
Cost of post-test genetic services	0.07	0.07	0.08	0.08	0.08
Cost of non-genetic tests and procedures averted	−0.03	−0.03	−0.03	−0.03	−0.03

3. Publicly Funding Whole Exome and Whole Genome Sequencing at Various Tiers in Ontario

Table 27 shows the budget impact of publicly funding whole exome and whole genome sequencing at various tiers in Ontario. For every 1,000 persons tested, publicly funding whole exome or whole genome sequencing after standard testing would lead to a budget impact of $2.58 million or $4.32 million yearly, respectively. More than 90% of the budget impact is attributable to the cost of genome-wide sequencing. However, early use of whole exome or whole genome sequencing would lead to cost savings in the provincial budget. The savings come from other genetic tests avoided as a result of using whole exome and whole genome sequencing. Using whole exome sequencing as second-tier testing would result in the most savings (−$3.45 million/y), and using whole genome sequencing as first-tier testing would lead to the least savings (−$0.97 million/y).

Table 27: Reference Case Results—Budget Impact of Funding WES/WGS at Various Tiers in Ontario (2019 $ Million CAD)

	Budget Impact of Publicly Funding WES or WGS in Ontario ($ Million)				
Testing Strategies	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
WES After Standard Testing					
Total Costs	**2.58**	**2.58**	**2.58**	**2.58**	**2.58**
Cost of genome-wide sequencing	2.39	2.39	2.39	2.39	2.39
Cost of other genetic tests	0.00	0.00	0.00	0.00	0.00
Cost of genetic services	0.21	0.21	0.21	0.21	0.21
Cost of non-genetic tests	−0.02	−0.02	−0.02	−0.02	−0.02
WES as Second-Tier Test					
Total Costs	**−3.45**	**−3.45**	**−3.45**	**−3.45**	**−3.45**
Cost of genome-wide sequencing	3.10	3.10	3.10	3.10	3.10
Cost of other genetic tests	−6.34	−6.34	−6.34	−6.34	−6.34
Cost of genetic services	−0.18	−0.18	−0.18	−0.18	−0.18
Cost of non-genetic tests	−0.03	−0.03	−0.03	−0.03	−0.03
WES Alone as First-Tier Test					
Total Costs	**−3.17**	**−3.17**	**−3.17**	**−3.17**	**−3.17**
Cost of genome-wide sequencing	3.44	3.44	3.44	3.44	3.44
Cost of other genetic tests	−6.35	−6.35	−6.35	−6.35	−6.35
Cost of genetic services	−0.24	−0.24	−0.24	−0.24	−0.24
Cost of non-genetic tests	−0.03	−0.03	−0.03	−0.03	−0.03
WES + CMA as First-Tier Test					
Total Costs	**−2.94**	**−2.94**	**−2.94**	**−2.94**	**−2.94**
Cost of genome-wide sequencing	3.44	3.44	3.44	3.44	3.44
Cost of other genetic tests	−6.00	−6.00	−6.00	−6.00	−6.00
Cost of genetic services	−0.35	−0.35	−0.35	−0.35	−0.35
Cost of non-genetic tests	−0.03	−0.03	−0.03	−0.03	−0.03
WGS After Standard Testing					
Total Costs	**4.32**	**4.32**	**4.32**	**4.32**	**4.32**
Cost of genome-wide sequencing	4.15	4.15	4.15	4.15	4.15
Cost of other genetic tests	0.00	0.00	0.00	0.00	0.00
Cost of genetic services	0.20	0.20	0.20	0.20	0.20
Cost of non-genetic tests	−0.02	−0.02	−0.02	−0.02	−0.02
WGS as First-Tier Test					
Total Costs	**−0.97**	**−0.97**	**−0.97**	**−0.97**	**−0.97**
Cost of genome-wide sequencing	6.24	6.24	6.24	6.24	6.24
Cost of other genetic tests	−6.83	−6.83	−6.83	−6.83	−6.83
Cost of genetic services	−0.36	−0.36	−0.36	−0.36	−0.36
Cost of non-genetic tests	−0.03	−0.03	−0.03	−0.03	−0.03

Abbreviations: CMA, chromosomal microarray; WES, whole exome sequencing; WGS, whole genome sequencing.

Sensitivity Analysis

1. Providing Whole Exome Sequencing After Standard Testing Through Out-of-Country Prior Approval Program

Results of the sensitivity analyses are shown in Table 28. The budget impact was expected to decrease when assuming no change in whole exome sequencing volume and was expected to increase when assuming a growing clinical demand (10% change in volume). When assuming a 10% drop in whole exome sequencing price over the next 5 years (e.g., from technology improvement or increased competition among vendors), the budget impact decreased. When assuming a 10% increase in whole exome sequencing price over the next 5 years (e.g., from increased equipment costs), the budget impact increased. When assuming more non-genetic tests and procedures could be averted by whole exome sequencing, the budget impact also decreased.

Table 28: Sensitivity Analysis Results—Budget Impact of Funding WES After Standard Testing Through Out-of-Country Prior Approval Program (2019 $ Million CAD)

	Budget Impact ($ Million)				
Out-of-Country Laboratories	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Reference case	3.99	4.19	4.40	4.62	4.85
WES volume (0% change)	3.80	3.80	3.80	3.80	3.80
WES volume (10% increase)	4.18	4.59	5.05	5.56	6.12
Price of WES (10% drop over 5 y)	3.91	4.03	4.15	4.27	4.39
Price of WES (10% increase over 5 y)	4.07	4.35	4.65	4.97	5.31
Non-genetic tests or procedures averted by WES: 10%	3.92	4.12	4.32	4.54	4.77
Non-genetic tests or procedures averted by WES: 30%	3.74	3.93	4.12	4.33	4.54
Non-genetic tests or procedures averted by WES: 50%	3.56	3.73	3.92	4.12	4.32

Abbreviation: WES, whole exome sequencing.

2. Publicly Funding Whole Exome Sequencing After Standard Testing in Ontario

Results of the sensitivity analyses are shown in Table 29. Budget impact was expected to decrease when assuming lower whole exome sequencing volume and increase when assuming a higher clinical demand. When assuming a 10% drop in whole exome sequencing price over the next 5 years, the budget impact decreased. When assuming more non-genetic tests and procedures could be averted by whole exome sequencing, the budget impact also decreased.

Table 29: Sensitivity Analysis Results—Budget Impact of Funding WES After Standard Testing in Ontario (2019 $ Million CAD)

	Budget Impact ($ Million)				
	Year 1	Year 2	Year 3	Year 4	Year 5
Increased Access in Ontario: Triple Current Level					
Reference case	**8.95**	**8.95**	**8.95**	**8.95**	**8.95**
WES volume (2,000/y)	7.45	7.45	7.45	7.45	7.45
WES volume (4,000/y)	14.89	14.89	14.89	14.89	14.89
Price of WES (10% drop over 5 y)	8.77	8.60	8.44	8.27	8.11
Price of WES (10% increase over 5 y)	9.11	9.28	9.45	9.61	9.78
Non-genetic tests or procedures averted by WES: 10%	8.74	8.74	8.74	8.74	8.74
Non-genetic tests or procedures averted by WES: 30%	8.21	8.21	8.21	8.21	8.21
Non-genetic tests or procedures averted by WES: 50%	7.67	7.67	7.67	7.67	7.67
Controlled Access in Ontario: Similar to Current Level					
Reference case	**3.05**	**3.20**	**3.36**	**3.53**	**3.71**
WES volume (0% change)	2.90	2.90	2.90	2.90	2.90
WES volume (10% increase)	3.19	3.51	3.87	4.25	4.68
Price of WES (10% drop over 5 y)	2.99	3.08	3.18	3.27	3.36
Price of WES (10% increase over 5 y)	3.11	3.33	3.55	3.80	4.05
Non-genetic tests or procedures averted by WES: 10%	2.98	3.13	3.29	3.45	3.63
Non-genetic tests or procedures averted by WES: 30%	2.80	2.94	3.09	3.24	3.40
Non-genetic tests or procedures averted by WES: 50%	2.62	2.75	2.89	3.03	3.18

Abbreviation: WES, whole exome sequencing.

Discussion

Currently whole exome sequencing after standard testing is provided through Ontario's Out-of-Country Prior Approval Program. Our analysis showed that, if whole exome sequencing continues to be funded through Out-of-Country Prior Approval Program, the budget impact would range from $3.99 to $4.85 million yearly in the next 5 years (819–995 people tested per year). If whole exome sequencing after standard testing is publicly funded in Ontario, the volume of whole exome sequencing is expected to triple (2,400 people tested yearly), and the budget impact would be about $8.95 million per year in the next 5 years. We also found that early use of whole exome or whole genome sequencing would lead to cost savings on the provincial budget. Savings come from other genetic tests avoided as a result of using whole exome sequencing and whole genome sequencing.

Strengths

Our analysis has several strengths:

- We estimated both potential demand (number of patients potentially eligible for genetic testing) and supply (number of patients receiving whole exome sequencing) in our target population. The number of people potentially eligible for genetic testing was estimated from published prevalence and incidence data and clinical expert opinion. The number of patients receiving whole exome sequencing was estimated

on the basis of data from the Out-of-Country Prior Approval Program. These data suggest that a gap exists between supply and demand for genome-wide sequencing.

- In addition to estimating the budget impact of using whole exome sequencing after standard testing, we also explored the potential budget impact of using genome-wide sequencing earlier in the diagnostic pathway (as first- and second-tier tests).

Limitations

Our analysis has several limitations:

- We did not model the long-term costs and consequences related to primary or secondary findings due to a lack of data (e.g., referral to specialists, preventive treatment related to secondary findings).
- We did not model implementation or service delivery and coordination costs.

Conclusions

For people with unexplained developmental disabilities or multiple congenital anomalies, the budget impact of continuing publicly funding whole exome sequencing through Ontario's Out-of-Country Prior Approval Program was estimated to be $3.99 to $4.85 million yearly in the next 5 years. If whole exome sequencing after standard testing is publicly funded in Ontario and conducted in local laboratories, the volume of whole exome sequencing is expected to triple compared with the current level, and the budget impact would be about $8.95 million yearly in the next 5 years. We also found that using whole exome sequencing as a second-tier test would lead to cost savings for the provincial budget ($3.4 million per 1,000 persons tested yearly).

PREFERENCES AND VALUES EVIDENCE

Objective

The objective of this analysis is to explore the underlying values, needs, and preferences of those who have lived experience with unexplained developmental disabilities or multiple congenital anomalies and the potential impact of genome-wide sequencing.

Background

Exploring patients' preferences and values provides unique information about people's experiences of a health condition and the health technologies or interventions used to diagnose, manage, or treat the health condition. It includes the effect 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).[126-128] Additionally, lived experience can provide information and perspectives on the ethical and social values implications of health technologies or interventions. We also considered the evidence on ethical considerations in a review conducted by the Canadian Agency for Drugs and Technologies in Health (CADTH).[129]

For this analysis, we examined in three ways the family perspectives and experiences of people with unexplained developmental disabilities or multiple congenital anomalies who sought genome-wide sequencing for diagnostic purposes:

- A review by Ontario Health (Quality) of the quantitative evidence of patient and provider preferences and values
- Direct engagement by Ontario Health (Quality) with family members of people with these conditions through interviews
- A review by the Canadian Agency for Drugs and Technologies in Health (CADTH) of the published qualitative evidence[130]

Quantitative Evidence

Research Question

What is the personal utility of genome-wide sequencing (including whole exome and whole genome sequencing) and providers' preferences compared with other genetic diagnostic tests, including combinations of such genetic tests as chromosomal microarray and gene panels, for people with unexplained developmental disabilities or multiple congenital anomalies?

Methods

We performed a targeted literature search for quantitative evidence of patient, family, and provider preferences and values for genome-wide sequencing testing on January 18, 2019, for studies published from inception to the search date in MEDLINE. 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.[131] See Appendix 1 for literature search strategies, including all search terms.

Eligibility Criteria

Studies

Our search strategy identified studies that applied quantitative methods of measuring and reporting our outcomes of interest. Additional primary studies identified through the clinical evidence review were also included. We excluded editorials, commentaries, and general discussions of genetic abnormalities or gene discovery.

Participants

We included studies of people with unexplained developmental disabilities or multiple congenital anomalies. Studies were included if their populations were of people with, or parents/guardians of people with:

- Intellectual disability
- Developmental delay
- Congenital anomalies
- Multisystem involvement or multi-differential diagnosis
- Rare diseases otherwise u specified

We did not limit studies on the basis of age but excluded studies that were in a screening or prenatal context. We also excluded studies in populations that were clinically diagnosed but had genetic testing conducted in a confirmatory or exploratory capacity.

Interventions

We included studies that examined genome-wide sequencing, including studies that examined any combination of whole exome or whole genome sequencing, with any comparator.

Outcome Measures

We included all outcomes related to personal utility as follows:

- Patient and family impact
    - Psychological impact
    - Preferences
- Health care providers' impact and preferences

Data Extraction

One reviewer extracted relevant data using a data extraction form that included the following study characteristics: study population, description of the interventions, outcomes, and results.

Statistical Analysis

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

Critical Appraisal of Evidence

No formal critical appraisal of the evidence was conducted.

Results

Literature Search

The literature search yielded 507 citations published from inception until January 18, 2019, after removing duplicates. We identified 8 additional studies through scoping from other sources. We added another 11 citations identified from the clinical evidence review, for a total of 19 additional citations. Figure 10 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.

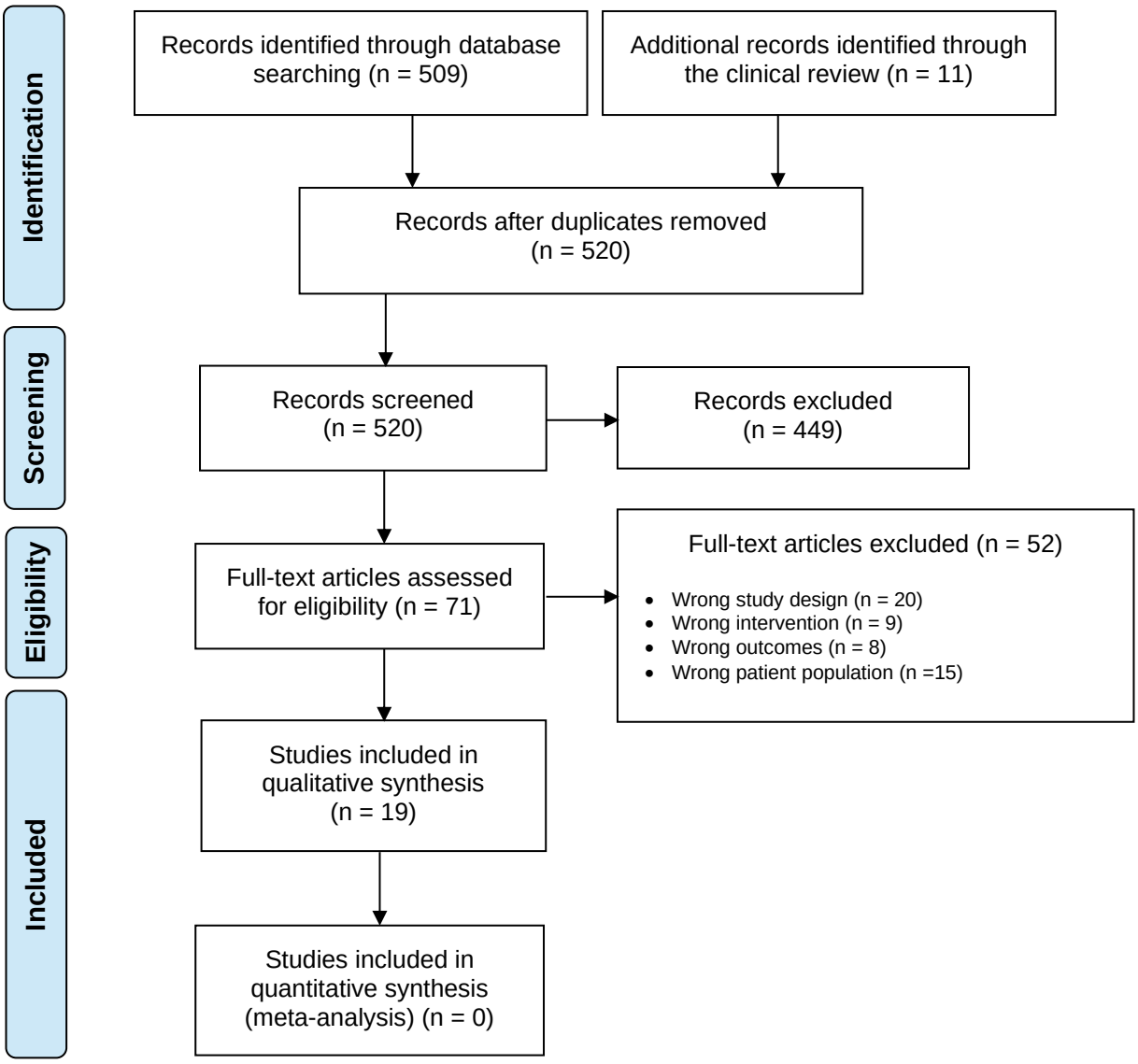

Figure 10: PRISMA Flow Diagram—Quantitative Evidence of Preferences and Values Search Strategy

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.
Source: Adapted from Moher et al.[42]

Characteristics of Included Studies

Eleven studies were identified in the clinical evidence and described elsewhere in this report (Appendix 2).[53,54,60,61,63-66,70,93,132] Eight additional studies[10,133-139] were identified through systematic literature searching the quantitative evidence on preferences; all used survey or interview methods and are briefly described in Table 30.

Table 30: Characteristics of Quantitative Studies on Preferences

Author, Year	Location	Population	No. of Included Respondents
Baldridge et al, 2017[63]	United States	Mixed suspected genetic disorders	155
Barajas and Ross, 2015[137]	United States	Pediatricians	179
Basel and McCarrier, 2017[10]	United States	Patients, and their families, who have received whole exome sequencing	139
Bick et al, 2017[64]	United States	Children with suspected genetic disorders	22
Brothers et al, 2017[133]	United States	Families recruited from a pediatric neurology centre	200
Costain et al, 2012[134]	Canada	Patients and families experiencing 22q11.2 deletion syndrome	73
Dikow et al, 2019[135]	Germany	Parents of children with intellectual disability undergoing diagnostic genetic testing	194
Jaitovich Groisman et al, 2017[138]	International[a]	Neurologists	204
Lee et al, 2014[65]	United States	Mixed, including developmental delay and ataxia	814
Mak et al, 2018[132]	Hong Kong	Patients referred for exome testing	104
Marshall et al, 2019[139]	Canada	Parents of children with rare diseases	319
Neveling et al, 2013[53]	Netherlands	Variety of specific disorders, results for only mitochondrial disorders included in our review	44
Peyron et al, 2018[136]	France	Parents of children with rare genetic disorders	513
Retterer et al, 2016[61]	United States	All patients referred for whole exome sequencing, results for multiple congenital anomalies reported in our review	729
Schofield et al, 2017[93]	Australia	Childhood-onset muscle disorders	30
Stark et al, 2016[54]	Australia	Pediatric suspected monogenic disorders	80
Stavropoulos et al, 2016[66]	Canada	Pediatric patients who met criteria for chromosomal microarray	100
Valencia et al, 2015[60]	United States	Mixed, including mitochondrial disorders and neurological disorders	40
Yang et al, 2014[70]	United States	Mixed, neurological, and non-neurological conditions	2,000

[a]Includes 215 countries.

Patients' and Family Perspectives About Genome-Wide Sequencing

Four studies reported patients' and family preferences for a diagnosis from genetic testing (Table 31).

Table 31: Patients' and Family Impressions of Impact of Diagnosis and Reasons for Seeking Diagnosis Through Genome-Wide Sequencing

Author, Year	Items Surveyed	Results
Costain et al, 2012[134]	Improved interaction with doctors	> 50% agreed
	Led to better care	> 50% agreed
	Diagnosis increased worry about future	< 50% agreed
	Diagnosis had positive impact	> 50% agreed
	Diagnosis should have come earlier	> 50% agreed
Dikow et al, 2019[135]	Finding etiologic diagnosis is important	Mean score 3.7 ± 0.5[a]
	Expect diagnosis to improve special needs education	Mean score 3.3 ± 0.9[a]
	Expect diagnosis to provide better therapies	Mean score 3.4 ± 0.8[a]
	Expect diagnosis to bring emotional relief	Mean score 3.2 ± 0.9[a]
	Expect better support from insurance and public financial aids	Mean score 3.3 ± 0.9[a]
	Suffered from uncertainty of not having diagnosis	Mean score 3.1 ± 1.0[a]
Jaitovich Groisman et al, 2017[65,138]	Needed to get answer	58.9% agreed
	Wanted to be sure about diagnosis or prognosis	67.4% agreed
	Wanted to know if blood relatives (e.g., other children) were at risk	58.9% agreed
Marshall et al, 2019[139]	Whole exome sequencing compared with other genetic tests, other tests, and operative procedures	Preference in favour of exome sequencing

[a]Score is from 1 to 4, where 4 is strongly agree; ± standard deviation.

Jaitovich Groisman et al[138] reported that 1.6% of parent and patient respondents thought whole genome sequencing should be offered to all patients, while 15.7% thought it should not be offered and 61.1% thought it should be offered to a limited group of patients.[138] The same survey found greater consensus on providing the test to patients with unclear phenotypes or complex inheritance (84%) as well as for patients with risk of comorbidity because of their genetic backgrounds (76%).[138]

Dikow et al[134] also found lower scores of agreement for the following: had contact with self-aid group, wished to contact families with children who had similar diagnose[135]

In a discrete choice experiment, Marshall et al [139] found that families were willing to wait 5.2 years for a test result or accept a reduction of receiving a diagnosis by 3.1% in hypothetical scenarios assessed as a thought experiment.[139]

In one survey of parents of children with rare diseases, respondents wanted the support of a geneticist more than that of a nurse, but showed no significant preference for support from a psychologist versus a geneticist.[136]

Clinicians' Perspectives on Genome-Wide Sequencing

Three studies examined clinicians' practices and clinicians' preferences for genome-wide sequencing (Table 32).

Table 32: Clinicians' Perspectives on Using Genome-Wide Sequencing

Author, Year	Impact on Clinical Care	Clinicians' Preferences
Baldridge et al, 2017[63]	21 (14%) cases were changed[a]	--
Jaitovich Groisman et al, 2017[65,138]	--	12.6% felt sufficiently informed
	--	37% thought benefits outweighed risks
Peyron et al, 2018[136]	--	Geneticists should be deciding what to disclose to patients (vs. ethics committee, $P < .01$)

[a]16 cases were promoted to a definitive diagnosis and 5 were demoted.

