



# Multi-gene Pharmacogenomic Testing That Includes Decision-Support Tools to Guide Medication Selection for Major Depression: Recommendation

## Final Recommendation

- Ontario Health, based on the guidance of the Ontario Health Technology Advisory Committee, recommends against publicly funding multi-gene pharmacogenomic testing that includes decision-support tools for guiding medication selection for people with major depression

## Rationale for the Recommendation

The Ontario Health Technology Advisory Committee has reviewed the findings of the health technology assessment<sup>1</sup> and the recommendation of a subcommittee, the Ontario Genetics Advisory Committee.

The Ontario Health Technology Advisory Committee's recommendation is based on the inconsistency and uncertainty of the evidence for the clinical utility and cost-effectiveness of multi-gene pharmacogenomic testing that includes decision-support tools to guide medication selection for people with major depression. It is also based on the uncertainty of the evidence for the budget impact analysis. The committee agreed with the subcommittee that, of the tests evaluated in the health technology assessment, the evidence for clinical utility was inconsistent across clinical outcomes and uncertain (very low- to low-quality evidence) for each test evaluated. The committee acknowledged that, for all tests evaluated, there was little to no improvement in depression scores. The committee also noted that, while some tests may improve response to treatment, remission from depression, or adverse events, inconsistent results were observed for other tests for these outcomes (see table). The committee also recognized that, because multi-gene pharmacogenomic tests that include decision-support tools differ, findings from one test could differ from another for the same patient. Additionally, new genes and variants have been added to some of the tests, limiting the ability to generalize the evidence to these newer versions of the tests. Finally, the level of uncertainty about cost-effectiveness for testing was high, as was the estimated total budget impact over 5 years.

In making their recommendation, Ontario Health Technology Advisory Committee members considered the lived experience of patients with depression to understand the impact of the health condition in their lives, the challenges of treating depression with medication, and preferences and values for their health care including the use of multi-gene pharmacogenomic testing that includes decision-support tools. Participants supported medication selection guided by multi-gene pharmacogenomic testing that

includes decision-support tools, as they valued the potential for the testing to help them receive effective treatment, to minimize side effects from treatment, and to reduce the duration of trial and error for finding an effective medication. Participants also expressed concerns that pharmacogenomic testing would reduce patient-centred care and patients' preferences for choice of pharmacotherapy treatment would not be considered in treatment decisions.

The committee suggested that future research should assess how this testing affects care providers' and patients' shared decision making with respect to medication choice. The committee also reflected upon other gaps in the evidence, including the fact that most of the published evidence was obtained from studies of people who were identified as White or of European ancestry and because of this, the evidence may not accurately represent the benefits or risks of these tests to other ethnic groups. The committee suggested that future research evaluate the impact of these tests in other ethnic groups to better support equitable care among all people and their communities.

## Decision Determinants for Multi-gene Pharmacogenomic Testing That Includes Decision-Support Tools to Guide Medication Selection for Major Depression

Decision Criteria	Subcriteria	Decision Determinants Considerations
<b>Overall clinical benefit</b> How likely is the health technology/intervention to result in high, moderate, or low overall benefit?	<b>Effectiveness</b> How effective is the health technology/intervention likely to be (taking into account any variability)?	<ul style="list-style-type: none"> <li>Evidence suggests little or no improvement on change in HAMD-17 depression score compared with treatment as usual for each test evaluated (GRADE: Low–Very Low).</li> <li>GeneSight- and NeuroIDgenetix-guided medication selection may improve response rates, while data are inconsistent and uncertain for the impact of Neuropharmagen on response. No difference was observed for Genecept or an unspecified test (GRADE: Low–Very Low).</li> <li>GeneSight and CNSDose may improve remission rates, while data are inconsistent and uncertain for the impact of NeuroIDgenetix and Neuropharmagen on remission. No difference was observed for Genecept or an unspecified test (GRADE: Low–Very Low)</li> <li>No data were identified for any test that evaluated suicide, treatment adherence, relapse, recovery, or recurrence of depression symptoms.</li> </ul>
	<b>Safety</b> How safe is the health technology/intervention likely to be?	Relative to treatment as usual, Neuropharmagen may reduce side effects (GRADE: Low), and CNSDose may reduce intolerance of medication (GRADE: Low). Little to no difference was observed in side effects with GeneSight (GRADE: Low) or an unspecified test, although the evidence is very uncertain (GRADE: Very Low). Genecept likely results in little to no difference in side effects (GRADE: Moderate).
	<b>Burden of illness</b> What is the likely size of the burden of illness pertaining to this health technology/intervention?	Major depression is a leading cause of disability in Ontario. Symptoms of depression can lead to serious distress or an inability to perform daily functions. Many people with depression may not be able to cope with aspects of everyday life,

