Genome-Wide Sequencing for Unexplained Developmental Disabilities or Multiple Congenital Anomalies: Recommendation

FINAL RECOMMENDATION

- The Quality business unit at Ontario Health, based on guidance from the Ontario Health Technology Advisory Committee, recommends publicly funding whole exome sequencing as a second-tier test (i.e., when chromosomal microarray testing results in no diagnosis) for people with unexplained developmental disabilities or multiple congenital anomalies

RATIONALE FOR THE RECOMMENDATION

The Ontario Health Technology Advisory Committee has reviewed the findings of the health technology assessment[1] and the recommendation of a subcommittee, the Ontario Genetics Advisory Committee. Ontario Health Technology Advisory Committee members determined that whole exome sequencing has demonstrated benefit when available at the appropriate time in the diagnostic pathway.

Ontario Health Technology Advisory Committee members considered the importance of a genetic diagnosis to people with developmental disabilities or multiple congenital anomalies unexplained by clinical examination and medical history and to their families. They are often dealing with a rare genetic condition. Having a diagnosis or identified genetic variant may help them gain access to health care services and to emotional and social support through online communities. The committee recognized the health technology assessment focused on the use of genome-wide sequencing in the population currently accessing whole exome sequencing in Ontario.

Ontario Health Technology Advisory Committee members noted that whole exome and whole genome sequencing demonstrate a higher diagnostic yield than standard genetic testing for people with unexplained developmental disabilities or multiple congenital anomalies. Economic modelling demonstrates the greatest cost savings when whole exome sequencing is offered as a second-tier test (after chromosomal microarray testing results in no diagnosis) in these patients.

The Ontario Health Technology Advisory Committee noted that the body of evidence was largely focused on whole exome sequencing and that whole genome sequencing was an evolving technology that could require revisiting as the evidence matures. The committee also advised that providing whole exome sequencing will require appropriate capacity in laboratories, medical genetics, genetic counselling, and other health professions as well as supporting an education component for the use of the test. Long-term downstream costs and consequences are not well known, especially as they pertain to secondary findings. Implementation of whole exome sequencing will also require consideration of how and which type of secondary findings should be shared with patients and resources required.

Public Comment: Held September 25 to October 15, 2019.

Decision Determinants for Genome-Wide Sequencing for Unexplained Developmental Disabilities or Multiple Congenital Anomalies

Decision Criteria	Subcriteria	Decision Determinants Considerations
Overall clinical benefit How likely is the health technology/intervention to result in high, moderate, or low overall benefit?	**Effectiveness** How effective is the health technology/intervention likely to be (taking into account any variability)?	Genome-wide sequencing for people with unexplained developmental disability and multiple congenital anomalies has a diagnostic yield of 37%, but the estimate is very uncertain (GRADE: Very Low). Compared with standard genetic testing, genome-wide sequencing could have a higher diagnostic yield (GRADE: Low). As well, for some people genome-wide sequencing can prompt some changes to medications, treatments and referrals to specialists (GRADE: Very Low).
	Safety How safe is the health technology/ intervention likely to be?	There is essentially no risk of harm with the test itself.
	Burden of illness What is the likely size of the burden of illness pertaining to this health technology/intervention?	1% to 3% of Canadians are estimated to have a developmental disability or congenital anomaly.
	Need How large is the need for this health technology/intervention?	Conventional testing, including clinical assessments, metabolic tests, and some genetic testing, might not provide a diagnosis for many people with unexplained developmental disability or multiple congenital anomalies. After conventional testing, there are currently no other testing options for diagnosis.
Patient preferences and values How likely is adoption of the health technology/intervention to be congruent with patient preferences and values, and ethical or legal standards?	**Patient preferences and values** Do patients have specific values, preferences, or needs related to the health condition, health technology/ intervention, or life impact that are relevant to this assessment? (Note: The values and preferences of family and informal caregivers are to be considered as appropriate.)	Patients and families value having a diagnosis to explain the cause of developmental disability and multiple congenital anomalies. They value a diagnosis to help access relevant worldwide social support groups and emerging treatment.
	Autonomy, privacy and confidentiality and/or other relevant ethical principles if applicable Are there concerns regarding accepted ethical or legal standards related to patient autonomy, privacy, confidentiality, or other ethical principles or values that are relevant to this assessment? (Note: The values and preferences of the public are to be considered as appropriate.)	Whether or not genome-wide sequencing fulfills duties to create benefit and minimize harms will depend on how it is implemented and delivered. What testing will reveal and whether results will lead to actionable results is unknown. Patients making autonomous choices (or their surrogates) must be made aware of the uncertainties, the many possible outcomes, and the possible responses to each of these outcomes. Robust informed consent processes will be necessary. Adequate training of involved professionals also will help to ensure ethical obligations are met. Continued attention to the vulnerability of the target population will be required.