Secondary Findings

Ten studies discussed patients' and family preferences for secondary findings and one study reported clinicians' perspectives (Table 33). Most people wanted some form of secondary findings reported. In two studies that reported details of respondents' preferences, there was a slight inclination toward wanting the findings for treatable compared with untreatable conditions.

Table 33: Preferences for Secondary Findings

Author, Year	Definition of Secondary Findings	N Who Wanted Secondary Results Specified (%)
Baldridge et al, 2017[63]	Secondary findings according to ACMG guidelines	167 (97)
Basel and McCarrier, 2017[10]	None	37 (26.6)
	Untreatable childhood onset	70 (50.4)
	Treatable adult onset	78 (56.1)
	Untreatable adult onset	58 (41.7)
	Carrier status	78 (56.8)
Bick et al, 2017[64]	None	3 (13.6)
	Untreatable childhood onset	15 (68)
	Treatable adult onset	18 (82)
	Untreatable adult onset	12 (54)
	Carrier status	15 (68)
Brothers et al, 2017[133]	Parents wanting to know their own secondary findings	> 80
Lee et al, 2014[65]	Secondary findings including genes identified that could extend beyond recommendations from ACMG guidelines	252 (97)
Peyron et al, 2018[136]	Comparison: more respondents wanted to know all secondary findings with possible treatable actions versus no secondary findings reported	NR[a]
Retterer et al, 2016[61]	Secondary findings according to ACMG guidelines	2,091 (87.8)
Stavropoulos et al, 2016[66]	Medically actionable adult-onset disorders	74 (74)
Valencia et al, 2015[60]	Secondary findings according to ACMG guidelines	36 (90)
Yang et al, 2014[70]	Secondary findings according to ACMG guidelines	1,808 (90.4)

Abbreviation: ACMG, American College of Genetics and Genomics; NR, not reported.
[a]Percentage not reported, but difference stated to be a significant with $P < .01$.

One study charged parents for getting tested for secondary findings when submitting their genetic information as part of trio testing (proband secondary findings were included). In this study, nine (8.7%) parents chose to pay to receive results for their secondary findings.[132]

Three studies reported on the rate of refusal for genome-wide sequencing, ranging between 3% and 10%.[53,54,93] One study elaborated that families declined any genomic testing after receiving pre-test counselling, saying they did not want unsolicited findings, especially in children.[53] A fourth study reported that 95 (47%) families declined whole genome sequencing after receiving only chromosomal microarray testing.[66]

Clinicians' Perspectives on Secondary Findings

The study by Barajas and Ross[137] surveyed clinicians about their support for the ACMG guidelines that promote reporting secondary findings. Of pediatricians surveyed who belonged to the section of bioethics, 34.7% supported reporting the 56 variants listed by the ACMG as reportable secondary findings not requiring explicit additional consent. On the other hand, 70.8% of pediatricians from the section of genetics and birth defects supported the guideline

($P < .001$). Only about 30% of both groups supported parents having access to findings for their children associated with adult-onset conditions.

Limitations

The 19 studies included in the quantitative evidence on preferences reported that patients and families sought genome-wide sequencing to get a diagnosis or to confirm a suspected disorder and that they generally want to hear about secondary findings in some form.

There are limitations to this review. The literature search was very focused to align with the clinical evidence review and was limited to the use of genome-wide sequencing in people with unexplained developmental disabilities or multiple congenital anomalies. It excluded studies that were conducted in broader populations (such as surveys among people in the general population) or that used alternative diagnostic testing (such as chromosomal microarray). However, it is reasonable to presume that the patients', families', and clinicians' preferences for a diagnosis would be similar when other genetic technologies, such as chromosomal microarray or single-gene tests, are used.

Qualitative Evidence

Ontario Health (Quality) collaborated with the Canadian Agency for Drugs and Technologies in Health (CADTH) to conduct this health technology assessment. CADTH conducted a review of qualitative literature on patient perspectives and experiences[140] and a review of ethical issues.[141]

Direct Patient Engagement

Methods

Partnership Plan

The engagement plan for this portion of the report focused on consultation to examine the experiences of families of people with unexplained developmental disabilities or multiple congenital anomalies. 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 families of those with these conditions.[142] 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 method.

Participant Outreach

We used an approach called purposive sampling,[143-146] 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 clinical experts, patient groups, and partner organizations, including the Canadian Organization for Rare Disorders and the Rare Disease Foundation, to spread the word about this engagement activity and to connect us with families of those with unexplained developmental disabilities or multiple congenital anomalies who have sought diagnoses through genome-wide sequencing.

Inclusion Criteria

We sought to speak with people with unexplained developmental disabilities or their family members and caregivers. Participants did not need to have direct experience with genome-wide sequencing to participate.

Exclusion Criteria

We did not set exclusion criteria.

Participants

For this assessment, we spoke with 12 people in Ontario, all family members of those with unexplained developmental disabilities or multiple congenital anomalies. Of these participants, 10 had experience receiving a diagnosis through genome-wide sequencing, one had not received a diagnosis, and one had been unable to access genome-wide sequencing. Participants were from various parts of Ontario, including the greater Toronto area, Ottawa, and Thunder Bay.

Approach

At the beginning of the interview, we explained the role of our organization, the purpose of this report, 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 if requested (Appendix 2). We then obtained participants' verbal consent before starting the interview. With participants' consent, we audio-recorded and then transcribed the interviews.

Interviews lasted approximately 20 to 60 minutes. The interview was loosely structured and consisted of several open-ended questions. Our list of questions (developed by the Health Technology Assessment International Interest Group on Patient and Citizen Involvement in Health Technology Assessment)[147] focused on participants' experience with unexplained developmental disabilities or multiple congenital anomalies, previous attempts to obtain diagnoses through testing and the effect of the diagnostic odyssey. We also inquired about values and motivations that guided their choice to pursue whole genome sequencing. Where applicable, we spoke about their perceptions of the benefits or limitations of whole genome sequencing and consequences of a genetic diagnosis. See Appendix 3 for our interview guide.

Data Extraction and Analysis

We used a modified version of a grounded-theory method 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.[148,149] We used the qualitative data analysis software program NVivo[150] to identify and interpret patterns in the data. The patterns we identified allowed us to highlight the effect of unexplained developmental disabilities or multiple congenital anomalies and of a diagnosis obtained through genome-wide sequencing.

Results

Impact of Developmental Disabilities and Congenital Anomalies

Congenital anomalies can impair a person's development intellectually or functionally and can have various degrees of severity. Additionally, congenital anomalies may or may not accompany development disabilities and intellectual disability. For this reason, the level and type of impairment and impact described by family members that we interviewed varied greatly. Some family members described their loved one's impairment as more physical, while for others it was more cognitive. Various physical impairments were mentioned, from difficulty eating and swallowing, to challenges with fine motor skills or the ability to walk. Cognitive impairment ranged from severe to mild:

> *He wasn't holding his head up; he wasn't tracking, and we had an older son, so we knew something was potentially wrong or … not functioning the way it should. [B]asically, … that one medical appointment … set off this whole slew of appointments.*
>
> *My daughter was non-verbal up until grade 3 and used an augmentive communication device. She tried to speak, but it was very difficult to understand, even for family, and almost impossible for people outside of the family.*

In each case family members described the accommodations and challenges they and their loved ones faced in navigating their condition within the health care system and in a larger

societal context. Family members spoke of the need to arrange support services, coordinate with school systems, and arrange therapeutic services. Making arrangements had a large impact on the daily lives of family members; some described the need to step away from their careers to manage care of their loved one. The varied ages of those with developmental disabilities also meant that some families had been navigating these challenges for many years, while for others their child was still young and the process was still relatively new:

> *[I]t was presenting in my daughter like a global developmental disability, so she needed support and therapy for [physical and occupational therapy], speech, and then finding adapted, accessible recreational opportunities for her. [We had to learn] about what school options were available to her and [about] academic cognitive support.*

> *So, I ended up leaving, … stepping away from my career for 12 years and being her care navigator during that time. [A]ll the while [she was] under the … umbrella category of global developmental delay, or global development disability.*

Search for a Diagnosis

Participants generally reported that their search for a diagnosis began upon realizing that their loved one was manifesting some sort of developmental disability or congenital anomaly. Parents described their initial suspicions and concerns about their child reaching certain milestones and how those concerns led to initial interactions with health care professionals to attempt to discover a cause:

> *So, the two sort of big things that were major flags for us, was sort of motor delays and speech delays, and the fact that there was both of those, which seems unlikely to be due to random chance.*

> *[W]e noticed pretty early on that she wasn't achieving some developmental milestones. She was not sitting independently by age 6 months. And I have a son, who is [developing typically], so I was already … aware that this wasn't the usual progression of development.*

> *And when we moved back to Canada, our daughter was about 14 months old, and we were, at that point, just starting to enter the … freak-out stage about her because she wasn't really standing much. She certainly wasn't walking. She didn't really walk until about 2 [years].*

For those with unexplained developmental disabilities or multiple congenital anomalies and their families, this search for a diagnosis could take years and include an array of tests. Participants we interviewed spoke of the long journey, sometimes known as the diagnostic odyssey, through medical appointments, administration of tests, and various processes:

> *[T]here were two or three things that they started with, just [in] general, like we did blood work and once those results came back, then we would have another follow-up … a few months later. [A]s we were doing this, they were ordering other tests, … other kinds of neurological testing. [The patient was] sent to cardiology, back to ophthalmology, just to rule things out.*

> *Genetics followed up with us at [the hospital], so we would go back. I think we probably went back maybe about four times from our very first visit to the time that we received our diagnosis. It might have been more.*
>
> *But nonetheless she ran microarray testing at that point; she screened for Fabry disease, homocysteine, just a bunch of testing, but nothing was found.*

This diagnostic odyssey could be challenging, and participants often spoke about these challenges and the frustration they experienced during these processes. Often, this frustration was caused by what were perceived to be long delays in obtaining results and the overall length of time it seemed to be taking to find a diagnosis:

> *And they got us in there, ruled out cataracts, and that wasn't an issue. [But we spent what] felt like … a few months just waiting. [T]he waiting even just to see someone in neurology was pretty gruelling actually, as you worry and Google and search for all the possible things that could go wrong.*

Participants also spoke of the strong emotions at various stages of their diagnostic odyssey. Each new round of testing could bring hope that a diagnosis would finally be found, only to result in a negative result, leading to contrasting feelings of relief and depression. Some of those interviewed spoke of occasions when a diagnosis was suspected or hinted at, only to be a false trail. One participant reported a wrong diagnosis being made, only to be corrected later. This could lead to extreme swings in emotions as family members learned and studied rare conditions, only to learn that their loved one did not have that condition:

> *We ended up going back to the geneticist, who said, "Oh, yes, look at that. We need to test your parents to make a definitive diagnosis," and of course, upon testing my parents, it was determined that he did not have Angelman's syndrome.*
>
> *So I'd been like on edge for 3 months wondering if he had this severe degenerative disease and then finding out, "Oh my God, I have to wait another 3 months." [F]or me, [that] was a big low, just [thinking], "How am I going to face another 3 months of wondering and worrying?" [S]o that was very impactful, and [results] came back negative.*
>
> *They said, "Oh, we want to test her for …" I can't even remember. I may have actually in some way blocked it out of my memory. … I think it was P10, which is a genetic syndrome and a big head is a marker for that syndrome. Then, of course, I looked up what P10 was and it is inevitable terminal cancer onset [at] age 20. So, there was a period of about 4 months, or more, where I was wondering if this was the diagnosis that we were going to receive. It was brutal. It was brutal.*

Some of those we interviewed reflected that at times they became so frustrated that they felt they no longer wanted to pursue diagnosis and could begin to question the ultimate purpose of the diagnostic odyssey:

> *That was horrible! [A]t that point, I had sort of sworn off pursuing genetic testing, because that was an incredibly stressful time and a difficult experience.*
>
> *But I was also thinking, why bother going back year after year, or every couple of years to [hospital], yet another appointment, when I'm already going to umpteen, like*

> *conservatively, 20 to 30 medical appointments for my daughter every year; why am I going back year after year when they're just telling me, "We don't know. We don't have an answer. We don't know."*
>
> *But again, it weighed heavily on us, are we going to have to do all this? Because it takes a drain out of you emotionally, because it's … at that time, it was heavily in an unknown category, right? So, do you want to do this again? Do you want to go through this again? Are we going to know more and if not, … are we being "selfish"? Is it fair to [the patient]?*

A couple of participants reported taking a break from pursuing genetic diagnostic testing entirely. They made this choice from a combination of frustration at perceived lack of progress and hope that perhaps time and advances in technology could provide more opportunity or could increase the likelihood of successful diagnosis:

> *The geneticist at [the hospital] said, "Well, this is as far as we can go at this time." I mean that would have been back in 2009. She said, "That's as far as we can go. Check in with us every couple of years." So, that was that.*

It is likely that some people with unexplained developmental disabilities or congenital anomalies and their families ultimately halted their diagnostic odyssey and no longer pursued genetic testing. However, the focus of our assessment and the participation bias in those we interviewed meant that we were more likely to hear from those who continued and eventually received a diagnosis through genome-wide sequencing.

Motivations for Search for Diagnosis

When considering the potential effect of genome-wide sequencing in providing a diagnosis, it is important to understand the motivations of people with unexplained developmental disabilities or multiple congenital anomalies and their families to continue to seek a diagnosis. Survey responses from the quantitative evidence review of preferences and values in this health technology assessment show a strong desire for diagnosis with an expectation that it will improve interactions with the health care system through improved understanding of the disease, potential therapies, and access to support programs.

Many of these expectations and motivations were found in the qualitative literature, as well as through direct patient interviews. Both direct interviews and the qualitative literature summarized in the CADTH report[130] illustrate that the primary motivations were numerous and varied, depending on the personal preferences and situations of each patient and family. Many factors influenced personal motivations, and these motivations could change over time, as described by participants. Given the data we collected, we can group motivations in several general categories: informational, medical and therapeutic, emotional, and family planning.

Information

Participants consistently remarked upon a desire for knowledge as a motivation: simply to know the cause of developmental disabilities, even if nothing further could be done with that knowledge:

> *I think the more information you have, the better you can … assess what needs to be done.*

> *I think … every little bit of knowledge you have is power, … and it can help you kind of forgo all this wasted time.*

The qualitative literature review by CADTH[130] found that "while parents often understood their child's clinical diagnosis, these had typically been established on the basis of symptomatic markers that were unable to ascribe causal associations. As such, the potential for genetic testing to provide specificity and clarity regarding their child's condition was highly valued and sought after" (CADTH report, pp. 7–8[130]).

Some participants described this as putting a label on the unexplained developmental disabilities or congenital anomalies and finding value in that label or diagnosis, even if that was the only result:

> *So, [my wife] is very matter-of-fact, scientific-minded in terms of everything has to have a definition, everything has to have a cause, a solution, a prognosis. Everything has to have, and yes, we're going to use the "label." That's just her.*

> *Like, you're not [operatingly blindly], right? You … have more detail. … So, it's almost like a control issue.*

The report from CADTH emphasizes that "for some, … naming and thus knowing what was wrong with their child was considered a satisfactory outcome for the time being, as it was one they had never thought they would have" (CADTH report, p. 8[130]).

Clinical Actionability and Therapies

Despite the stated value placed on simply having a firm diagnosis, most participants remarked that they hoped a diagnosis would ultimately lead to further medical treatment and advances. Expecting that a diagnosis would lead to clinical action was a powerful motivation. Participants remarked upon the hope that clinical treatments or therapies would be better targeted and achieve more success with a proper diagnosis:

> *So, I think having a label, although comforting, [is] only step 1 of many, many, many, many. [I]t's almost like, "Where do we go from here?" Clearly, … a label alone isn't enough.*

> *I guess [I] was always thinking, "If we know, we might be able to do something," so I might be missing a key piece of treatment just by not knowing what his diagnosis is. [W]hat's the actual problem here that we're trying to correct, that could help him in his development physically, developmentally, whatever?*

> *I think that'd be wonderful, actually, because … quite honestly, without a firm diagnosis and even with one in the mental health realm, it seems there's still lots of, I would say, inappropriate and improper sort of treatment and caretaking and how you're treated.*

The report by CADTH[130] supports this observation, finding in the literature that family members' "goals of genetic testing tended to be articulated in conjunction with hopeful conversations around treatment outcomes, management strategies, and prognostic timelines among other things" (CADTH report, p. 8[130]).

Some participants reported that, when it came to potential medical treatments or interventions, their motivations could change over time. Given how long a diagnostic odyssey could take, often the expectations of people with developmental disabilities or congenital anomalies and their families had to be adjusted:

> *Obviously, you know, when he was younger, [we were] looking for a cure, looking for some sort of treatment. [O]ver time, when [they get older] and you get older and understand … the issues and stuff like that, it really is just good to know, because in the future it may actually solve something, right?*

Similar to participants' motivation to find clinical actionability through a diagnosis, participants also expressed the hope that a diagnosis could increase access to financial services or therapies that previously had been restricted or inaccessible to them. This sentiment was common in both direct interviews and the qualitative literature. "While whole exome sequencing and other genetic tests are not officially indicated to assess appropriateness of current treatment regimens and monitoring strategies, or the accuracy of current prognoses, it is clear that both families and clinicians engage with [the] test as a way of getting at these concerns" (CADTH report, p. 10[130]).

Restricted access to services or supports could be a cause of frustration for people with developmental disabilities and their families; participants reported feeling as though they were being denied access to services or to financial resources that could be beneficial to their health:

> *Sure, so I [knew] that if we had a clear diagnosis, then I would probably have access to funding. I've never received a dime from anyone for anything, because there is no funding for somebody with global developmental disability. So, I probably would've had access to some funding opportunities.*

> *I never was able to receive any pro-active recommendations or directions on what therapies to pursue for her. So, … if we had had a diagnosis, I understood that it probably would have been easier for me to navigate the system and maybe access some additional supports.*

Challenges in accessing services or supports led to some family members even reporting feeling emotions such as jealousy or a desire to have their loved one diagnosed with a more common condition because it would help in accessing resources or support from community groups:

> *I remember … I had lots of friends with kids with an [autism spectrum disorder] diagnosis or a [cerebral palsy] diagnosis and thinking, "It would have been so much easier if this were our path as well," but it wasn't.*

> *I was very envious of people who had a diagnosis of Down syndrome or autism or, you know, where you can instantly find a community of people that know what you're going through. My son's symptoms and everything associated with him was just … there was nothing. I couldn't find [any] community of people that had children … going through similar challenges.*

Family Planning and Emotions

Beyond the immediate medical and therapeutic needs of people with developmental disabilities or congenital anomalies, some participants reported that their motivations for a diagnosis were more long-term. These participants reported that motivation to find a diagnosis also came from a desire to do family planning. This motivation was common in the qualitative literature as well: "This ability of genetic testing to move beyond the child in question through to those who share genetic material was also made clear by the way in which testing was used by both parents and clinicians to engage with conversations around family planning" (CADTH report, p. 11[130]). When developmental disabilities or congenital anomalies appeared in the first child, parents often felt the need to know whether it was an inheritable trait and whether they risked passing the trait on to a future child:

> *What if we have another and the same thing happens? Should we have another and what if this happens? That really weighed heavily, I must admit.*
>
> *That was a huge piece of it for me. … We did want more kids, but we didn't have them because we were too worried about the impact of another child having the same condition and what that would do, for example, to our other son.*
>
> *And yes, I was pushing for … I mean we wanted ... he was our first child; we wanted to have another child. That was one of the reasons we wanted answers.*

Some participants mentioned personal and emotional reasons for wanting to know the diagnosis and cause of the developmental disabilities or congenital anomalies. Parents spoke of feelings of blame and of guilt that they perhaps had caused the impairment, that perhaps they had done something wrong during pregnancy. As expressed in CADTH's report, "Whether concerned that they had done something during pregnancy to prompt their child's current condition or that they were carriers of the genetic mutation affecting their child, parents struggled to make sense of causality" (p. 11[130]):

> *So, for [my wife], it was very important to not only put a label on it, but also … to find out the cause. Was she responsible for it? That really weighed [on her].*
>
> *[T]here's always the guilt, and that was a big thing that I noticed. There's the guilt [over] what did we do wrong? What could we have done differently, or more important (and I've heard this word used from her before), what could we have done correctly to prevent this?*
>
> *I guess you can't understand unless you really experience it, but it was just a void that we wanted to know and to understand [my sister] better. [A]lso, … I saw my parents unfairly blamed for her, for the way she was.*

Genetic counselling was helpful in alleviating and understanding these emotions and the causality of genetic conditions. Counselling sessions could provide valuable information and insight and were reported as a standard part of the process before receiving genome-wide sequencing.

Genome-Wide Sequencing

Through interactions, such as genetic counselling, or through their own research, participants we interviewed were generally familiar with the nature of genome-wide sequencing before undergoing the tests. However, this familiarity could reflect a participation bias in that those who spoke to us were highly motivated to pursue information and to research the potential diagnosis of their loved one's developmental disabilities or congenital anomalies. Several participants gained access to genome-wide sequencing through research projects, which involved a great deal of genetic education and counselling before the test.

This education and counselling were considered particularly valuable in allowing patients and their families to understand the nature of the testing, the likelihood that a positive result could be obtained. It also allowed for discussion of secondary or incidental findings.

Discussions of Secondary or Incidental Findings in Genome-Wide Sequencing

Results of genome-wide sequencing could potentially involve secondary or incidental findings. Pathogenic variants could be revealed by genomic testing and could affect all family members. The review of the literature by CADTH[130] found that choosing to learn of secondary or incidental findings was a complicated decision for many patients and their families. "Associations between guilt, fear, and the possibility to have some sort of 'knowledge' could act both as a draw to incidental findings as well as a push not to engage with them. Framed as negotiations with uncertainty, parental desires to know 'of' incidental findings that may later become knowing 'about' clinically actionable conditions were often articulated from competing perspectives" (CADTH report, p.13[130]).

