Ontario Health

Molecular Testing for Thyroid Nodules of Indeterminate Cytology: Recommendation

Final Recommendation

- Ontario Health, based on guidance from the Ontario Health Technology Advisory Committee, recommends against publicly funding molecular testing for thyroid nodules of indeterminate cytology

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.

The Ontario Health Technology Advisory Committee agreed with the subcommittee's conclusion that compared to usual care (biopsy), molecular testing for thyroid nodules of indeterminate cytology (The Bethesda System for Reporting Thyroid Cytopathology categories III and IV) may have good diagnostic accuracy to rule out thyroid cancer (high sensitivity), and it may lead to lower rates of surgical removal of all or part of the thyroid gland, but the evidence is very uncertain.

The committee's recommendation was also made after considering the cost-effectiveness profile of the test, the use of test findings to guide treatment decisions, and the demand for the test in Ontario. The committee noted that with the tests that are commercially available, molecular testing is unlikely to be cost-effective at current list prices; a substantial reduction in price would be needed to achieve a reasonable cost-effectiveness profile. As well, the committee recognized the lived experience of people with thyroid nodules: although molecular testing is aligned with patient preferences for additional information to guide treatment choice, in some cases, people may undergo surgery regardless of the results from molecular testing. Finally, at the time this recommendation was made, the demand in Ontario for molecular testing for thyroid nodules of indeterminate cytology—from patients or clinicians—was low.

Public Comment: Held December 17, 2021, to January 21, 2022

Decision Determinants for Molecular Testing for Thyroid Nodules of Indeterminate Cytology

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)?	Molecular testing for thyroid nodules of indeterminate cytology has a sensitivity of 91% to 94% and a specificity of 68% to 82% for the detection of malignancy (GRADE: Low). As well, lower rates of surgical resections were reported in nodules of indeterminate cytology compared to usual care (molecular testing vs. no molecular testing; GRADE: Very low).
	Safety How safe is the health technology/intervention likely to be?	There are no concerns about patient safety with the use of the molecular testing for thyroid nodules of indeterminate cytology.
	Burden of illness What is the likely size of the burden of illness pertaining to this health technology/intervention?	Thyroid nodules are quite common; they are identifiable in 19% to 68% of the general population. However most thyroid nodules are benign; only 7% to 15% are malignant. In 2018, thyroid cancers made up 3.7% of all Ontario cancer diagnoses (3,341 cases). Overall survival with thyroid cancers is 98%, and death rates have remained stable over time, despite an increase in incidence.
	Need How large is the need for this health technology/intervention?	The current standard of care is no molecular testing. Molecular testing proposes to reduce the number of unnecessary surgeries, because many thyroid glands with nodules are partially or fully resected as a precaution, and many of these nodules turn out to be benign.

Decision criteria	Subcriteria	Decision determinants considerations
Patient preferences and values How likely is adoption of the health technology/intervention to be congruent with patient preferences and values and with ethical or legal standards?	**Patient preferences and values** 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: The preferences and values of family members and informal caregivers are to be considered as appropriate.) **Autonomy, privacy, confidentiality, and/or other relevant ethical principles as applicable** 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: The preferences and values of the public are to be considered as appropriate.)	It is reasonable to assume that people would like to avoid unnecessary surgery. However, people may undergo thyroid nodule surgery for a number of reasons beyond finding a malignancy, including anxiety; respiratory and/or digestive complications resulting from a growth; or symptoms from conditions such as uncontrolled hyperthyroidism. Patients expressed concern about the time required to obtain results, especially if the findings were not conclusive or useful for treatment decision-making. There are no concerns about patient privacy or confidentiality related to the use of molecular testing for nodules of indeterminate cytology. To support patient autonomy in terms of preferences and values for care, clinicians should talk with patients about the accuracy of the tests for ruling out cancer and the options for surgery.
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? **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?	At present, molecular testing is available only when patients pay for it as an out-of-pocket expense. Thyroid cancers affect approximately three times more women than men, and people of Asian descent have a higher incidence of thyroid cancers. Access to molecular testing may require a second fine-needle aspiration biopsy. It is uncertain whether the test would reduce the number of unnecessary surgeries.

Decision criteria	Subcriteria	Decision determinants considerations
Cost-effectiveness How efficient is the health technology/ intervention likely to be?	**Economic evaluation** How efficient is the health technology/intervention likely to be?	Compared to diagnostic thyroid lobectomy, our model predicted that molecular testing would increase the probability of predicting a correct diagnosis, reduce the probability of unnecessary surgery, and lead to a slight improvement in QALYs, but it would increase costs. At commonly used willingness-to pay values of $50,000 and $100,000 per QALY gained, molecular testing is moderately likely not to be cost-effective at its current list price.[a] The most likely ICER estimates were between $220,572 and $298,653 per QALY gained. The estimated break-even point (when the cost of molecular test would be completely offset by the cost of the surgery avoided) was $2,150 for the Afirma GSC (a 55% price reduction) and $2,488 for the ThyroSeq v3 (a 48% price reduction).
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?	Molecular testing costs $4,785 per test. We estimated that publicly funding molecular testing in Ontario would lead to additional costs of $6.24 million over the next 5 years (about 1,117 people per year are expected to receive the test).
	Organizational feasibility How organizationally feasible is it to implement the health technology/ intervention?	The available molecular tests are based in the United States. Experts noted that that TBSRTC classification is not the standard used across Ontario to report cytology; requiring standardization may be a key first step in implementation, because it would ensure consistency in identifying nodules of indeterminate cytology. As well, experts suggested that it may be feasible to develop an Ontario-based laboratory molecular test for thyroid nodules that has similar effectiveness and lower costs, which could improve the cost-effectiveness profile of the test.

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; GSC, gene sequencing classifier; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years; TBSRTC, The Bethesda System for Reporting Cytology.

Note for table:

[a] Uncertainty was classified into one of five categories based on the Ontario Decision Framework[2]: 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).

References

(1) Ontario Health. Molecular testing for thyroid nodules of indeterminate cytology: a health technology assessment. Ont Health Technol Assess Ser [Internet]. 2022 Apr;22(2):1–111. Available from: https://www.hqontario.ca/evidence-to-improve-care/health-technology-assessment/reviews-and-recommendations/molecular-testing-for-thyroid-nodules-of-indeterminate-cytology

(2) Krahn M, Miller F, Bayoumi A, Brooker AS, Wagner F, Winsor S, et al. Development of the Ontario decision framework: a values based framework for health technology assessment. Int J Technol Assess Health Care. 2018;34(3):290-9.

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