Decision Criteria	Subcriteria	Decision Determinants Considerations
Equity and patient care How could the health technology/intervention affect equity of access and coordination of patient care?	**Equity of access or outcomes** Are there disadvantaged populations or populations in need whose access to care or health outcomes might be improved or worsened that are relevant to this assessment?	Ensuring fair access could be challenging, given genome-wide sequencing is a new and specialized test. Additionally, European ancestry is likely to be overrepresented in known databases.
	Patient care Are there challenges in the coordination of care for patients or other system-level aspects of patient care (e.g., timeliness of care, care setting) that might be improved or worsened that are relevant to this assessment?	Receiving a diagnosis may improve access to patient support programs. Access to whole exome sequencing (WES) could improve the timeliness of diagnosis, shorten the search for a diagnosis, and reduce time required to connect patients to relevant support services.
Cost-effectiveness How efficient is the health technology/ intervention likely to be?	**Economic evaluation** How efficient is the health technology/intervention likely to be?	When WES is used as a second-tier genetic test (after CMA results in no diagnosis), it is less costly and more effective than standard testing (CMA, Fragile X testing, targeted single-gene, or gene panel tests). When WES is used for patients who have no diagnosis from standard testing, it would cost an additional $13,591 to identify the genetic cause of one additional case compared with standard testing.
Feasibility of adoption into health system How feasible is it to adopt the health technology/intervention into the Ontario health care system?	**Economic feasibility** How economically feasible is the health technology/intervention?	The average cost of WES is $4,589 through out-of-country health services and $3,444 in Ontario laboratories. We estimated the annual budget impact of WES (when used for people who have no diagnosis after standard testing) in Ontario to be $9 million yearly. We also found that using WES as a second-tier test (after CMA results in no diagnosis) would save $3.4 million yearly for every 1,000 persons tested.
	Organizational feasibility How organizationally feasible is it to implement the health technology/ intervention?	The technology and capacity to conduct genome-wide sequencing exists in Ontario laboratories set up for research purposes at this time.

Abbreviations: CMA; chromosomal microarray; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; WES, whole exome sequencing.

REFERENCE

(1) Ontario Health (Quality). Genome-wide sequencing for unexplained developmental disabilities or multiple congenital anomalies: a health technology assessment. Ont Health Technol Assess Ser [Internet]. 2020 Mar;20(11):1–178. Available from: https://www.hqontario.ca/evidence-to-improve-care/health-technology-assessment/reviews-and-recommendations/genome-wide-sequencing-for-unexplained-developmental-disabilities-and-multiple-congenital-anomalies

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ISBN 978-1-4868-4219-3 (PDF)

Citation

Ontario Health (Quality). Genome-wide sequencing for unexplained developmental disabilities or multiple congenital anomalies: recommendation [Internet]. Toronto (ON): Queen's Printer for Ontario; 2020 Mar. 4 p. Available from: https://www.hqontario.ca/evidence-to-improve-care/health-technology-assessment/reviews-and-recommendations/genome-wide-sequencing-for-unexplained-developmental-disabilities-and-multiple-congenital-anomalies