In the quantitative surveys tabulated in evaluating preferences described elsewhere in this report, 75% of people surveyed across 10 studies (> 4,500 persons) would like to have results from secondary findings shared with them. In our direct participant interviews, less emphasis or concern was reported about secondary or incidental findings. Most participants reported that their discussions with health care providers or genetic counsellors were beneficial in this regard. They felt comfortable with any information or knowledge gained, and did not typically hesitate to undergo genome-wide sequencing. This perception could be a participation bias in those we interviewed, given genome-wide sequencing successfully diagnosed most cases; participants could view any secondary or incidental findings as "worth the price" of receiving that diagnosis:

> *She actually gave us documentation that my husband and I both needed to sign. She explained [what it means very thoroughly to me] and [that] I'm saying [whether] I want to know about secondary findings. Me, I know I would say yes. I was 99% positive my husband would say yes, and he did as well when I came home and talked to him about it. So, we signed the documents and checked off "yes" and sent them back. We were very aware. They did a very good job of educating us on that.*
>
> *[W]ith so many things, it feels like when you do have information you can act somewhat differently, and even if you couldn't, … the information does not create the problem. It just tells you the problem that's already there is there. … I just don't understand … why I would want ignorance.*
>
> *They did take us through the process of what the secondary findings might reveal, but we signed-off on everything. We were prepared to hear whatever secondary findings came out.*

Expectations of Genome-Wide Sequencing

Given the relatively good knowledge of genome-wide sequencing among participants, they reported that their expectation of successful diagnosis from the tool was fairly low. Almost all participants we interviewed had journeyed along a diagnostic odyssey for several years. Many different tests had failed to produce a diagnosis. Genome-wide sequencing was sometimes viewed as the latest technology to try:

> *She explained what whole exome sequencing was. I really didn't have a lot of hope because we had [undergone] so much genetic testing already, that I just anticipated another closed door and that we'd have to wait another 10 years.*

> *I guess we were so focused on finding what really was wrong, that was the primary concern. [I was wondering, "O]kay so it wasn't all these things that I thought it was; well, what is it?" But I didn't really hold out that much hope. I mean, look at all the testing she's already went through; maybe they can't find it.*

> *It's in a way, my prediction: so who cares if we get a diagnosis? Because nobody's going to know what it is, and it's just going to be … applying a random name to the condition.*

Despite some moderate expectations, participants generally described substantial effect when a successful diagnosis was made through genome-wide sequencing.

Impact of a Diagnosis Through Genome-Wide Sequencing

While genome-wide sequencing successfully diagnoses less than 50% of conditions, participation bias in our interviews meant that most received a diagnosis through this testing and could report on the various effects of the diagnosis on the lives of both the people with developmental disabilities or congenital anomalies and their families.

Given the variety of motivations participants described in their pursuit of a diagnosis through genome-wide sequencing, it is unsurprising that effects varied in multiple aspects of the lives of these patients and their families. Overwhelmingly, participants reported that effects were positive, though some did acknowledge ongoing challenges or areas of regret when it comes to genome-wide sequencing. Participants described consequences of receiving a diagnosis through genome-wide sequencing in categories similar to categories of their original motivations; medical and therapeutic, social, and emotional and family planning.

Medical and Therapeutic Benefit

As described previously, several of those we interviewed spoke about improving medical treatment or access to therapy as a primary motivator for pursing a diagnosis. Once a diagnosis was made and the rare genetic condition was identified, some participants reported that they were indeed able to improve the clinical therapy and treatment offered. Often this occurred through contacts and interactions with other people who had the rare genetic condition and their family members, to share information and compare strategies for treatment:

> *A lot of these [medical concerns] were reported by a number of families who had children with this diagnosis. [I]f I thought … that any of this was a [potential] factor in my daughter's current condition, I was going to … investigate and try to rule it out. [I]'m still working my way through the list.*

Participants also reported that receiving a diagnosis allowed them to target expert clinicians and researchers who focus on the rare disease in question. This could allow affected people and their families to be involved in further research or learn the latest trials or therapies targeting the genetic condition. This benefit was mentioned in the qualitative literature as well; "Though test results, even when indicating pathogenic or likely pathogenic variants, rarely changed treatment regimens…in some cases they were used to support referrals to new specialists or to support additional monitoring and testing strategies. Once engaged with new specialists, it may then become possible for new treatment regimens to be suggested" (CADTH report, p. 10[130]):

> *I can't actually read the stuff myself, because I'm not a physician or a geneticist, but … I can find the people that work on it, and so I think within 2 days of the diagnosis I was on the phone with a doctor at a children's hospital in Arkansas, who does research on this specific condition.*
>
> *[A]ll of a sudden it was like, "Okay, we need to get the deaf and hard of hearing people at school involved," and … they [made] all the accommodations around that, so [the diagnosis] definitely was a help there.*
>
> *And so, … we started pretty intensive speech language therapy. Our daughter started prompt speech language therapy, which is working, slowly.*

Not all participants found that a diagnosis increased access to services. In some cases, this was described as particularly frustrating because participants had hoped obtaining a diagnosis would unlock services and increase access:

> *Services? Services have sucked for my son since he started school, and this didn't impact it one way or the other. So, … I can't say [the diagnosis has] impacted that.*

Social Benefit

Several participants reported that they valued the social benefits that had occurred following the rare disease diagnosis. Existing rare disease communities could be found and accessed, allowing people with rare conditions and their families to connect with similar people around the world, providing great social benefits through the sharing of information and experiences. Some found this particularly helpful after the initial surprise and emotional occurrence of receiving a diagnosis:

> *[The diagnosis] initially was devastating. I don't think I got out of bed for a week, but then after that first week and the shock settles in and then you just sort of pull yourself up, and that's when I started joining all these groups. It was a relief.*
>
> *And sharing, you know, experience and knowledge and feeling a sense of connection with families now, all over the world, who are experiencing pretty much exactly what we have experienced.*
>
> *So then I got quite a bit of support and I was very happy to actually be connected with this parent group, and it has been, I will speak about the positive aspects of having the diagnosis, and how it's benefitted our lives to be connected with this group with such a similar experience to ours.*

Qualitative literature also indicated that a benefit of diagnosis could be social connections; "For many, a genetic diagnosis helped to pen doors and build new social ties by introducing them to families living with similar conditions and experiencing similar difficulties" (CADTH report, p. 12[130]). Some participants found that they became a resource for other families with rare conditions, depending on the age and nature of the impairment of the rare disease:

> *I don't know. I'm not sure it actually changed anything in our actions. I know consulting with me has changed things for other parents*

> *Then, I've been grateful to be able to support a number of other families in the community because it turns out, my daughter is one of the highest functioning people with this diagnosis. She does speak verbally, communicate verbally, and I think she's actually one of the only ones who does.*

Not all diagnoses resulted in this social benefit. In those instances of an extremely rare genetic disorder, there may not be a community to connect with; 'Others expressed that a genetic diagnosis could be detrimental and promote a sense of isolation among families as results tended to indicate a rare disease, which no or few other child(ren) may be living with.' (CADTH report, p.12[130]):

> *So, as far as we know, the only report we can find…we've been able to see that there is at least one other child that has the exact same deletion as… or anomaly that my son has and I have no idea how to connect with that person.*

Family Planning and Emotional Benefit

Several participants commented that one of the benefits of a genetic diagnosis was the ability to make informed choices and decisions around family planning. Understanding whether developmental disabilities or congenital anomalies were inherited traits or not allowed families to share or act upon this information in an informed way, both for themselves or for other family members:

> *[M]y sister has two children; … they're adults … now, and they are not affected either way. Now we were told though, that they have a 50% chance of passing the syndrome down to their children, so at least now … they're in a position of making informed reproductive and family planning.*

> *It was a brand-new mutation in her and I don't pretend to understand the science enough to know how they know that, but that is some knowledge that I have just taken and that has given me a lot of comfort to know that my son is not a carrier and would not need to worry about this if he were to have children.*

Some participants expressed regret that the information provided by genome-wide sequencing was not obtained earlier as decisions around family planning may already have been made:

> *We did want more kids, but we didn't have them because we were too worried about the impact of another child having the same condition and what that would do. … So if we'd known earlier it might have … impacted our family planning as well.*

Participants reported that a diagnosis could lead to feelings of relief and removal of any sense of guilt or blame attached to unexplained developmental disabilities or congenital anomalies:

> *And so, receiving this diagnosis also lifted any last lingering veil of guilt or worry or responsibility. It relieved a sense of worry if my son was a potential carrier as well.*
>
> *But I would like to add, one of the most wonderful gifts was to be able to tell my mother it wasn't her fault, because … that was wonderful. [S]he … didn't understand the science behind it. [She had] always wondered maybe it was the antibiotics or [something else in pregnancy].*

Concerns with Genome-Wide Sequencing

Overall, participants did not express many concerns or regrets when it came to seeking out a diagnosis for unexplained developmental disabilities or congenital anomalies through genome-wide sequencing. While they reported challenges with access and wait times, participants generally felt that the benefits to a diagnosis outweighed any drawbacks.

However, as reported previously, not all diagnoses resulted in immediate clinical action or increased access to therapeutic services or social benefits. As expressed in CADTH's report,[130] a diagnosis could result in learning *of* a rare condition, but very little *about* that rare condition, depending on the rare disease diagnosed. Additionally, some participants said during their interviews that they felt "dropped" by the health care system once the diagnosis was made through genome-wide sequencing; often very little follow-up was offered because the condition diagnosed was rare and few support structures exist for that diagnosis:

> *But at the end of the day, did we walk out of there with any new information about my daughter's prognosis or what our abilities might be in the future, or ideas for therapy that would be particularly beneficial to her related to the new diagnosis? No, to all of the above, and furthermore, it was clear that that would be my last contact with Genetics at [the hospital].*

One fairly consistent regret reported was that the diagnosis and information this provided was not received sooner. Several participants lamented that effective therapies or medical actionability could have been started had the diagnosis been made earlier:

> *I just wish it had been available sooner, because 13 years … well, I guess he was 11 when we finally got the answer. [H]e has severe seizures and now we know. We had been pursuing pharmaceutical remedies to these seizures and now, because of this test result, we know that we probably will never have full control of his seizures.*
>
> *So, if we would have had that diagnosis right at 18 months, we could have done a whole bunch of speech therapy, and all that type of stuff, and you know, hearing aids, potentially.*
>
> *But … she's not doing anything differently now that she has the result of the test, but I think I'm sensing a sort of a resentment that she wasn't offered this testing earlier.*

Limitations

The amount of direct patient engagement conducted for this analysis was moderate. While many people have unexplained developmental disabilities or congenital anomalies in Ontario, access to genome-wide sequencing is limited to request through the Out-of-Country Prior

Approval Program or research initiatives through hospital programs. Some private companies provide genome-wide sequencing, but the cost can be prohibitive for many families.

Participant bias in our direct interviews included patients and families who had actively sought out genome-wide sequencing and responded to our inquiries. Increased participation from patients or families currently in the middle of their diagnostic odyssey could have provided more insight into the motivations and expectations of genome-wide sequencing.

Several participants we interviewed had accessed genome-wide sequencing through research conducted through major hospitals. Clinical experts who were consulted indicated that this population might be more informed and feel more comfortable with genome-wise sequencing than the population as a whole, owing to the supports and genetic counselling they receive as part of their participation in research.

While direct engagement allowed us to speak to people from various parts of the province, the overall number was too small to elucidate concerns of equity of access of genome-wide sequencing faced by the general public.

Discussion

Robust evidence provided through the quantitative literature on preferences, the qualitative literature, and through direct experience illustrates the strong desire for genome-wide sequencing and the potential diagnosis it can provide for people with unexplained developmental disabilities or congenital anomalies and their families.

All sources of evidence point to multiple motivations and goals for genome-wide sequencing, as expressed by affected patients and their families. The desire for knowledge and information, for the hope of clinical actionability, for better access to therapeutic support, for direction in family planning, and for relief from emotional burdens of guilt and from sense of blame are consistently presented as motivators in the pursuit of genome-wide sequencing.

Genome-wide sequencing comes with a great deal of uncertainty, which presents challenges for preserving patient autonomy in choice.[129] The best way autonomy can be preserved in these circumstances is by providing a robust informed consent process to support a thorough understanding of all possible outcomes.[129] This is reflected in the qualitative findings from CADTH that report on families seeking genome-wide sequencing, and clinicians emphasizing the importance and value of genetic counselling to carefully and thoroughly present and discuss genetic findings, including secondary and incidental findings. While quantitative and qualitative evidence showed that participants want to learn about incidental findings, exactly what information they want to receive can vary and depends on personal circumstances.

Receiving a diagnosis through genome-wide sequencing was seen as beneficial to people with developmental disabilities or congenital anomalies. Most participants we interviewed reported benefits in clinical actionability and knowledge, as well as social, familial, and emotional benefits to obtaining a diagnosis. These benefits were also reported in the quantitative and qualitative literature as well.

Conclusions

Patient preferences and values, obtained through interviews and through a review of the qualitative and quantitative evidence, point to consistent motivations and benefits to obtaining a

diagnosis for unexplained developmental delay or congenital anomalies through genome-wide sequencing. Patients and families also greatly value the support and information provided through genetic counselling when considering genome-wide sequencing and learning of a diagnosis.

CONCLUSIONS OF THE HEALTH TECHNOLOGY ASSESSMENT

Genome-wide sequencing for people with unexplained developmental disabilities or multiple congenital anomalies has a diagnostic yield of 37%, but we are very uncertain about this estimate (GRADE: Very Low). Compared with standard genetic testing, genome-wide sequencing may have a higher diagnostic yield (GRADE: Low). Genome-wide sequencing could have some modest clinical utility in the form of active medical management as well as long-term clinical management, but we are very uncertain (GRADE: Very Low).

Our economic literature review showed that cost-effectiveness of whole exome and whole genome sequencing varies depending on the clinical context, when it is used in the diagnostic pathway, the extent to which it can replace current diagnostic investigations and procedures, and many other factors. We were unable to determine the cost-effectiveness of whole exome and whole genome sequencing from the results of the literature review.

Incorporating whole exome sequencing after standard testing increased diagnostic yield (over standard testing alone) at an additional cost. Early use of whole exome sequencing (as a second-tier test, when used after chromosomal microarray) yielded more diagnoses at a lower cost than late use of whole exome sequencing or standard testing alone.

The budget impact of publicly funding whole exome sequencing for people with unexplained developmental disabilities or multiple congenital anomalies through Ontario's Out-of-Country Prior Approval Program was estimated to be $3.99 to $4.85 million yearly in the next 5 years. If whole exome sequencing after standard testing is publicly funded in Ontario and conducted in local laboratories, the volume of whole exome sequencing is expected to triple compared with the current level, and the budget impact would be about $8.95 million yearly in the next 5 years. Early use of genome-wide sequencing (whole exome sequencing as a second-tier test) could enable more timely diagnosis for patients with unexplained developmental disabilities or multiple congenital anomalies and could lead to cost savings for the provincial budget ($3.4 million per 1,000 persons tested yearly).

Patients' preferences and values show consistent motivations for and benefits to obtaining a diagnosis for unexplained developmental delay or congenital anomalies through genome-wide sequencing. Patients and families also greatly value the support and information provided through genetic counselling when they consider undergoing genome-wide sequencing and identifying a diagnosis.

ABBREVIATIONS

ACMG	American College of Medical Genetics and Genomics
CADTH	Canadian Agency for Drugs and Technologies in Health
CI	Confidence interval
FY	Fiscal year
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
ICER	Incremental cost-effectiveness ratio
IQR	Interquartile range
OR	Odds ratio
QALY	Quality-adjusted life-year
ROBIS	Risk of bias in systematic review
RR	Relative risk
WES	Whole exome sequencing
WGS	Whole genome sequencing

GLOSSARY

Budget impact analysis	A budget impact analysis estimates the financial impact of adopting a new health care intervention on the current budget (i.e., its affordability). It is based on predictions of how changes in the intervention mix 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).
Chromosomal microarray	A genetic test that looks for extra or missing sections of chromosomal segments including an abnormal chromosome number (e.g., Down syndrome).
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 sensitivity analysis. It illustrates the probability of health care interventions being cost-effective over a range of different 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 are 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 specific 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-effectiveness plane	In economic evaluations, a cost-effectiveness plane is a graph used to show the differences in cost and effectiveness between a health care intervention and its comparator(s). Differences in effects are plotted on the horizontal axis, and differences in costs are plotted on the vertical axis.
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 (QALYs), 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.
Diagnostic yield	The number of persons for whom a diagnostic procedure used to determine the cause of their condition yielded a definitive diagnosis, out of the total number of persons who received the diagnostic procedure.
Discounting	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 (Quality) use an annual discount rate of 1.5% for both future costs and future benefits.
Discrete event simulation model	A technique to present the operation of a system as a sequence of events. Each event occurs at a particular instant in time and marks a change of state in the system.
Dominant	A health care intervention is considered dominant when it is more effective and less costly than its comparator(s).
Fine motor/vision control	The control of fine motor skills required to coordinate muscles for activities such as grasping. Fine motor control differs from gross motor control, which is the control required to coordinate large movements such as walking.
Genome-wide sequencing	Genome-wide sequencing, as whole exome or whole genome sequencing, examines the entire genetic makeup of a person in a single test, capturing genetic information that other genetic tests (such as targeted gene tests) can miss.
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.
Incremental cost	An 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 consumer must pay to get an additional unit of benefit relative to an alternative intervention. It is obtained by dividing the incremental cost of the intervention by its 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.
Ministry of Health perspective	The perspective adopted in economic evaluations determines the types of cost and health benefit to include. Ontario Health (Quality) develops health technology assessment reports from the perspective of the Ontario Ministry of Health. This perspective includes all costs and health benefits attributable to the Ministry of Health, such as treatment costs (e.g., drugs, administration, monitoring, hospital stays) and costs associated with managing adverse events caused by treatments. This perspective does not include out-of-pocket costs incurred by patients related to obtaining care (e.g., transportation) or loss of productivity (e.g., absenteeism).
Multiple congenital anomalies	The presence of two or more unrelated congenital anomalies (anomalies that existed at or before birth; also known as congenital disorders, or congenital malformations) in the same person that cause major structural malformations and cannot be explained by an underlying syndrome or gene sequence.
Natural history of a disease	The natural history of a disease is the progression of a disease over time in the absence of any health care intervention.
Probabilistic sensitivity analysis (PSA)	A probabilistic sensitivity analysis (PSA) is used in economic models to explore uncertainty in several parameters simultaneously. It 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.
Qualitative research	Some research topics are not well suited for objective data-driven (quantitative) studies. The qualitative study was developed to gather non-numerical data. Using this method, the researcher analyzes meanings, concepts, characteristics, and descriptions of individuals or groups through observation, historical record search, and/or other non-statistical research approaches.

Quality-adjusted life-year (QALY)	The quality-adjusted life-year 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.
Quantitative research	A scientific method of observation via statistical, mathematical, or computational techniques to gather numerical data.
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.
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 cost and health benefit to include. The societal perspective reflects the broader economy and is the aggregation of all perspectives (e.g., health care payer perspective, patient perspective). 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).
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.
Unexplained developmental disability	Developmental disability comprises a diverse group of chronic conditions caused by mental or physical impairments that arise before adulthood. It is unexplained when doctors do not know the reason for the disability.

Utility	Utilities are values that represent people's preferences 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.
Whole exome sequencing	A method of examining all of the DNA in the protein-coding regions of the genome (this part of the genome is known as the exome).
Whole genome sequencing	A method to examine the complete DNA sequence of the genome, including both the chromosomal DNA (the genetic material of the cell) and mitochondrial DNA (the DNA contained within the mitochondria).
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: January 17, 2019

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

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to January 16, 2019>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2019 Week 02>, Ovid MEDLINE(R) ALL <1946 to January 16, 2019>

Search strategy:

---

1 exp Intellectual Disability/ (538670)
2 (((mental* or intellectual) adj2 (defici* or disorder* or disabil* or disabl* or retard*)) or idiocy).ti,ab,kf. (205646)
3 Developmental Disabilities/ (25270)
4 ((development or developmental*) adj2 (deviat* or disorder* or delay* or disabil* or disabl* or impair*)).ti,ab,kf. (101508)
5 Congenital Abnormalities/ (34931)
6 (((congenital or birth) adj3 (abnormal* or defect* or malform*)) or deformit*).ti,ab,kf. (248628)
7 ((angelman* or fragile x or fragilex or prader-willi* or praderwilli* or rett* or rubinstein-taybi* or rubinsteintaybi* or smith-magenis* or smithmagenis* or williams*) adj3 syndrome*).ti,ab,kf. (32621)
8 exp Abnormalities, Multiple/ (151590)
9 (multiple adj2 abnormalit*).ti,ab,kf. (6977)
10 exp Chromosome Disorders/ (113935)
11 (chromosom* adj2 (disorder* or abnormalit*)).ti,ab,kf. (45327)
12 exp Child Development Disorders, Pervasive/ (89559)
13 (pervasive adj2 development* adj2 (disorder* or deviat* or delay* or disabil* or deficienc*)).ti,ab,kf. (4865)
14 (autism or (autistic adj2 disorder*) or kanner* syndrome).ti,ab,kf. (87496)
15 Rare Diseases/ (17204)
16 ((rare or orphan) adj2 (disease or diseases)).ti. (8783)
17 *Genetic Diseases, Inborn/ (15773)
18 (inborn adj2 genetic adj2 (disease* or disorder* or defect*1)).ti,ab,kf. (79)
19 Metabolism, Inborn Errors/ (16557)
20 (inborn adj2 error*1 adj2 metaboli*).ti,ab,kf. (10138)
21 Neurodevelopmental Disorders/ (140539)
22 ((neurodevelopmental or neuro developmental) adj2 (disorder* or deviat* or delay* or disabil* or disabl* or deficien*)).ti,ab,kf. (22263)
23 or/1-22 (1433184)
24 Whole Exome Sequencing/ (12093)
25 (((exome or transcriptome) adj2 sequenc*) or whole exome* or WES).ti,ab,kf. (45024)

26 Whole Genome Sequencing/ (10655)
27 ((genom* adj2 sequenc*) or massively parallel sequenc* or whole genom* or WGS).ti,ab,kf. (201438)
28 ((next gen or nextgen or next generation) adj2 sequenc*).ti,ab,kf. (69430)
29 High-Throughput Nucleotide Sequencing/ (36536)
30 (((high throughput or high through put) adj2 (sequenc* or analys#s)) or deep sequenc*).ti,ab,kf. (53641)
31 ((genomic* or personali?ed or precision) adj2 medicine).ti. (13502)
32 or/24-31 (362999)
33 Genetic Testing/ (76570)
34 ((genetic* or gene*1) adj2 (test or tests or testing or diagnos#s or screen*)).ti,ab,kf. (133849)
35 Oligonucleotide Array Sequence Analysis/ (117941)
36 ((array* or chip*1 or microarray* or microchip*) adj2 (DNA or oligonucleotide* or oligo nucleotide* or oligodeoxyribonucleotide* or oligodeoxyribo nucleotide* or CDNA or gene)).ti,ab,kf. (89386)
37 Sequence Analysis, DNA/ (318968)
38 ((sequence analys#s or sequence determination*1 or sequencing) adj2 DNA).ti,ab,kf. (76871)
39 or/33-38 (682606)
40 Exome/ (20697)
41 (exome or exomes).ti,ab,kf. (40266)
42 Genome/ (136978)
43 (genome or genomes).ti,ab,kf. (809099)
44 Genomics/ (95139)
45 (genomic or genomics).ti,ab,kf. (570851)
46 or/40-45 (1257906)
47 39 and 46 (176802)
48 or/32,47 (480774)
49 23 and 48 (22245)
50 exp Animals/ not Humans/ (15664222)
51 49 not 50 (13825)
52 Case Reports/ or Comment.pt. or Editorial.pt. or (Letter not (Letter and Randomized Controlled Trial)).pt. or Congresses.pt. (5064183)
53 51 not 52 (11807)
54 limit 53 to english language [Limit not valid in CDSR; records were retained] (11367)
55 (Systematic Reviews or Meta Analysis).pt. (96315)
56 Systematic Review/ or Meta-Analysis/ or exp Meta-Analysis as Topic/ or exp Technology Assessment, Biomedical/ (444119)
57 (((systematic* or methodologic*) adj3 (review* or overview*)) or pool* analy* or published studies or published literature or hand search* or handsearch*
or medline or pubmed or embase or cochrane or cinahl or data synthes* or data extraction* or data abstraction* or HTA or HTAs or (technolog* adj (assessment* or overview* or appraisal*))).ti,ab,kf. (687924)
58 (meta analy* or metaanaly* or health technolog* assess*).ti,ab,kf. (338087)
59 (meta regression* or metaregression*).ti,ab,kf. (15656)
60 (((integrative or collaborative or quantitative) adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf. (27202)
61 (cochrane or (health adj2 technology assessment) or evidence report).jw. (54968)