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	<p><b>Need</b> How large is the need for this health technology/intervention?</p>	<p>which can greatly affect quality of life, personal relationships, and the ability to go to school or work, and can lead to social isolation. Some people may have thoughts about self-harm, death, or suicide.</p> <p>An estimated 11.3% of Canadian adults will have depression at some point during their lifetime, and an estimated 4.8% of the Ontario population 15 years of age and older reported symptoms for major depression in the previous 12 months.</p>
<p><b>Patient preferences and values</b> How likely is adoption of the health technology/intervention to be congruent with patient preferences and values and with ethical or legal standards?</p>	<p><b>Patient preferences and values</b> Do patients have specific preferences, values, or needs related to the health condition, health technology/intervention, or life impact that are relevant to this assessment? (Note: preferences and values of family members and informal caregivers are to be considered as appropriate.)</p> <p><b>Autonomy, privacy, confidentiality, and/or other relevant ethical principles as applicable</b> Are there concerns regarding accepted ethical or legal standards related to patient autonomy, privacy, confidentiality, or other ethical principles that are relevant to this assessment? (Note: preferences and values of the public are to be considered as appropriate.)</p>	<p>Participants had a strong preference for pharmacogenomic testing, as they valued the potential to receive effective treatment, with little to no side effects, in a timely manner.</p> <p>If pharmacogenomic testing were to become part of routine treatment, there may be concerns about whether patients can decline pharmacogenomic testing, if physicians will be reluctant to prescribe medications to patients who have not undergone pharmacogenomic testing, or if effective medications would be stopped because results of pharmacogenomic testing indicated their medication was not genetically congruent.</p> <p>There is the potential that some pharmacogenomic tests may predict future risk or probability of disease, raising concerns about how informed consent is sought and obtained, how test results should be shared with patients, and whether genetic counselling should be part of testing.</p>

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		<p>There may be potential privacy concerns from patients related to the confidentiality of stored genetic data and who has access to the data.</p>
<p><b>Equity and patient care</b> How could the health technology/intervention affect equity of access and coordination of patient care?</p>	<p><b>Equity of access or outcomes</b> 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?</p> <p><b>Patient care</b> 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?</p>	<p>Currently, only people who can afford out-of-pocket payment for pharmacogenomic testing can receive the test in Ontario. Additionally, current evidence for testing may not reflect the Ontario population and is primarily focused on women identified as White or of European ancestry, 40 to 50 years of age. Therefore, results may not accurately reflect other racial or ethnic groups that have not been studied as extensively.</p> <p>No issues directly related to patient care were identified in the review.</p>
<p><b>Cost-effectiveness</b> How efficient is the health technology/intervention likely to be?</p>	<p><b>Economic evaluation</b> How efficient is the health technology/intervention likely to be?</p>	<p>Multi-gene pharmacogenomic testing that includes decision-support tools is a heterogeneous class of interventions with varying effectiveness and costs. Over a 1-year time horizon, multi-gene pharmacogenomic testing with GeneSight (at a price of \$2,500) was more effective (0.03 QALYs) and more costly (\$1,906) than treatment as usual, resulting in an ICER of \$60,564/QALY. Probability of this intervention being cost-effective at willingness-to-pay values of \$50,000/QALY and \$100,000/QALY was 37% (i.e., moderately likely not to be cost-effective) and 71% (i.e., moderately likely to be cost-effective), respectively.<sup>a</sup> If the test price were assumed to be about \$2,160, the intervention would be cost-effective at a willingness-to-pay value of \$50,000/QALY.</p>

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<b>Feasibility of adoption into health system</b> How feasible is it to adopt the health technology/intervention into the Ontario health care system?	<b>Economic feasibility</b> How economically feasible is the health technology/intervention?	At an increasing uptake of 1%/y and a test price of \$2,500, the annual budget impact of publicly funding multi-gene pharmacogenomic testing in Ontario over the next 5 years ranged from an additional \$3.5 million in year 1 (at uptake of 1%) to \$16.8 million in year 5. The 5-year budget impact was estimated at about \$52 million.
	<b>Organizational feasibility</b> How organizationally feasible is it to implement the health technology/intervention?	It may be feasible to incorporate this intervention in the Ontario health care system. For example, a feasibility study evaluating the implementation of the GeneSight test through primary care providers and psychiatrists was conducted in Ontario. However, implementation strategies would depend on the specific tests being approved.

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HAMD-17, 17-item Hamilton Depression Rating Scale; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

<sup>a</sup>Uncertainty was classified into one of five categories based on the Ontario Decision Framework: highly likely to be cost-effective (80%–100% probability of being cost-effective), moderately likely to be cost-effective (60%–79% probability), uncertain if cost-effective (40%–59% probability), moderately likely to not be cost-effective (20%–39% probability), or highly likely to not be cost-effective (0–19% probability).

## Reference

1. Ontario Health. Multi-gene pharmacogenomic testing that includes decision-support tools to guide medication selection for major depression: a health technology assessment. Ont Health Technol Assess Ser [Internet]. 2021 August;21(13):1–214. Available from: <https://www.hqontario.ca/evidence-to-improve-care/health-technology-assessment/reviews-and-recommendations/multi-gene-pharmacogenomic-testing-that-includes-decision-support-tools-to-guide-medication-selection-for-major-depression>

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