62 ((comparative adj3 (efficacy or effectiveness)) or outcomes research or relative effectiveness or ((indirect or indirect treatment or mixed-treatment) adj comparison*)).ti,ab,kf. (50004)
63 or/55-62 (985649)
64 54 and 63 (250)
65 64 use medall (128)
66 54 use coch,clhta,cleed (3)
67 or/65-66 (131)
68 intellectual impairment/ (21157)
69 exp mental deficiency/ (206856)
70 (((mental* or intellectual) adj2 (defici* or disorder* or disabil* or disabl* or retard*)) or idiocy).tw,kw. (198780)
71 exp developmental disorder/ (38226)
72 ((development or developmental*) adj2 (deviat* or disorder* or delay* or disabil* or disabl* or impair*)).tw,kw. (103389)
73 congenital disorder/ (63311)
74 *congenital malformation/ (21909)
75 (((congenital or birth) adj3 (abnormal* or defect* or malform*)) or deformit*).tw,kw. (246673)
76 ((angelman* or fragile x or fragilex or prader-willi* or praderwilli* or rett* or rubinstein-taybi* or rubinsteintaybi* or smith-magenis* or smithmagenis* or williams*) adj3 syndrome*).tw,kw. (33034)
77 exp multiple malformation syndrome/ (42921)
78 (multiple adj2 abnormalit*).tw,kw. (7108)
79 exp chromosome disorder/ (113935)
80 (chromosom* adj2 (disorder* or abnormalit*)).tw,kw. (45297)
81 exp autism/ (78147)
82 (pervasive adj2 development* adj2 (disorder* or deviat* or delay* or disabil* or deficienc*)).tw,kw. (5274)
83 (autism or (autistic adj2 disorder*) or kanner* syndrome).tw,kw. (89135)
84 *rare disease/ (10019)
85 ((rare or orphan) adj2 (disease or diseases)).ti. (8783)
86 *genetic disorder/ (22794)
87 (inborn adj2 genetic adj2 (disease* or disorder* or defect*1)).tw,kw. (137)
88 "inborn error of metabolism"/ (8133)
89 (inborn adj2 error*1 adj2 metaboli*).tw,kw. (10296)
90 ((neurodevelopmental or neuro developmental) adj2 (disorder* or deviat* or delay* or disabil* or disabl* or deficien*)).tw,kw. (22610)
91 or/68-90 (980497)
92 whole exome sequencing/ (12093)
93 (((exome or transcriptome) adj2 sequenc*) or whole exome* or WES).tw,kw,dv. (45461)
94 whole genome sequencing/ (10655)
95 ((genom* adj2 sequenc*) or massively parallel sequenc* or whole genom* or WGS).tw,kw,dv. (203089)
96 next generation sequencing/ (33713)
97 ((next gen or nextgen or next generation) adj2 sequenc*).tw,kw,dv. (70123)
98 *high throughput sequencing/ (3522)
99 (((high throughput or high through put) adj2 (sequenc* or analys#s)) or deep sequenc*).tw,kw,dv. (54092)
100 ((genomic* or personali?ed or precision) adj2 medicine).ti. (13502)
101 or/92-100 (361965)

102 genetic screening/ (108216)
103 ((genetic* or gene*1) adj2 (test or tests or testing or diagnos#s or screen*)).tw,kw,dv. (136158)
104 *DNA microarray/ (28879)
105 ((array* or chip*1 or microarray* or microchip*) adj2 (DNA or oligonucleotide* or oligo nucleotide* or oligodeoxyribonucleotide* or oligodeoxyribo nucleotide* or CDNA or gene)).tw,kw,dv. (91103)
106 *DNA sequence/ (25570)
107 ((sequence analys#s or sequence determination*1 or sequencing) adj2 DNA).tw,kw,dv. (77942)
108 or/102-107 (394103)
109 exome/ (20697)
110 (exome or exomes).tw,kw,dv. (40489)
111 genome/ (136978)
112 (genome or genomes).tw,kw,dv. (812158)
113 genomics/ (95139)
114 (genomic or genomics).tw,kw,dv. (578517)
115 or/109-114 (1264122)
116 108 and 115 (91433)
117 or/101,116 (423803)
118 91 and 117 (19142)
119 (exp animal/ or nonhuman/) not exp human/ (10139570)
120 118 not 119 (18359)
121 Case Report/ or Comment/ or Editorial/ or (letter.pt. not (letter.pt. and randomized controlled trial/)) or conference abstract.pt. (10128746)
122 120 not 121 (10941)
123 limit 122 to english language [Limit not valid in CDSR; records were retained] (10469)
124 meta analysis/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or biomedical technology assessment/ (323855)
125 (((systematic* or methodologic*) adj3 (review* or overview*)) or pool* analy* or published studies or published literature or hand search* or handsearch*
or medline or pubmed or embase or cochrane or cinahl or data synthes* or data extraction* or data abstraction* or HTA or HTAs or (technolog* adj (assessment* or overview* or appraisal*))).tw,kw. (710838)
126 (meta analy* or metaanaly* or health technolog* assess*).tw,kw. (364480)
127 (meta regression* or metaregression*).tw,kw. (16546)
128 (((integrative or collaborative or quantitative) adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).tw,kw. (28094)
129 (cochrane or (health adj2 technology assessment) or evidence report).jw. (54968)
130 ((comparative adj3 (efficacy or effectiveness)) or outcomes research or relative effectiveness or ((indirect or indirect treatment or mixed-treatment) adj comparison*)).tw,kw. (53137)
131 or/124-130 (986790)
132 123 and 131 (286)
133 132 use emez (157)
134 67 or 133 (288)
135 134 use medall (128)
136 134 use emez (157)
137 134 use coch (2)
138 134 use clhta (0)
139 134 use cleed (1)

140 remove duplicates from 134 (199)

Economic Evidence Search

Search date: January 17, 2019

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: EBM Reviews - Cochrane Central Register of Controlled Trials <December 2018>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to January 16, 2019>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2019 Week 02>, Ovid MEDLINE(R) ALL <1946 to January 16, 2019>

Search strategy:

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1 exp Intellectual Disability/ (539893)
2 (((mental* or intellectual) adj2 (defici* or disorder* or disabil* or disabl* or retard*)) or idiocy).ti,ab,kf. (209971)
3 Developmental Disabilities/ (25815)
4 ((development or developmental*) adj2 (deviat* or disorder* or delay* or disabil* or disabl* or impair*)).ti,ab,kf. (103571)
5 Congenital Abnormalities/ (35150)
6 (((congenital or birth) adj3 (abnormal* or defect* or malform*)) or deformit*).ti,ab,kf. (251202)
7 ((angelman* or fragile x or fragilex or prader-willi* or praderwilli* or rett* or rubinstein-taybi* or rubinsteintaybi* or smith-magenis* or smithmagenis* or williams*) adj3 syndrome*).ti,ab,kf. (32985)
8 exp Abnormalities, Multiple/ (152159)
9 (multiple adj2 abnormalit*).ti,ab,kf. (7047)
10 exp Chromosome Disorders/ (114699)
11 (chromosom* adj2 (disorder* or abnormalit*)).ti,ab,kf. (45588)
12 exp Child Development Disorders, Pervasive/ (90593)
13 (pervasive adj2 development* adj2 (disorder* or deviat* or delay* or disabil* or deficienc*)).ti,ab,kf. (4991)
14 (autism or (autistic adj2 disorder*) or kanner* syndrome).ti,ab,kf. (89531)
15 Rare Diseases/ (17221)
16 ((rare or orphan) adj2 (disease or diseases)).ti. (8852)
17 *Genetic Diseases, Inborn/ (15785)
18 (inborn adj2 genetic adj2 (disease* or disorder* or defect*1)).ti,ab,kf. (80)
19 Metabolism, Inborn Errors/ (16606)
20 (inborn adj2 error*1 adj2 metaboli*).ti,ab,kf. (10207)
21 Neurodevelopmental Disorders/ (140598)

22 ((neurodevelopmental or neuro developmental) adj2 (disorder* or deviat* or delay* or disabil* or disabl* or deficien*)).ti,ab,kf. (22612)
23 or/1-22 (1445974)
24 Whole Exome Sequencing/ (12099)
25 (((exome or transcriptome) adj2 sequenc*) or whole exome* or WES).ti,ab,kf. (45287)
26 Whole Genome Sequencing/ (10657)
27 ((genom* adj2 sequenc*) or massively parallel sequenc* or whole genom* or WGS).ti,ab,kf. (201965)
28 ((next gen or nextgen or next generation) adj2 sequenc*).ti,ab,kf. (70088)
29 High-Throughput Nucleotide Sequencing/ (36588)
30 (((high throughput or high through put) adj2 (sequenc* or analys#s)) or deep sequenc*).ti,ab,kf. (53904)
31 ((genomic* or personali?ed or precision) adj2 medicine).ti. (13608)
32 or/24-31 (364642)
33 Genetic Testing/ (76930)
34 ((genetic* or gene*1) adj2 (test or tests or testing or diagnos#s or screen*)).ti,ab,kf. (135073)
35 Oligonucleotide Array Sequence Analysis/ (118165)
36 ((array* or chip*1 or microarray* or microchip*) adj2 (DNA or oligonucleotide* or oligo nucleotide* or oligodeoxyribonucleotide* or oligodeoxyribo nucleotide* or CDNA or gene)).ti,ab,kf. (89719)
37 Sequence Analysis, DNA/ (319150)
38 ((sequence analys#s or sequence determination*1 or sequencing) adj2 DNA).ti,ab,kf. (77102)
39 or/33-38 (684880)
40 Exome/ (20703)
41 (exome or exomes).ti,ab,kf. (40510)
42 Genome/ (136986)
43 (genome or genomes).ti,ab,kf. (811120)
44 Genomics/ (95175)
45 (genomic or genomics).ti,ab,kf. (572785)
46 or/40-45 (1261600)
47 39 and 46 (177201)
48 or/32,47 (482655)
49 23 and 48 (22302)
50 exp Animals/ not Humans/ (15664229)
51 49 not 50 (13882)
52 Case Reports/ or Comment.pt. or Editorial.pt. or (Letter not (Letter and Randomized Controlled Trial)).pt. or Congresses.pt. (5068037)
53 51 not 52 (11864)
54 limit 53 to yr="2008 -Current" (9413)
55 limit 54 to english language [Limit not valid in CDSR; records were retained] (9122)
56 economics/ (250446)

57 economics, medical/ or economics, pharmaceutical/ or exp economics, hospital/ or economics, nursing/ or economics, dental/ (805837)
58 economics.fs. (414154)
59 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).ti,ab,kf. (841609)
60 exp "costs and cost analysis"/ (565064)
61 (cost or costs or costing or costly).ti. (252742)
62 cost effective*.ti,ab,kf. (306877)
63 (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. (201649)
64 models, economic/ (12144)
65 markov chains/ or monte carlo method/ (77219)
66 (decision adj1 (tree* or analy* or model*)).ti,ab,kf. (39824)
67 (markov or markow or monte carlo).ti,ab,kf. (123013)
68 quality-adjusted life years/ (37921)
69 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).ti,ab,kf. (67844)
70 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).ti,ab,kf. (110495)
71 or/56-70 (2441758)
72 55 and 71 (375)
73 72 use medall,coch,cctr (227)
74 55 use clhta,cleed (1)
75 or/73-74 (228)
76 intellectual impairment/ (21157)
77 exp mental deficiency/ (208079)
78 (((mental* or intellectual) adj2 (defici* or disorder* or disabil* or disabl* or retard*)) or idiocy).tw,kw. (203395)
79 exp developmental disorder/ (38226)
80 ((development or developmental*) adj2 (deviat* or disorder* or delay* or disabil* or disabl* or impair*)).tw,kw. (105560)
81 congenital disorder/ (63311)
82 *congenital malformation/ (21909)
83 (((congenital or birth) adj3 (abnormal* or defect* or malform*)) or deformit*).tw,kw. (250686)
84 ((angelman* or fragile x or fragilex or prader-willi* or praderwilli* or rett* or rubinstein-taybi* or rubinsteintaybi* or smith-magenis* or smithmagenis* or williams*) adj3 syndrome*).tw,kw. (33402)
85 exp multiple malformation syndrome/ (42921)
86 (multiple adj2 abnormalit*).tw,kw. (7178)
87 exp chromosome disorder/ (114699)
88 (chromosom* adj2 (disorder* or abnormalit*)).tw,kw. (45566)
89 exp autism/ (78948)
90 (pervasive adj2 development* adj2 (disorder* or deviat* or delay* or disabil* or deficienc*)).tw,kw. (5409)
91 (autism or (autistic adj2 disorder*) or kanner* syndrome).tw,kw. (91236)

92 *rare disease/ (10028)
93 ((rare or orphan) adj2 (disease or diseases)).ti. (8852)
94 *genetic disorder/ (22794)
95 (inborn adj2 genetic adj2 (disease* or disorder* or defect*1)).tw,kw. (138)
96 "inborn error of metabolism"/ (8133)
97 (inborn adj2 error*1 adj2 metaboli*).tw,kw. (10369)
98 ((neurodevelopmental or neuro developmental) adj2 (disorder* or deviat* or delay* or disabil* or disabl* or deficien*)).tw,kw. (22959)
99 or/76-97 (986341)
100 whole exome sequencing/ (12099)
101 (((exome or transcriptome) adj2 sequenc*) or whole exome* or WES).tw,kw,dv. (45729)
102 whole genome sequencing/ (10657)
103 ((genom* adj2 sequenc*) or massively parallel sequenc* or whole genom* or WGS).tw,kw,dv. (203633)
104 next generation sequencing/ (33713)
105 ((next gen or nextgen or next generation) adj2 sequenc*).tw,kw,dv. (70799)
106 *high throughput sequencing/ (3522)
107 (((high throughput or high through put) adj2 (sequenc* or analys#s)) or deep sequenc*).tw,kw,dv. (54370)
108 ((genomic* or personali?ed or precision) adj2 medicine).ti. (13608)
109 or/100-108 (363634)
110 genetic screening/ (108576)
111 ((genetic* or gene*1) adj2 (test or tests or testing or diagnos#s or screen*)).tw,kw,dv. (137736)
112 *DNA microarray/ (28879)
113 ((array* or chip*1 or microarray* or microchip*) adj2 (DNA or oligonucleotide* or oligo nucleotide* or oligodeoxyribonucleotide* or oligodeoxyribo nucleotide* or CDNA or gene)).tw,kw,dv. (91612)
114 *DNA sequence/ (25570)
115 ((sequence analys#s or sequence determination*1 or sequencing) adj2 DNA).tw,kw,dv. (78179)
116 or/110-115 (396589)
117 exome/ (20703)
118 (exome or exomes).tw,kw,dv. (40741)
119 genome/ (136986)
120 (genome or genomes).tw,kw,dv. (814249)
121 genomics/ (95175)
122 (genomic or genomics).tw,kw,dv. (580509)
123 or/117-122 (1267910)
124 116 and 123 (91875)
125 or/109,124 (425743)
126 99 and 125 (18955)
127 (exp animal/ or nonhuman/) not exp human/ (10139583)
128 126 not 127 (18189)

129 Case Report/ or Comment/ or Editorial/ or (letter.pt. not (letter.pt. and randomized controlled trial/)) or conference abstract.pt. (10184169)
130 128 not 129 (10817)
131 limit 130 to yr="2008 -Current" (9133)
132 limit 131 to english language [Limit not valid in CDSR; records were retained] (8788)
133 Economics/ (250446)
134 Health Economics/ or Pharmacoeconomics/ or Drug Cost/ or Drug Formulary/ (125637)
135 Economic Aspect/ or exp Economic Evaluation/ (442304)
136 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw,kw. (866246)
137 exp "Cost"/ (565064)
138 (cost or costs or costing or costly).ti. (252742)
139 cost effective*.tw,kw. (318147)
140 (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. (209874)
141 Monte Carlo Method/ (61734)
142 (decision adj1 (tree* or analy* or model*)).tw,kw. (43534)
143 (markov or markow or monte carlo).tw,kw. (128007)
144 Quality-Adjusted Life Years/ (37921)
145 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw,kw. (71659)
146 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw,kw. (130184)
147 or/133-146 (2086475)
148 132 and 147 (401)
149 148 use emez (236)
150 75 or 149 (464)
151 150 use medall (225)
152 150 use emez (236)
153 150 use coch (0)
154 150 use cctr (2)
155 150 use clhta (0)
156 150 use cleed (1)
157 remove duplicates from 150 (348)

Quantitative Preferences Evidence Search

Search date: January 18, 2019

Databases searched: Ovid MEDLINE

Search filter used: Quantitative preference evidence filter, modified from Selva et al.[131]

Database: Ovid MEDLINE(R) ALL <1946 to January 17, 2019>

Search strategy:

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1 exp Intellectual Disability/ (91850)
2 (((mental* or intellectual) adj2 (defici* or disorder* or disabil* or disabl* or retard*)) or idiocy).ti,ab,kf. (100881)
3 Developmental Disabilities/ (18658)
4 ((development or developmental*) adj2 (deviat* or disorder* or delay* or disabil* or disabl* or impair*)).ti,ab,kf. (43998)
5 Congenital Abnormalities/ (33572)
6 (((congenital or birth) adj3 (abnormal* or defect* or malform*)) or deformit*).ti,ab,kf. (119759)
7 ((angelman* or fragile x or fragilex or prader-willi* or praderwilli* or rett* or rubinstein-taybi* or rubinsteintaybi* or smith-magenis* or smithmagenis* or williams*) adj3 syndrome*).ti,ab,kf. (14814)
8 exp Abnormalities, Multiple/ (108586)
9 (multiple adj2 abnormalit*).ti,ab,kf. (3121)
10 exp Chromosome Disorders/ (68062)
11 (chromosom* adj2 (disorder* or abnormalit*)).ti,ab,kf. (20340)
12 exp Child Development Disorders, Pervasive/ (30556)
13 (pervasive adj2 development* adj2 (disorder* or deviat* or delay* or disabil* or deficienc*)).ti,ab,kf. (2067)
14 (autism or (autistic adj2 disorder*) or kanner* syndrome).ti,ab,kf. (38876)
15 Rare Diseases/ (9433)
16 ((rare or orphan) adj2 (disease or diseases)).ti. (3678)
17 *Genetic Diseases, Inborn/ (8120)
18 (inborn adj2 genetic adj2 (disease* or disorder* or defect*1)).ti,ab,kf. (46)
19 Metabolism, Inborn Errors/ (10277)
20 (inborn adj2 error*1 adj2 metaboli*).ti,ab,kf. (4519)
21 Neurodevelopmental Disorders/ (1169)
22 ((neurodevelopmental or neuro developmental) adj2 (disorder* or deviat* or delay* or disabil* or disabl* or deficien*)).ti,ab,kf. (9686)
23 or/1-22 (513650)
24 Whole Exome Sequencing/ (951)
25 (((exome or transcriptome) adj2 sequenc*) or whole exome* or WES).ti,ab,kf. (16739)
26 Whole Genome Sequencing/ (1677)
27 ((genom* adj2 sequenc*) or massively parallel sequenc* or whole genom* or WGS).ti,ab,kf. (96210)
28 ((next gen or nextgen or next generation) adj2 sequenc*).ti,ab,kf. (27932)
29 High-Throughput Nucleotide Sequencing/ (23408)
30 (((high throughput or high through put) adj2 (sequenc* or analys#s)) or deep sequenc*).ti,ab,kf. (24216)
31 ((genomic* or personali?ed or precision) adj2 medicine).ti. (5895)
32 or/24-31 (163024)
33 Genetic Testing/ (34239)
34 ((genetic* or gene*1) adj2 (test or tests or testing or diagnos#s or screen*)).ti,ab,kf. (54802)
35 Oligonucleotide Array Sequence Analysis/ (64493)
36 ((array* or chip*1 or microarray* or microchip*) adj2 (DNA or oligonucleotide* or oligo nucleotide* or oligodeoxyribonucleotide* or oligodeoxyribo nucleotide* or CDNA or gene)).ti,ab,kf. (38494)
37 Sequence Analysis, DNA/ (150505)

38 ((sequence analys#s or sequence determination*1 or sequencing) adj2 DNA).ti,ab,kf. (34954)
39 or/33-38 (326326)
40 Exome/ (5049)
41 (exome or exomes).ti,ab,kf. (14247)
42 Genome/ (27670)
43 (genome or genomes).ti,ab,kf. (380610)
44 Genomics/ (39697)
45 (genomic or genomics).ti,ab,kf. (261328)
46 or/40-45 (576066)
47 39 and 46 (89562)
48 or/32,47 (220429)
49 23 and 48 (8308)
50 exp Animals/ not Humans/ (4538357)
51 49 not 50 (8071)
52 Case Reports/ or Comment.pt. or Editorial.pt. or (Letter not (Letter and Randomized Controlled Trial)).pt. or Congresses.pt. (3462339)
53 51 not 52 (6204)
54 limit 53 to english language (5958)
55 Attitude to Health/ (81047)
56 Health Knowledge, Attitudes, Practice/ (100480)
57 Patient Participation/ (23342)
58 Patient Preference/ (6839)
59 Attitude of Health Personnel/ (113810)
60 *Professional-Patient Relations/ (10918)
61 *Physician-Patient Relations/ (33665)
62 Choice Behavior/ (30218)
63 (choice or choices or value* or valuation*).ti. (186384)
64 (preference* or expectation* or attitude* or acceptab* or knowledge or point of view).ti,ab. (1078911)
65 ((patient*1 or user*1 or men or women or child* or parent*2 or personal or provider* or practitioner* or professional*1 or (health* adj2 worker*) or clinician* or physician* or doctor* or geneticist*) adj2 (participation or perspective* or perception* or misperception* or perceiv* or view* or understand* or misunderstand* or value*1)).ti,ab. (132140)
66 health perception*.ti,ab. (2478)
67 *Decision Making/ (38009)
68 (patient*1 or user*1 or men or women or child* or parent*2 or personal or provider* or practitioner* or professional*1 or (health* adj2 worker*) or clinician* or physician* or doctor* or geneticist*).ti. (2960999)
69 67 and 68 (8329)
70 (decision* and mak*).ti. (25629)
71 (decision mak* or decisions mak*).ti,ab. (121523)
72 70 or 71 (122961)
73 (patient*1 or user*1 or men or women or child* or parent*2 or personal or provider* or practitioner* or professional*1 or (health* adj2 worker*) or clinician* or physician* or doctor* or geneticist*).ti,ab. (8340189)
74 72 and 73 (80206)
75 (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. (29199)
76 Decision Support Techniques/ (18314)
77 (health and utilit*).ti. (1293)

78 (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. (11741)
79 (preference based or preference score* or preference elicitation or multiattribute or multi attribute).ti,ab. (2455)
80 or/55-66,69,74-79 (1648067)
81 54 and 80 (509)

Grey Literature Search

Performed: January 4–22, 2019; updated May 2–3, 2019

Websites searched:
HTA Database Canadian Repository, Alberta Health Technologies Decision Process reviews, 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), Laval University, McGill University Health Centre Health Technology Assessment Unit, National Institute for Health and Care Excellence (NICE), Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers, Australian Government Medical Services Advisory Committee, Queensland Health Technology Evaluation, Centers for Medicare & Medicaid Services Technology Assessments, Institute for Clinical and Economic Review, Healthcare Improvement Scotland, Ireland Health Information and Quality Authority Health Technology Assessments, Washington State Health Care Authority Health Technology Reviews, ClinicalTrials.gov, PROSPERO, EUnetHTA, Epistemonikos, Tufts Cost-Effectiveness Analysis Registry

Keywords used:
genome, genomes, genomics, exome, exomes, sequencing, sequence analysis, transcriptome, next gen, next generation, high throughput, high through put, personalized medicine, personalised medicine, precision medicine, genetic testing

Clinical results (included in PRISMA): 13

Economic results (included in PRISMA): 20

Ongoing health technology assessments (PROSPERO/EUnetHTA): 2

Ongoing clinical trials (ClinicalTrials.gov): 9

Appendix 2: Summary of Included Studies—Clinical Evidence

Table A1: Characteristics of Included Primary Studies

Author, Year	Location	Population	Sample Size	Proband Age at Enrollment[a]	Age of Symptom Onset[a]	Sex, % Male	Consanguinity, %
Al-Shamsi et al, 2016[57]	United Arab Emirates	Children with inborn errors of metabolism and other disorders	85	93% < 18 y	NR	54	48
Baldridge et al, 2017[63]	United States	Mixed suspected genetic disorders	155	6 y (3 d–33 y)	11 mo (0–22 mo)	56	3.9
Bick et al, 2017[64]	United States	Children with suspected genetic disorders	22	All < 18 y	NR	NR	NR
Bowling et al, 2017[44]	United States	Intellectual disability or developmental delay	127	11 y (2–40 y)	NR	58	NR
Charng et al, 2016[151]	Saudi Arabia	Developmental delay or intellectual disability with or without brain malformations	31	Mixed	NR	42	90
Cordoba et al, 2018[152]	Argentina	Patients with neurogenetic disorders	40	23 y (3–70 y)	11.5 y (3-42 y)	NR	NR
DDD, 2015[153]	United Kingdom	Children with suspected genetic disorders	1,133	5.5 y	NR	51.4	4
de Ligt et al, 2012[154]	Netherlands	Unexplained severe intellectual disability	100	78% < 20 y	NR	47	0
Dixon-Salazar et al, 2012[51]	International study[b]	Neurodevelopmental disorder with unknown but suspected genetic origin	118	Children	NR	NR	100
Eldomery et al, 2017[155]	United States	Unsolved suspected genetic disorders	74	All < 18 y	NR	NR	NR
Evers et al, 2017[156]	Germany	Undiagnosed suspected genetic conditions	72	6.4 y	NR	50	25
Farnaes et al, 2018[48]	United States	Infants in hospital with suspected genetic disorder	42	62 d (1–301 d)	NR	50	2
Farwell et al, 2015[58]	United States	Patients referred for genetic diagnostic testing	416	11.21 y (0–84 y)	NR	NR	NR

Author, Year	Location	Population	Sample Size	Proband Age at Enrollment[a]	Age of Symptom Onset[a]	Sex, % Male	Consanguinity, %
Gilissen et al, 2014[47]	Netherlands	Patients referred for genetic testing for intellectual disability	100	NR	NR	NR	NR
Hayeems et al, 2017[36]	Canada	Children with structural malformation or unexplained developmental delay	93	All < 18 y	NR	53.5	NR
Helsmoortel et al, 2015[157]	Belgium	People with unexplained intellectual disability	10	7 y	NR	60	0
Iglesias et al, 2014[74]	United States	People who had WES conducted as part of their care	115	78.9% < 18 y	NR	51.3	11
Kuperberg et al, 2016[71]	Israel	Pediatric patients with a suspected monogenic disorder	57	7 y (± 4 y)	NR	56.1	5
Lee et al, 2014[65]	United States	Mixed, including developmental delay and ataxia	814	64% < 18 y	NR	56	6
Lionel et al, 2018[45]	Canada	Outpatients with well characterized conditions but in line for genetics testing as next steps of investigation	70	All < 18 y	8 y[c]	50.2	9
Mak et al, 2018[132]	Hong Kong	Patients referred for exome testing	104	4 y (1 mo–33 y)	NR	62.5	NR
Meng et al, 2017[72]	United States	Critically ill infants with suspected genetic disorders	278	28 d (0–100 d)	NR	54.3	NR
Monies et al, 2017[52]	Saudi Arabia	Patients referred for genetic diagnostic testing	347	9.9 y	NR	49.9	37
Monroe et al, 2016[89]	Netherlands	Intellectual disability or developmental delay	17	3.0 y (0.0 y–11.8 y)	6.6 y (3.3–16.2 y)[c]	41	0
Neveling et al, 2013[53]	Netherlands	Variety of specific disorders; results for only mitochondrial disorders were included in our review	44	11.4 y (2–30 y)	NR	NR	NR

Author, Year	Location	Population	Sample Size	Proband Age at Enrollment[a]	Age of Symptom Onset[a]	Sex, % Male	Consanguinity, %
Petrikin et al, 2018[56]	United States	Neonatal and pediatric intensive care unit patients referred for genetic testing	37	22 d (0 y–101 y)	NR	57	5
Retterer et al, 2016[61]	United States	All patients referred for WES; results for multiple congenital anomalies are reported in our review	729	6.8 y	NR	NR	NR
Sawyer et al, 2016[158]	Canada	Rare diseases	362	NR	NR	NR	21
Schofield et al, 2017[93]	Australia	Childhood-onset muscle disorders	30	NR	7.7 y (2 mo–26 y)[c]	53.6	12.5
Soden et al, 2014[46]	United States	Pediatric neurodevelopmental disorders	100	7 y (1 mo–21 y)	6.6 mo (0 mo–7.5 y)[d]	NR	5
Srivastava et al, 2014[62]	United States	Patients who had WES as part of their neurodevelopmental disabilities care	78	9 y (1–26 y)	NR	53	12
Stark et al, 2016[54]	Australia	Pediatric suspected monogenic disorders	80	8 mo (1 wk–34 mo)	0 y	62.5	21
Stark et al, 2018[159]	Australia	Patients with suspected monogenic disorders	80	8 mo (1 wk–34 mo)	0 y	NR	NR
Stavropolous et al, 2016[66]	Canada	Pediatric patients who met criteria for chromosomal microarray	100	5.5 y	NR	57	8
Tan et al, 2017[75]	Australia	Children with suspected genetic disorders that cannot be typically diagnosed from clinical assessment	44	68% 2–10 y 32% 10–18 y	Younger children: mean 3.8 y[c] Older children: mean 10.6 y[c]	52	NR
Tarailo-Graovac et al, 2016[67]	Canada	Patients with intellectual disability and potentially treatable inborn errors of metabolism	41	5.9 (8 mo–31 y)	NR	63	15
Thevenon et al, 2016[68]	France	Families with a diagnostic odyssey for intellectual disability or epileptic encephalopathy	43	14 y (2–40 y)	NR	56	11.6
Trujillano et al, 2017[59]	International study[e]	Patients referred for WES diagnostic testing	1,000	84.3% < 15 y	NR	NR	45

Author, Year	Location	Population	Sample Size	Proband Age at Enrollment[a]	Age of Symptom Onset[a]	Sex, % Male	Consanguinity, %
Valencia et al, 2015[60]	United States	Mixed, including mitochondrial disorders and neurological disorders	40	6.9	5.3 mo	68	NR
Vissers et al, 2017[55]	Holland	Complex pediatric patients with undiagnosed neurological disorder of suspected genetic origin	150	5.6 y (5 mo–18 y)	NR	53	5
Willig et al, 2015[50]	United States	Acute neonatal and pediatric illness	35	26 d	NR	51	3
Yang et al, 2013[69]	United States	Rare genetic disorders	250	89% children	NR	NR	NR
Yang et al, 2014[70]	United States	Mixed, neurological, and non-neurological conditions	2,000	6 y	NR	55	NR
Zhu et al, 2015[160]	United States and Israel	Patients with severe suspected genetic disorders	119	9.5 y	7.7 y (1–31 y)[c]	56	8

Abbreviations: d, day; DDD, Deciphering Developmental Disorders study; mo, month; NR, not reported; WES, whole exome sequencing; wk, week; y, year.
[a]Median (range) unless otherwise stated, as reported in primary studies.
[b]Middle East, North Africa, and Central Asia.
[c]Length of diagnostic odyssey.
[d]Also reported mean time until diagnosis: 7.9 y (16 mo–21.8 y).
[e]54 countries, 78.5% from Middle East.

Appendix 3: Selected Excluded Studies—Clinical Evidence

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

Table A2: Primary Reasons for Exclusion of Select Excluded Studies

Citation	Primary Reason for Exclusion
Cheon CK, Sohn YB, Ko JM, Lee YJ, Song JS, Moon JW, et al. Identification of KMT2D and KDM6A mutations by exome sequencing in Korean patients with Kabuki syndrome. J Hum Genet. 2014;59(6):321-5.	Population: clinically explained Kabuki syndrome
Fan Y, Wu Y, Wang L, Wang Y, Gong Z, Qiu W, et al. Chromosomal microarray analysis in developmental delay and intellectual disability with comorbid conditions. BMC Med Genomics. 2018;11(1):49.	Intervention: chromosomal microarray
Gieldon L, Mackenroth L, Kahlert AK, Lemke JR, Porrmann J, Schallner J, et al. Diagnostic value of partial exome sequencing in developmental disorders. PloS One. 2018;13(8):e0201041.	Intervention: partial exome testing
Martinez F, Caro-Llopis A, Rosello M, Oltra S, Mayo S, Monfort S, et al. High diagnostic yield of syndromic intellectual disability by targeted next-generation sequencing. J Med Genet. 2017;54(2):87-92.	Outcomes: data on clinical utility not discernible
Nambot S, Thevenon J, Kuentz P, Duffourd Y, Tisserant E, Bruel AL, et al. Clinical whole-exome sequencing for the diagnosis of rare disorders with congenital anomalies and/or intellectual disability: substantial interest of prospective annual reanalysis. Genet Med. 2018;20(6):645-54.	Outcomes: data on clinical utility not discernible
Navarrete R, Leal F, Vega AI, Morais-Lopez A, Garcia-Silva MT, Martin-Hernandez E, et al. Value of genetic analysis for confirming inborn errors of metabolism detected through the Spanish neonatal screening program. Eur J Hum Genet. 2019;27:556-562.	Population: screening in newborns with atypical amino acid levels
Nolan D, Carlson M. Whole-exome sequencing in pediatric neurology patients: clinical implications and estimated cost analysis. J Child Neurol. 2016;31(7):887-94.	Outcomes: data on clinical utility not discernible
Jegathisawaran J, Tsiplova K, Ungar WJ. A microcosting and cost-consequence analysis of genomic testing strategies (including trios) in autism spectrum disorder: an update of the report No. 2016-02.2. Technology Assessment at SickKids. Toronto (ON): The Hospital for Sick Children; 2019.	Study type: not a systematic search for studies
Sansovic I, Ivankov AM, Bobinec A, Kero M, Barisic I. Chromosomal microarray in clinical diagnosis: a study of 337 patients with congenital anomalies and developmental delays or intellectual disability. Croat Med J. 2017;58(3):231-8.	Intervention: chromosomal microarray
Schieving JH. PP05.5 – 3064: The role of exome sequencing in daily pediatric neurology practice. Eur J Paediatr Neurol. 2015;19:S47.	Study type: conference abstract
Tammimies K, Marshall CR, Walker S, Kaur G, Thiruvahindrapuram B, Lionel AC, et al. Molecular diagnostic yield of chromosomal microarray analysis and whole-exome sequencing in children with autism spectrum disorder. JAMA. 2015;314(9):895-903.	Population: clinically diagnosed autism disorder
Taylor JC, Martin HC, Lise S, Broxholme J, Cazier JB, Rimmer A, et al. Factors influencing success of clinical genome sequencing across a broad spectrum of disorders. Nat Genet. 2015;47(7):717-26.	Population: immunological disorders
van Nimwegen KJ, Schieving JH, Willemsen MA, Veltman JA, van der Burg S, van der Wilt GJ, et al. The diagnostic pathway in complex paediatric neurology: a cost analysis. Eur J Paediatr Neurol. 2015;19(2):233-9.	Intervention: combined various interventions

Appendix 4: Critical Appraisal of Clinical Evidence

Table A3: Risk of Bias[a] Among Systematic Reviews (ROBIS Tool)

	Phase 2				Phase 3
Author, Year	Study Eligibility Criteria	Identification and Selection of Studies	Data Collection and Study Appraisal	Synthesis and Findings	Risk of Bias in the Review
Clark et al, 2018[37]	Low	Low[b]	High[d]	High[g]	High[h]
Schwarze et al, 2018[38]	Low	Low[b]	High[d]	Low	Low
Shakiba and Keramatipour, 2018[39]	Low	High[c]	High[d,e]	Low	High[h]
Sun et al, 2015[40]	Low	Low[b]	High[d]	High[g]	High
Washington Health Authority, 2017[41]	Low	Low[b]	Low[f]	Low	Low

Abbreviation: ROBIS, risk of bias in systematic reviews.
[a]Possible risk of bias levels: low, high, unclear.
[b]Date or language restriction; it is unlikely parameters selected led to missing studies.
[c]Literature search criteria were insufficiently robust.
[d]No risk of bias or other quality of study assessment was conducted or effort to minimize error in risk of bias assessment.
[e]No effort to minimize data collection error.
[f]Included data obtained only from abstracts where full-text publications were unavailable.
[g]Biases in primary studies were not accounted for and review conducted meta-analyses.
[h]Authors did not address all concerns or drew conclusions that extended beyond evidence provided.

Table A4: Risk of Bias[a] With Risk of Bias Assessment Tool for Non-randomized Studies (RoBANS)

Author, Year	Selection of Participants	Confounding Variables	Measurement of Exposure	Blinding of Outcome Assessments	Incomplete Outcome Data
Al-Shamsi et al, 2016[57]	High[b]	High[c]	Unclear[d]	High[e]	Low
Baldridge et al, 2017[63]	High[b]	High[c]	Unclear[d]	High[e]	Low
Bick et al, 2017[64]	High[b]	High[c]	Unclear[d]	High[e]	Low
Bowling et al, 2017[44]	High[b]	High[c]	Unclear[d]	High[e]	Low
Charng et al, 2016[151]	High[b]	High[c]	Unclear[d]	High[e]	Low
Cordoba et al, 2018[152]	High[b]	High[c]	Unclear[d]	High[e]	Low
DDD, 2015[153]	High[b]	High[c]	Unclear[d]	High[e]	Low
de Ligt et al, 2012[154]	High[b]	High[c]	Unclear[d]	High[e]	Low
Dixon-Salazar et al, 2012[51]	Low	High[c]	Unclear[d]	High[e]	Low
Eldomery et al, 2017[155]	High[b]	High[c]	Unclear[d]	High[e]	Low
Evers et al, 2017[156]	High[b]	High[c]	Unclear[d]	High[e]	Low
Farnaes et al, 2018[48]	Low	High[c]	Unclear[d]	High[e]	Low
Farwell et al, 2015[58]	High[b]	High[c]	Unclear[d]	High[e]	Low
Gilissen et al, 2014[47]	High[b]	High[c]	Unclear[d]	High[e]	Low
Hayeems et al, 2017[36]	High[b]	High[c]	Unclear[d]	High[e]	Low
Helsmoortel et al, 2015[157]	High[b]	High[c]	Unclear[d]	High[e]	Low
Iglesias et al, 2014[74]	High[b]	High[c]	Unclear[d]	High[e]	Low
Kuperberg et al, 2016[71]	High[b]	High[c]	Unclear[d]	High[e]	Low
Lee et al, 2014[65]	High[b]	High[c]	Unclear[d]	High[e]	Low
Lionel et al, 2018[45]	Low	High[c]	Unclear[d]	High[e]	Low
Mak et al, 2018[132]	High[b]	High[c]	Unclear[d]	High[e]	Low
Meng et al, 2017[72]	High[b]	High[c]	Unclear[d]	High[e]	Low
Monies et al, 2017[52]	Low	High[c]	Unclear[d]	High[e]	Low
Monroe et al, 2016[89]	High[b]	High[c]	Unclear[d]	High[e]	Low
Neveling et al,2013[53]	Low	High[c]	Unclear[d]	High[e]	Low
Petrikin et al, 2018[56]	Low	High[c]	Unclear[d]	High[e]	Low

Author, Year	Selection of Participants	Confounding Variables	Measurement of Exposure	Blinding of Outcome Assessments	Incomplete Outcome Data
Retterer et al, 2016[61]	High[b]	High[c]	Unclear[d]	High[e]	Low
Sawyer et al, 2016[158]	High[b]	High[c]	Unclear[d]	High[e]	Low
Schofield et al, 2017[93]	High[b]	High[c]	Unclear[d]	High[e]	Low
Soden et al, 2014[46]	High[b]	High[c]	Unclear[d]	High[e]	Low
Srivastava et al, 2014[62]	High[b]	High[c]	Unclear[d]	High[e]	Low
Stark et al, 2016[54]	Low	High[c]	Unclear[d]	High[e]	Low
Stark et al, 2018[159]	High[b]	High[c]	Unclear[d]	High[e]	Low
Stavropolous et al, 2016[66]	High[b]	High[c]	Unclear[d]	High[e]	Low
Tan et al, 2017[75]	High[b]	High[c]	Unclear[d]	High[e]	Low
Tarailo-Graovac et al, 2016[67]	High[b]	High[c]	Unclear[d]	High[e]	Low
Thevenon et al, 2016[68]	High[b]	High[c]	Unclear[d]	High[e]	Low
Trujillano et al, 2017[59]	High[b]	High[c]	Unclear[d]	High[e]	Low
Valencia et al, 2015[60]	High[b]	High[c]	Unclear[d]	High[e]	Low
Vissers et al, 2017[55]	Low	High[c]	Unclear[d]	High[e]	Low
Willig et al, 2015[50]	Low	High[c]	Unclear[d]	High[e]	Low
Yang et al, 2013[69]	High[b]	High[c]	Unclear[d]	High[e]	Low
Yang et al, 2014[70]	High[b]	High[c]	Unclear[d]	High[e]	Low
Zhu et al, 2015[160]	High[b]	High[c]	Unclear[d]	High[e]	Low

Abbreviation: DDD, Deciphering Developmental Disorders study.

[a]Possible risk of bias levels: low, high, and unclear.

[b]Study lacked control group, and participant recruitment was determined through a clinician's interpretation of complex symptoms and referral for testing.

[c]Learning effect of past experiences influencing future execution and interpretation and skills cannot be controlled for.

[d]Assessment of outcome is based on database of genes that is constantly in flux as new genes are discovered and analytical strategies of laboratory techniques are improved upon.

[e]It is impossible to blind the assessor, as proband phenotype and clinical history are integral components of determining a diagnosis. There is also bias introduced given the subjective nature of treatment decisions, such as determining if a change in therapy is warranted.

Table A5: GRADE Evidence Profiles

No. of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Whole Exome Sequencing							
Diagnostic Yield							
34 (observational)	Very serious limitations (−2)[a]	No limitations[b]	No limitations[c]	Serious limitations (−1)[d]	Undetected	None	⊕ Very Low
Diagnostic Yield of Comparative Studies							
5 (observational)	No limitations[a,e]	No limitations[b]	No limitations[c]	Serious limitations (−1)[d]	Undetected	None	⊕⊕ Low
Clinical Utility							
15 (observational)	Very serious limitations (−2)[a]	No limitations[b]	Serious limitations (−1)[f]	Serious limitations (−1)[g]	Undetected	None	⊕ Very Low
Whole Genome Sequencing							
Diagnostic Yield							
9 (observational)	Very serious limitations (−2)[a]	No limitations[b]	No limitations[c]	Serious limitations (−1)[d]	Undetected	None	⊕ Very Low
Diagnostic Yield of Comparative Studies							
4 (observational)	No limitations[a,e]	No limitations[b]	No limitations[c]	Serious limitations (−1)[d]	Undetected	None	⊕⊕ Low
Clinical Utility							
4 (observational)	Very serious limitations (−2)[a]	No limitations[b]	Serious limitations (−1)[f]	Serious limitations (−1)[g]	Undetected	None	⊕ Very Low

Abbreviation: GRADE, Grading of Recommendations Assessment, Development, and Evaluation.
[a]See risk of bias assessment in Table A4.
[b]Studies all demonstrated consistency in direction of effect.
[c]Yield is directly reported by included studies.
[d]Confidence intervals are sufficiently wide to compromise certainty of effect estimate, and magnitude of results was inconsistent across studies.
[e]Considered not a limitation, as risk of bias was balanced between study group and control.
[f]Clinical utility measures reported are assumed to affect patient care and ultimately patient outcomes.
[g]Clinical utility measures were not estimable and were considered imprecise.

Appendix 5: Additional Analyses—Clinical Evidence

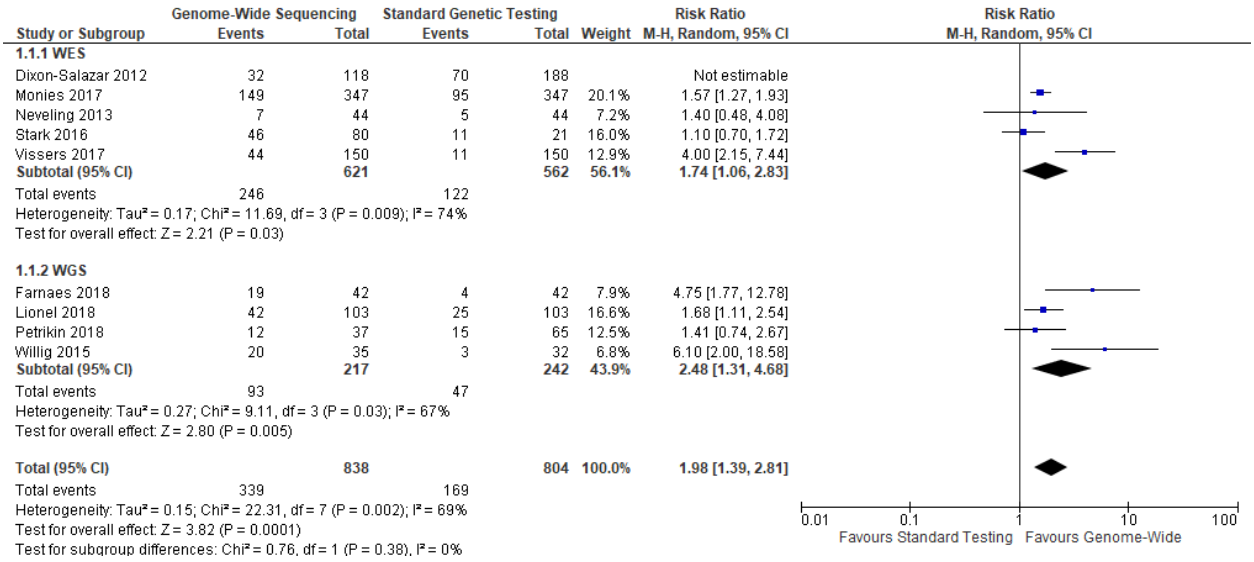


Figure A1: Sensitivity Analysis[a] of Comparative Diagnostic Yield of Genome-Wide Sequencing Versus Standard Genetic Testing

Abbreviations: CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel test; WES, whole exome sequencing; WGS, whole genome sequencing.

[a]This analysis removes the study by Dixon-Salazar et al[51] as a sensitivity analysis to that reported in the main report.

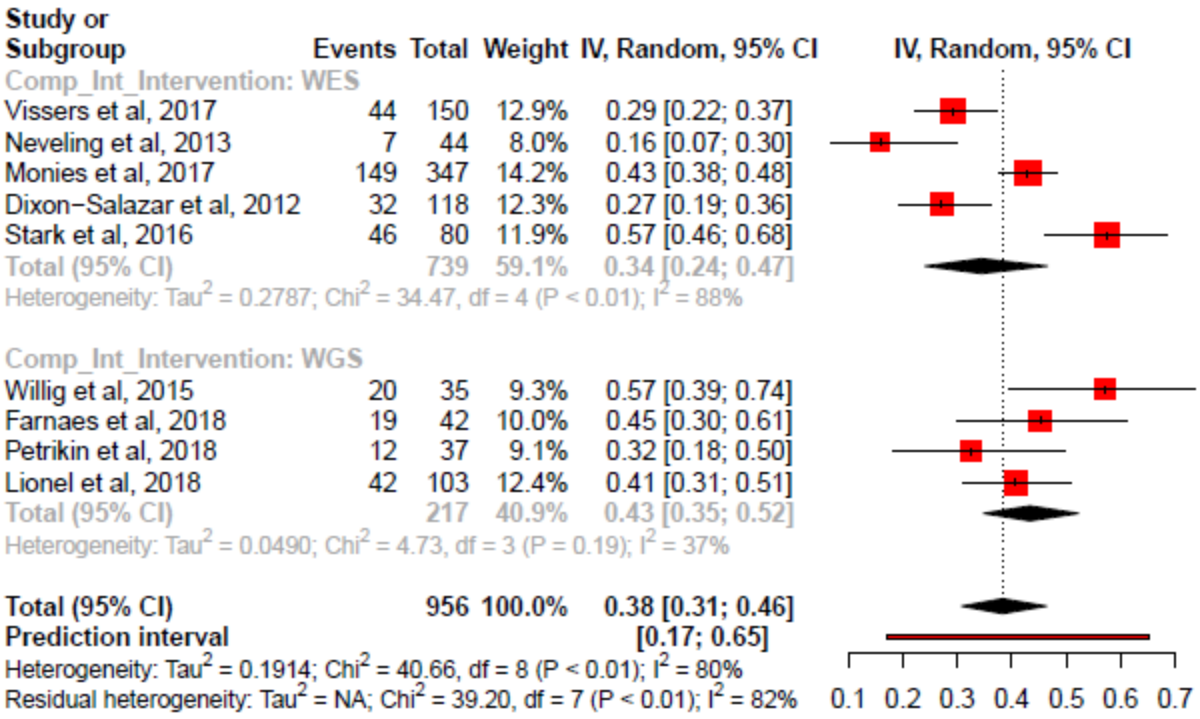


Figure A2: Diagnostic Yield of Genome-Wide Sequencing Among a Subset of Comparative Effectiveness Studies

Abbreviations: CI, confidence interval; Comp_Int, comparative studies intervention group; df, degrees of freedom; IV, inverse variance; NA, not available; WES, whole exome sequencing; WGS, whole genome sequencing.

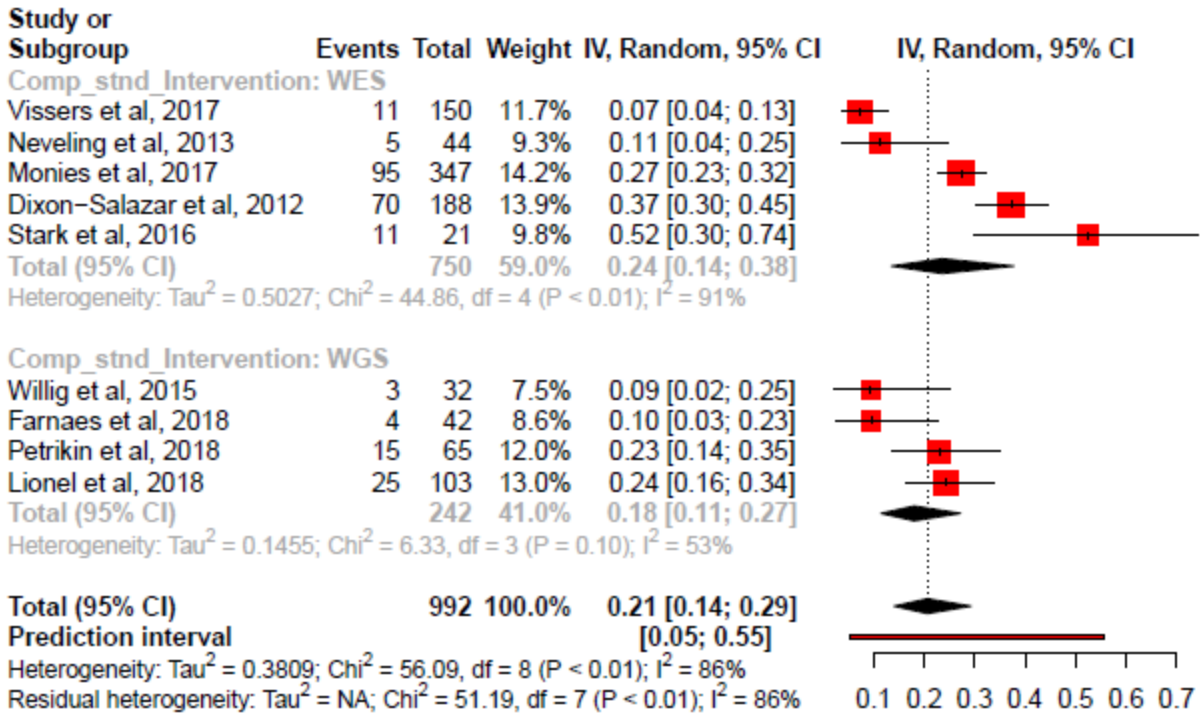


Figure A3: Diagnostic Yield of Standard Testing Among a Subset of Comparative Effectiveness Studies

Abbreviations: CI, confidence interval; Comp_stnd, comparative studies standard-care group; df, degrees of freedom; IV, inverse variance; NA, not applicable; WES, whole exome sequencing; WGS, whole genome sequencing.

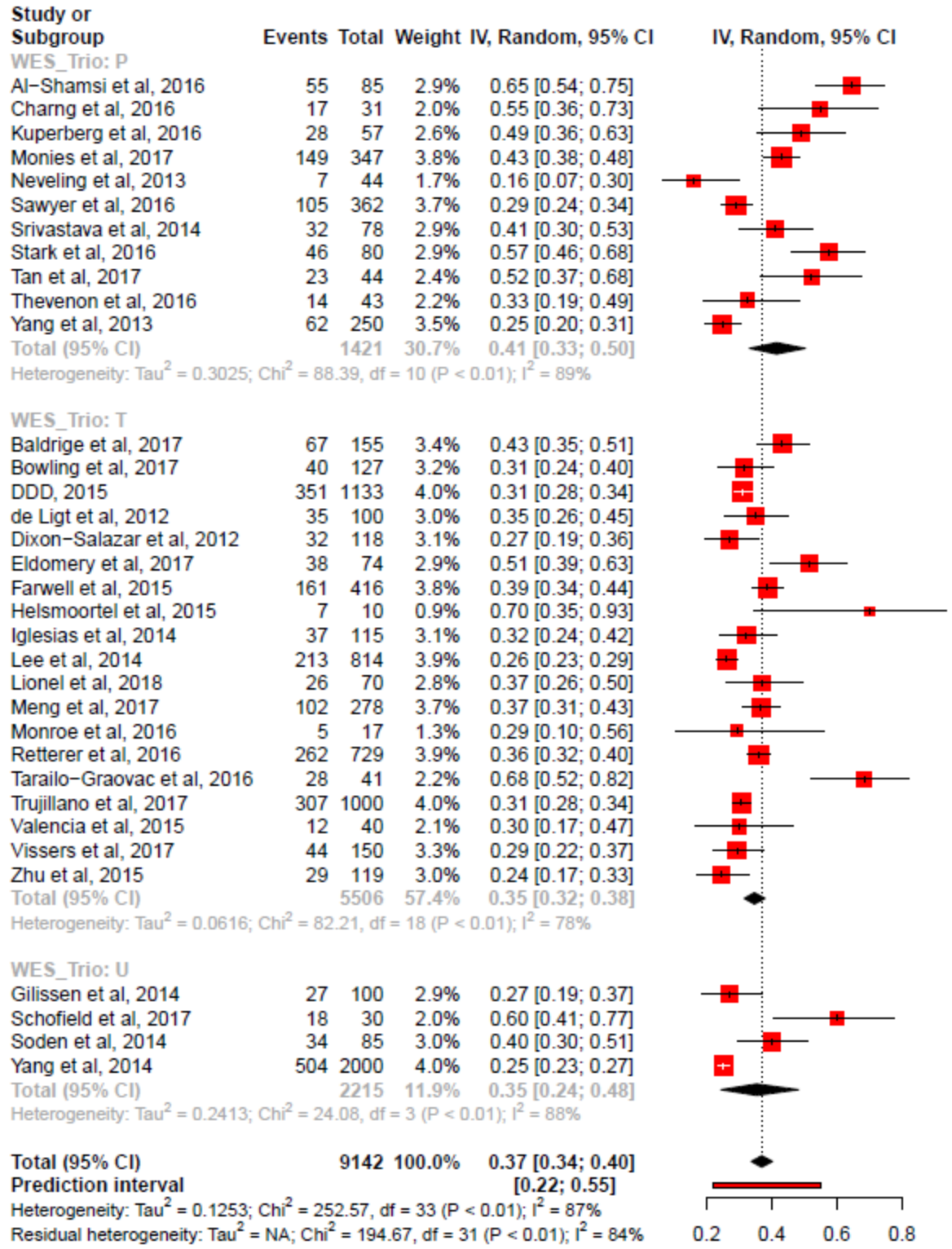


Figure A4: Diagnostic Yield of Whole Exome Sequencing by Use of Trio Testing

Abbreviations: CI, confidence interval; DDD, Deciphering Developmental Disorders study; df, degrees of freedom; IV, inverse variance; NA, not applicable; P, proband only; T, trio testing; U, uncertain/unclear/mix of proband and trio testing; WES, whole exome sequencing.

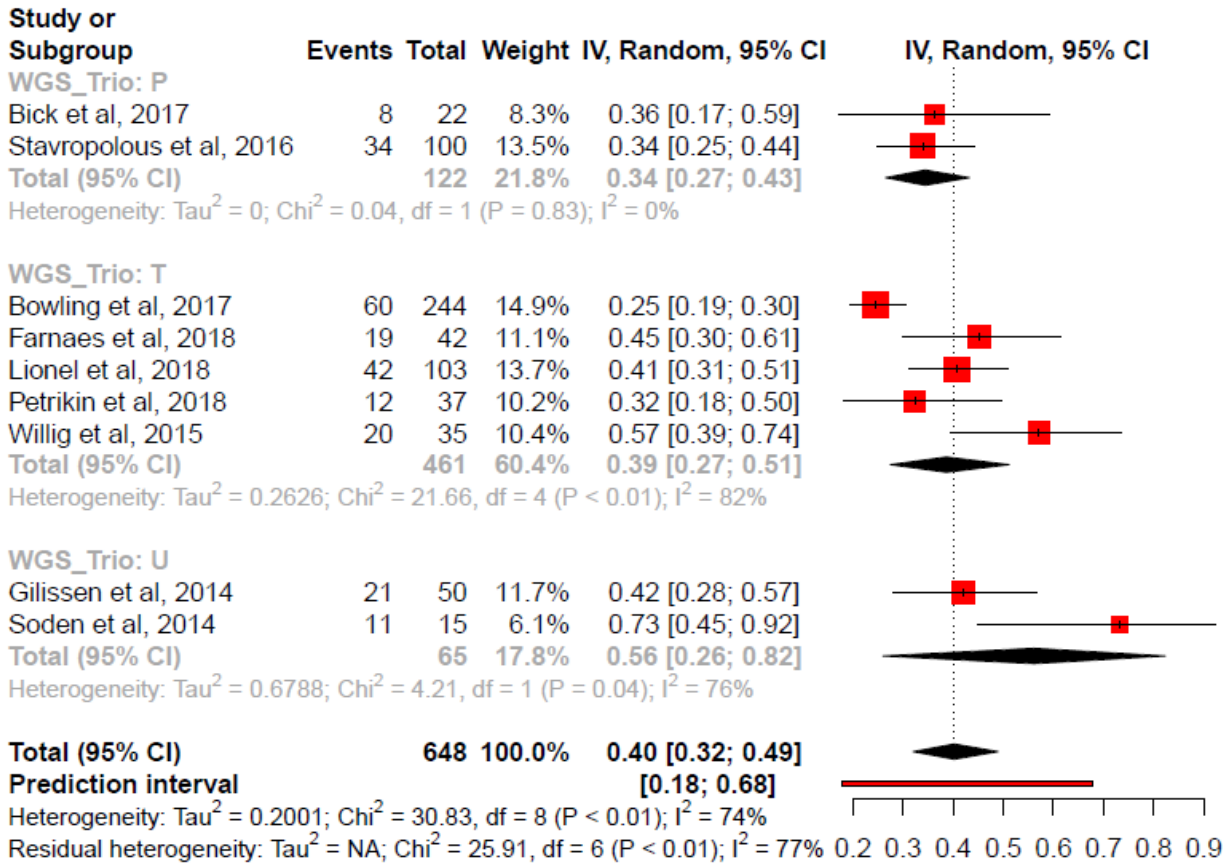


Figure A5: Diagnostic Yield of Whole Genome Sequencing by Use of Trio Testing

Abbreviations: CI, confidence interval; df, degrees of freedom; IV, inverse variance; NA, not applicable; P, proband only; T, trio testing; U, uncertain/unclear/mixed proband and trio testing; WGS, whole genome sequencing.

Table A6: Breakdown of Trio Use by Study

Author, Year	Trio Testing, %	No. Diagnosed	Sample Size	Diagnostic Yield
Mix of mostly trio, but also proband, duo, quad, and non-parental family testing				
Baldridge et al, 2017[63]	78	67	155	0.45
Bowling et al, 2017[44]	83	40	127	0.39
Eldomery et al, 2017[155]	85	38	74	0.32
Farwell et al, 2015[58]	81	161	416	0.49
Iglesias et al, 2014[74]	83	37	115	0.26
Petrikin et al, 2018[56]	84	28	41	0.41
Tarailo-Graovac et al, 2016[67]	68	307	1,000	0.37
Trujillano et al, 2017[59]	83	12	40	0.37
Valencia et al, 2015[60]	95	67	155	0.45
100% trio testing				
DDD, 2015[153]	100	351	1,133	0.65
de Ligt et al, 2012[154]	100	35	100	0.43
Dixon-Salazar et al, 2012[51]	100	32	118	0.36
Farnaes et al, 2018[48]	100	19	42	0.43
Helsmoortel et al, 2015[157]	100	7	10	0.70
Lee et al, 2014[65]	100	127	410	0.31
Lionel et al, 2018[45]	100	26	70	0.25
Meng et al, 2017[72]	100	45	102	0.55
Monroe et al, 2016[89]	100	5	17	0.31
Retterer et al, 2016[61]	100	647	2,088	0.35
Vissers et al, 2017[55]	100	44	150	0.27
Willig et al, 2015[50]	100	20	35	0.55
Zhu et al, 2015[160]	100	29	119	0.51

Abbreviation: DDD, Deciphering Developmental Disorders study.

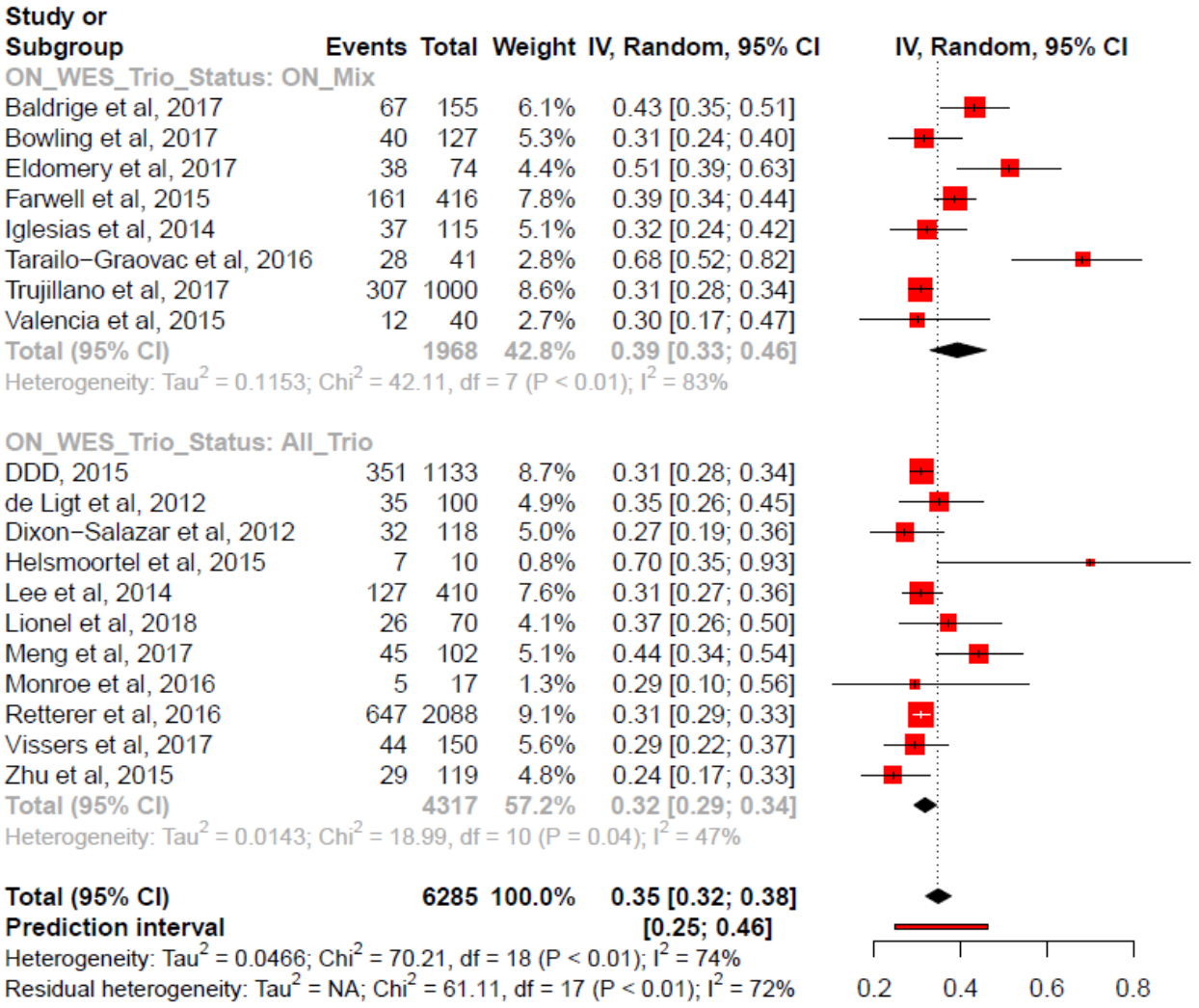


Figure A6: Diagnostic Yield of Whole Exome Sequencing by Testing Method Using Trio or Mixed Methods

Abbreviations: CI, confidence interval; DDD, Deciphering Developmental Disorders study; df, degrees of freedom; IV, inverse variance; NA, not applicable; ON_Mix, studies with a mix of trio testing that more closely represents the Ontario context; WES, whole exome sequencing.

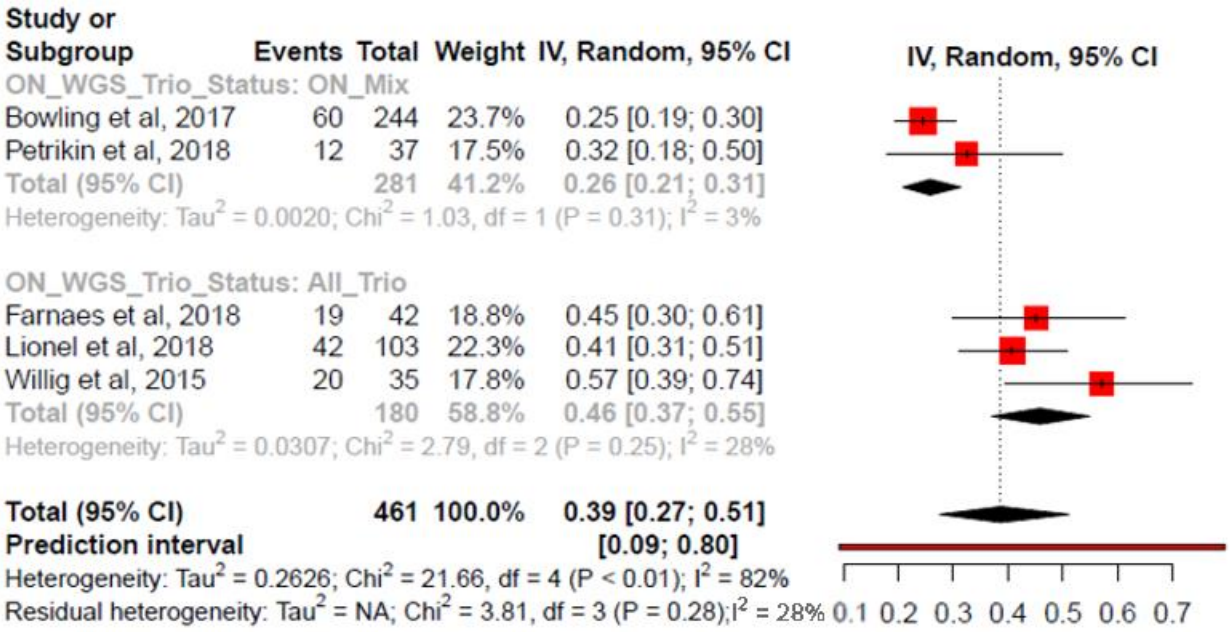


Figure A7: Diagnostic Yield of Whole Genome Sequencing by Testing Method Using Trio or Mixed Methods

Abbreviations: CI, confidence interval; df, degrees of freedom; IV, inverse variance; ON_Mix, studies with a mix of trio testing that more closely represents Ontario context; WGS, whole genome sequencing.

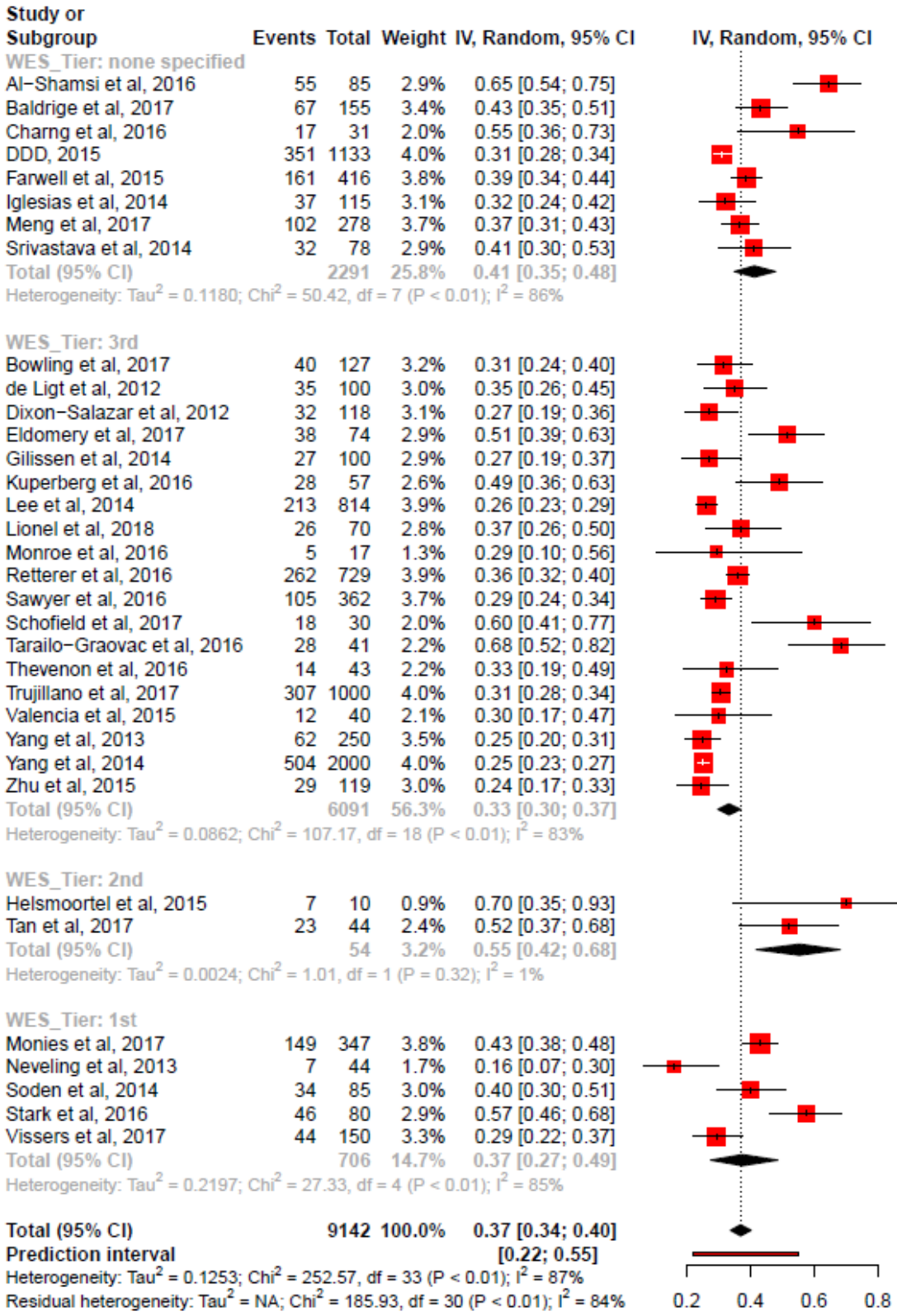


Figure A8: Diagnostic Yield of Whole Exome Sequencing by Timing of Use

Abbreviations: 1st, first-tier test (before any other genetic testing); 2nd, second-tier test (after very limited genetic testing, such as just chromosomal microarray); 3rd, third-tier test (after chromosomal microarray, targeted gene or gene panel assessments); CI, confidence interval; DDD, Deciphering Developmental Disorders study; df, degrees of freedom; IV, inverse variance; NA, not applicable; WES, whole exome sequencing.

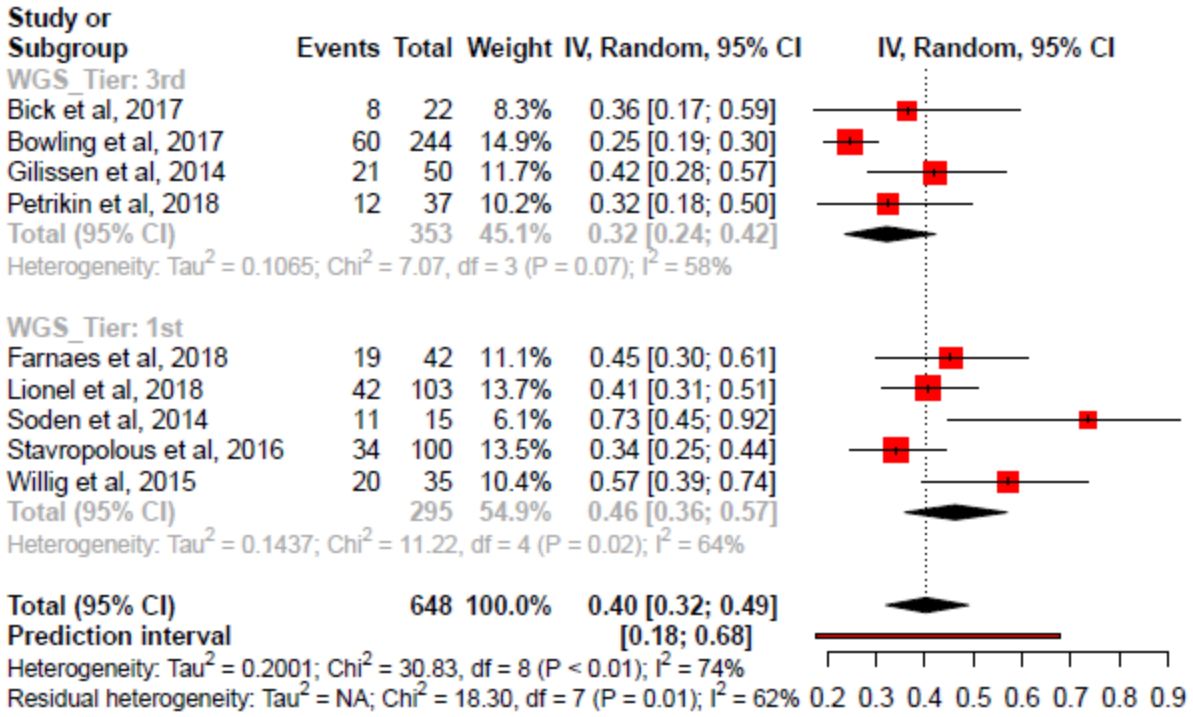


Figure A9: Diagnostic Yield of Whole Genome Sequencing by Timing of Use

Abbreviations: 1st, first-tier test (before any other genetic testing); 3rd, third-tier test (after more exhaustive genetic testing, including targeted gene or gene panel assessments); CI, confidence interval; df, degrees of freedom; IV, inverse variance; NA, not applicable; WGS, whole genome sequencing.

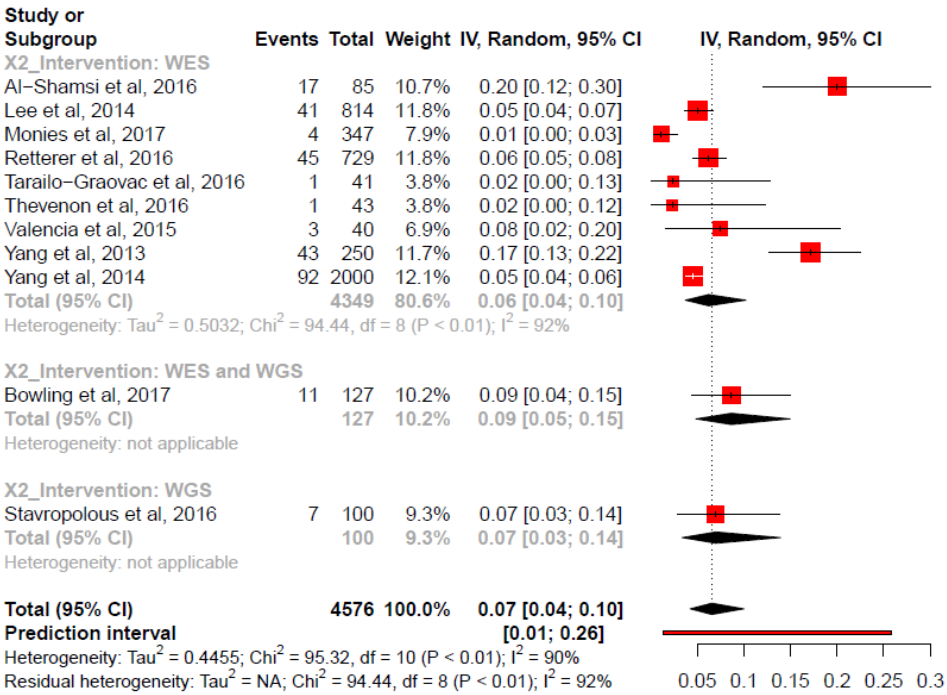


Figure A10: Secondary Findings Yield by Genome-Wide Sequencing Test

Abbreviations: CI, confidence interval; df, degrees of freedom; IV, inverse variance; NA, not applicable; WES, whole exome sequencing; WGS, whole genome sequencing, X2, secondary findings.

Table A7: Clinical Utility Activities From Use of Genome-Wide Sequencing

Author, Year	Active Medical Management Activities, n				Monitoring and Long-Term Clinical Management Activities, n					Total Clinical Utility Activities, n
	Modifications to Medications	Procedure	Treatment	Sum	Additional Diagnostics or Alterations to Surveillance	Changes to Specialist Involvement/ Referrals	Referral to Clinical Trial	Social Services/ Impact on Prognosis or Lifestyle	Sum	
Baldridge et al, 2017[63]	8[a]			**8**	84		36		**120**	**128**
Bick et al, 2017[64]	4			**4**	6				**6**	**10**
Cordoba et al, 2018[152]	7			**7**					**0**	**7**
Evers et al, 2017[156]	1			**1**	7				**7**	**8**
Farnaes et al, 2018[156]		4	6	**10**	4			11	**15**	**25**
Iglesias et al, 2014[74]	3			**3**	22			7	**29**	**32**
Kuperberg et al, 2016[71]	5			**5**					**0**	**5**
Mak et al, 2018[132]	12	3		**15**	33	19		6	**58**	**73**
Martinez et al, 2017[161]				**0**					**0**	**0**
Meng et al, 2017[72]	4	4		**8**	17				**17**	**25**
Petrikin et al, 2018[56]	1	2		**3**	2	5		1	**8**	**11**
Sawyer et al, 2016[158]	6			**6**					**0**	**6**
Soden et al, 2014[46]			13	**13**	9				**9**	**22**
Srivastava et al, 2014[62]	7			**7**	10		3	10	**23**	**30**
Stark et al, 2016[54]			8	**8**	10				**10**	**18**
Stark et al, 2018[159]				**0**	9				**9**	**9**
Tan et al, 2017[75]				**0**		6[b]			**6**	**6**
Tarailo-Graovac et al, 2016[67]	5	4	7	**16**				5	**5**	**21**
Thevenon et al, 2016[68]				**0**	4				**4**	**4**
Valencia et al, 2015[60]	1		4	**5**	5				**5**	**10**

[a]Includes referrals to other specialists.
[b]Includes surveillance changes.

Appendix 6: Summary of Genetic Testing Advisory Committee (GTAC) Criteria

To use genome-wide sequencing for undiagnosed rare genetic diseases in Ontario, patients must meet one or more of the following criteria:

- Clinical presentation:
    - Moderate to severe developmental or functional impairment
    - Multisystem involvement
    - Progressive clinical course
    - Differential diagnosis includes two or more conditions that would be evaluated in separate panels
- Impact on clinical management:
    - Will limit further invasive diagnostic investigations
    - Will allow for specific and informed reproductive decision-making
    - Will enable identification of at-risk family members and facilitate early intervention

AND

Patient must meet all of the following conditions:

- Detailed phenotypic characterization (physical examination, investigations) has occurred and is documented
- Pre-test genetic counseling and consent has been completed
- Chromosomal microarray has been completed and does NOT explain the patient's phenotype (for patients with developmental delay, intellectual disability, multiple congenital anomalies, dysmorphic features)
- Other causative circumstances (e.g. environmental exposures, injury, and infection) do NOT explain the patient's clinical presentation
- Previous targeted testing has been unrevealing (if specific monogenetic disorder suspected)
- Previous comprehensive panel testing has NOT been completed in the last 3 years (panel contained virtually all known genes for that clinical indication)

Patient must NOT have:

- Isolated mild intellectual disability or learning disabilities
- Non-syndromic autism
- Isolated neurobehavioural disabilities (e.g., attention deficit disorder)
- A phenotype highly specific to a known genetic condition for which optimized genetic panel testing exists. If so, then the targeted gene test should be given priority, assuming it is more sensitive (e.g., for Noonan spectrum disorders)

Appendix 7: Results of Applicability Checklists for Studies Included in the Economic Literature Review

Table A8: Applicability of Studies Evaluating Cost-Effectiveness of Genome-Wide Sequencing

Author, Year, Country of Publication	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 estimates of relative treatment effect from the best available source?	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]
Dragojlovic et al, 2018, Canada (British Columbia)[84]	Partially	Partially	Yes	Yes, health care payer	Partially	NA	No	No	Not applicable
Ewans et al, 2018, Australia[79]	Partially	Partially	Yes	Yes, health care payer	No	NA	No	No	Not applicable
Jegathisawaran et al, 2019, Canada (Ontario)[90]	Yes	Partially	Yes	Yes, hospital	Partially	NA	No	No	Partially applicable
Monroe et al, 2016, Netherlands[89]	Partially	Partially	Yes	Yes, health care payer	No	NA	No	No	Not applicable
Schofield et al, 2017, Australia[93]	Partially	Partially	Yes	Yes, health care payer	No	NA	No	No	Not applicable
Stark et al, 2017, Australia[94]	Partially	Partially	Yes	Yes, health care payer	No	NA	No	No	Not applicable
Tan et al, 2017, Australia[75]	Partially	Partially	Yes	Yes, health care payer	No	NA	No	No	Not applicable
Vissers et al, 2017, Netherlands[55]	Partially	Partially	Yes	Yes, health care payer	No	NA	No	No	Not applicable

Note: Response options for all items were “yes,” “partially,” “no,” “unclear,” and “NA” (not applicable).
[a]Overall judgment can be “directly applicable,” “partially applicable,” or “not applicable.”

Appendix 8: Diagnostic Yield of Chromosomal Microarray

To estimate the diagnostic yield of chromosomal microarray in people with developmental disabilities or multiple congenital anomalies, we conducted a summary effect estimate analysis using studies systematically identified by Miller et al[11] (Figure A11). The average yield is estimated to be 0.10 (95% confidence interval [CI] 0.09–0.12). This is consistent with other published studies in this patient population.[2,37,66]

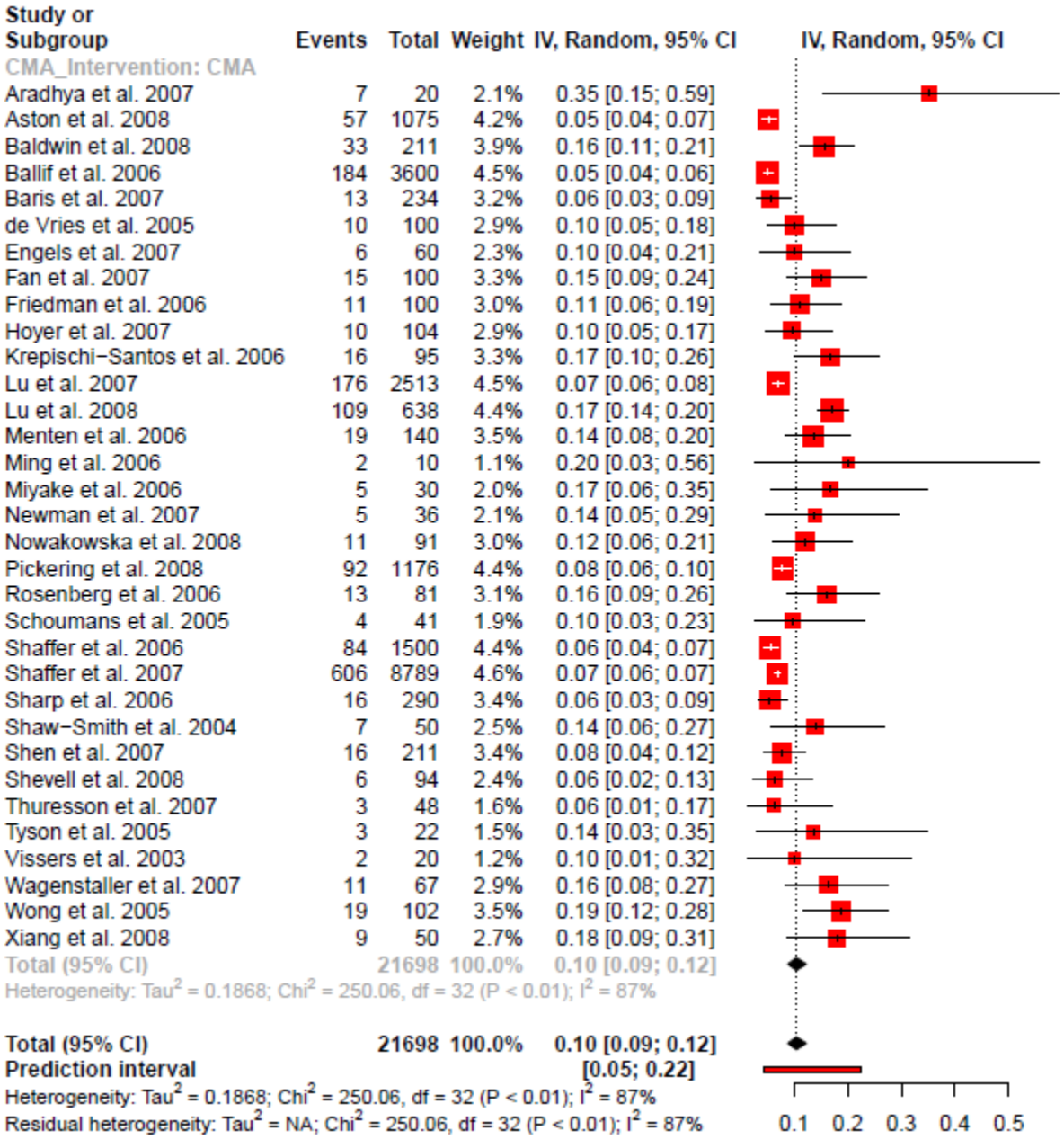


Figure A11: Diagnostic Yield of Chromosomal Microarray

Abbreviations: CI, confidence interval; CMA, chromosomal microarray; df, degrees of freedom; IV, inverse variance; NA, not applicable.

Appendix 9: Cost-Effectiveness Planes and Acceptability Curves

Research Question 1

Results of the probabilistic sensitivity analysis are plotted on the cost-effectiveness plane (Figure A12). Figure A13 is the cost-effectiveness acceptability curve, which shows the probability of each testing strategy being cost-effective across a range of willingness-to-pay values. Unlike quality-adjusted life-years (QALYs), willingness-to-pay values for molecular diagnostic yield are unknown. Assuming a willingness-to-pay of $13,000, $15,000, and $17,000 per additional molecular diagnosis, the probability of whole exome sequencing after standard testing being cost-effective was 25%, 92%, and 100%, respectively.

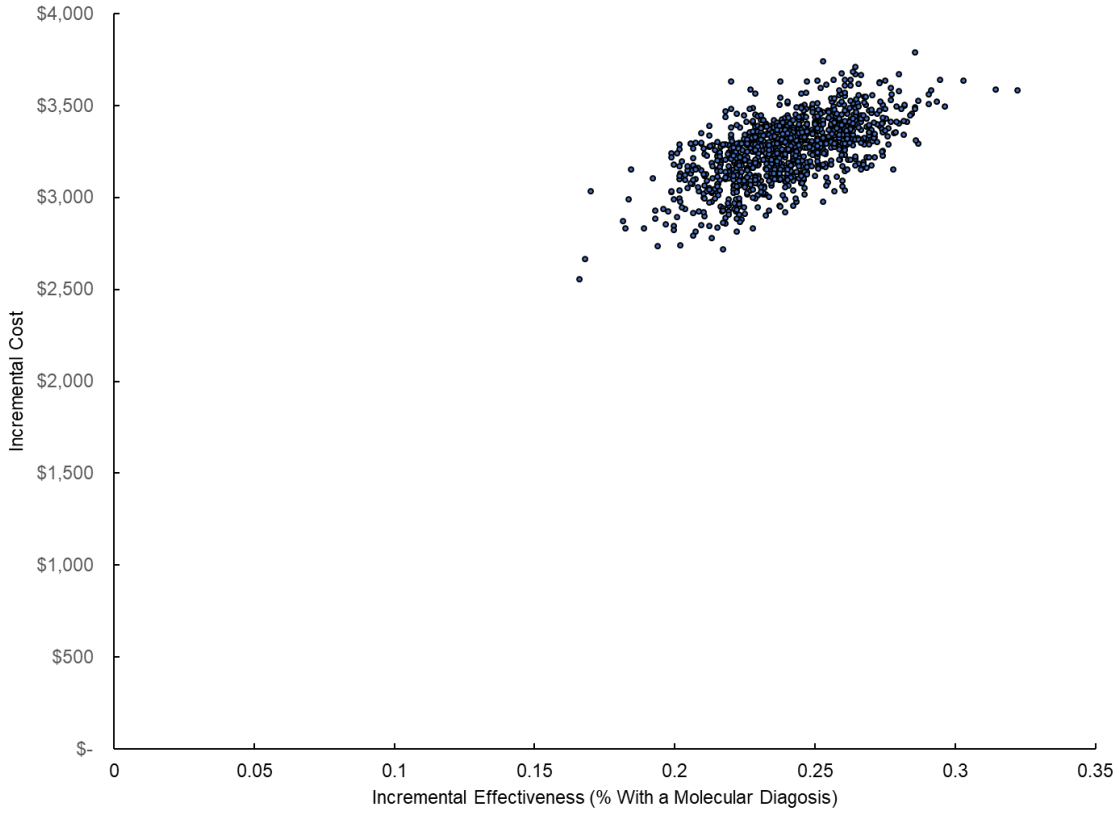


Figure A12: Cost-Effectiveness Plane Showing Incremental Cost and Effectiveness of Whole Exome Sequencing After Standard Testing Versus Standard Testing

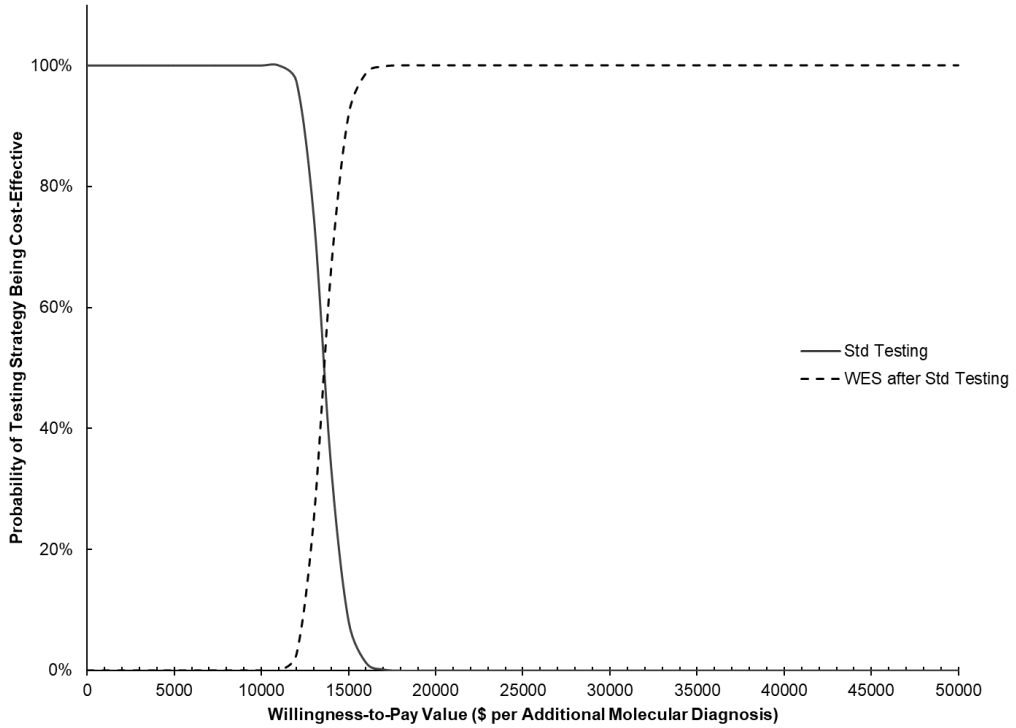


Figure A13: Cost-Effectiveness Acceptability Curve—Whole Exome Sequencing After Standard Testing Versus Standard Testing

Abbreviations: Std, standard; WES, whole exome sequencing.

Research Question 2

Results of the probabilistic sensitivity analysis are plotted on the cost-effectiveness plane (Figure A14). The cost-effectiveness acceptability curve (Figure A15) shows that whole exome sequencing as second-tier testing is the most cost-effective option until the willingness-to-pay value exceeds about $11,831 per additional molecular diagnosis. If the willingness-to-pay is more than $11,831 per additional molecular diagnosis, then whole exome sequencing plus chromosomal microarray as first tier becomes the most cost-effective option. Again, unlike QALYs, willingness-to-pay values for molecular diagnostic yield are not known. Assuming a willingness-to-pay of $13,000, $15,000, and $17,000 per additional molecular diagnosis, the probability of WES plus chromosomal microarray as first tier being cost-effective was 45%, 51%, and 53%, respectively.

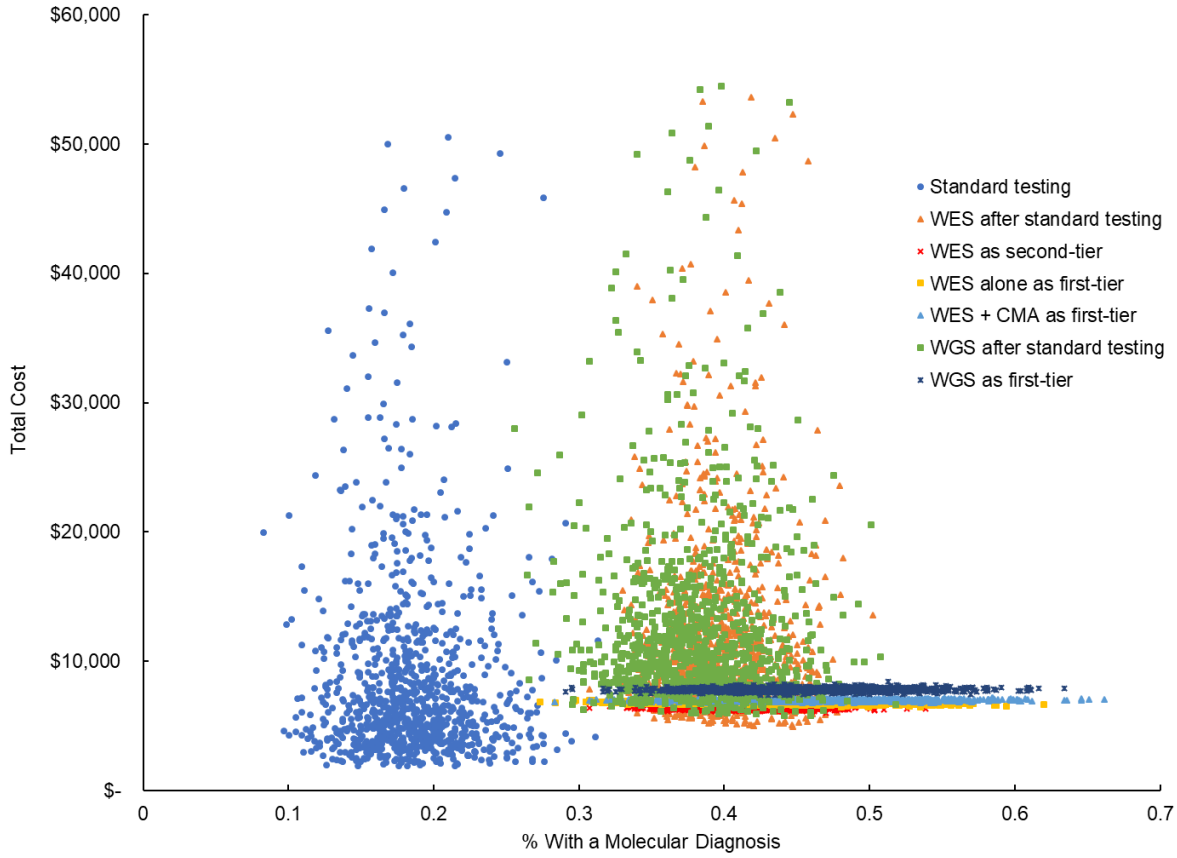


Figure A14: Cost-Effectiveness Plane Showing Total Cost and Effectiveness of Various Testing Strategies

Abbreviations: CMA, chromosomal microarray; WES, whole exome sequencing; WGS, whole genome sequencing.

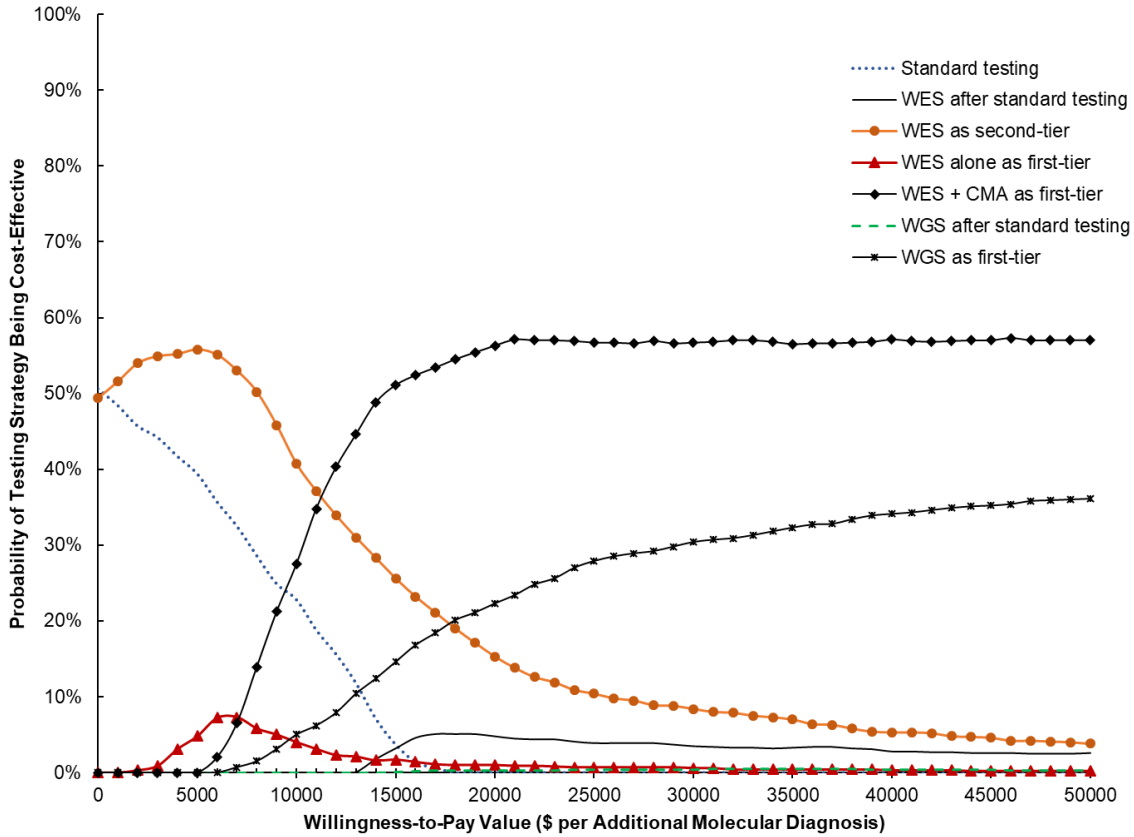
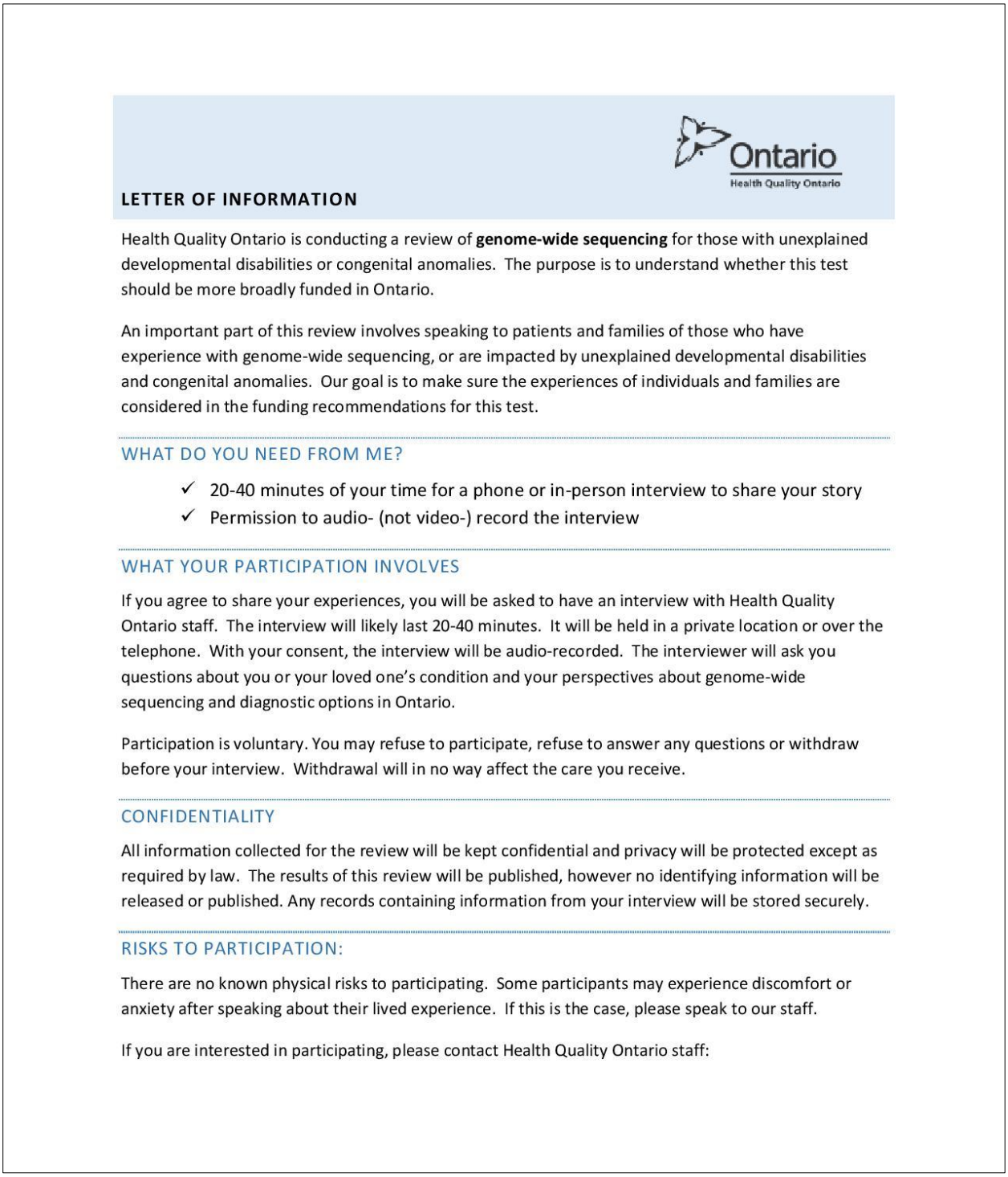


Figure A15: Cost-Effectiveness Acceptability Curves Showing Probability of Testing Strategies Being Cost-Effective Across a Range of Willingness-to-Pay Values

Abbreviations: CMA, chromosomal microarray; WES, whole exome sequencing; WGS, whole genome sequencing.

Appendix 10: Letter of Information[a]



LETTER OF INFORMATION

Health Quality Ontario is conducting a review of **genome-wide sequencing** for those with unexplained developmental disabilities or congenital anomalies. The purpose is to understand whether this test should be more broadly funded in Ontario.

An important part of this review involves speaking to patients and families of those who have experience with genome-wide sequencing, or are impacted by unexplained developmental disabilities and congenital anomalies. Our goal is to make sure the experiences of individuals and families are considered in the funding recommendations for this test.

WHAT DO YOU NEED FROM ME?

- ✓ 20-40 minutes of your time for a phone or in-person interview to share your story
- ✓ Permission to audio- (not video-) record the interview

WHAT YOUR PARTICIPATION INVOLVES

If you agree to share your experiences, you will be asked to have an interview with Health Quality Ontario staff. The interview will likely last 20-40 minutes. It will be held in a private location or over the telephone. With your consent, the interview will be audio-recorded. The interviewer will ask you questions about you or your loved one's condition and your perspectives about genome-wide sequencing and diagnostic options in Ontario.

Participation is voluntary. You may refuse to participate, refuse to answer any questions or withdraw before your interview. Withdrawal will in no way affect the care you receive.

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 your interview will be stored securely.

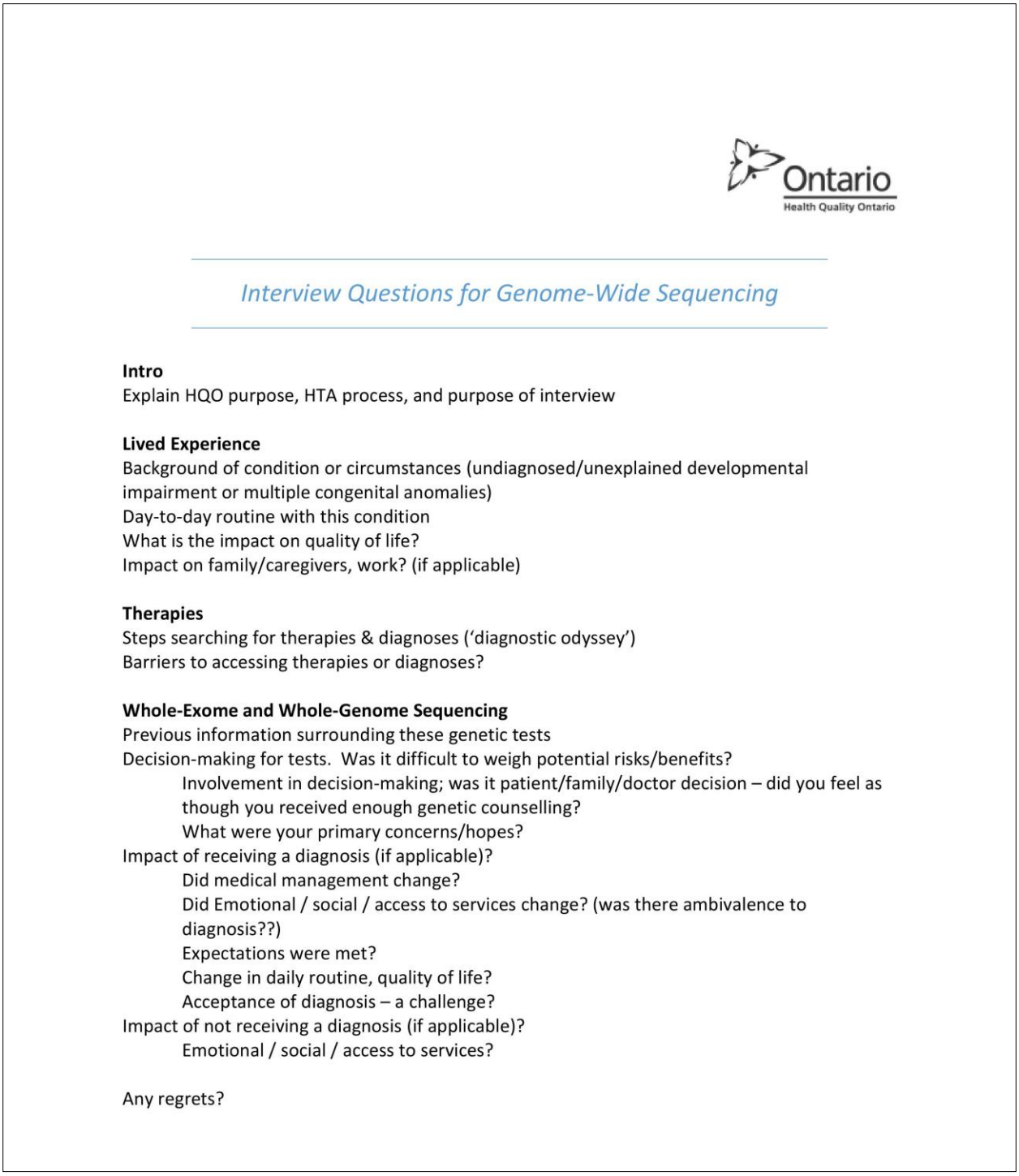
RISKS TO PARTICIPATION:

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, please speak to our staff.

If you are interested in participating, please contact Health Quality Ontario staff:

[a] Health Quality Ontario is now the Quality business unit at Ontario Health.

Appendix 11: Interview Guide[b]



Ontario
Health Quality Ontario

Interview Questions for Genome-Wide Sequencing

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

Lived Experience
Background of condition or circumstances (undiagnosed/unexplained developmental impairment or multiple congenital anomalies)
Day-to-day routine with this condition
What is the impact on quality of life?
Impact on family/caregivers, work? (if applicable)

Therapies
Steps searching for therapies & diagnoses ('diagnostic odyssey')
Barriers to accessing therapies or diagnoses?

Whole-Exome and Whole-Genome Sequencing
Previous information surrounding these genetic tests
Decision-making for tests. Was it difficult to weigh potential risks/benefits?
- Involvement in decision-making; was it patient/family/doctor decision – did you feel as though you received enough genetic counselling?
- What were your primary concerns/hopes?

Impact of receiving a diagnosis (if applicable)?
- Did medical management change?
- Did Emotional / social / access to services change? (was there ambivalence to diagnosis??)
- Expectations were met?
- Change in daily routine, quality of life?
- Acceptance of diagnosis – a challenge?

Impact of not receiving a diagnosis (if applicable)?
- Emotional / social / access to services?

Any regrets?

[b] Health Quality Ontario is now the Quality business unit at Ontario Health.

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About Us

This health technology assessment was produced by the Quality business unit at Ontario Health, the government agency that when fully established will be responsible for ensuring all Ontarians receive high-quality health care where and when they need it.

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