DNA Methylation–Based Classification for Central Nervous System Tumours

Recommendation

JUNE 2025

Ontario Health

Draft Recommendation

Ontario Health, based on guidance from the Ontario Health Technology Advisory Committee, recommends publicly funding DNA methylation–based classifier tests as an adjunct tool for the classification of central nervous system tumours when substantial clinical uncertainty remains after conventional testing.

Rationale for the Recommendation

The Ontario Health Technology Advisory Committee considered the clinical and economic evidence reported in the health technology assessment (HTA)[1] and the recommendation of a subcommittee, the Ontario Genetics Advisory Committee.

The committee recognized the potential benefits of DNA methylation–based classifier tests for central nervous system tumour (CNS) classification. These classifier tests are most beneficial for CNS tumour cases that are particularly challenging and difficult to classify (i.e., when classification remains uncertain after conventional testing has been performed). They are also valuable in situations where tissue samples are limited or difficult to obtain (e.g., CNS tumours that are difficult to biopsy due to their location or size).

The committee also discussed the ability of DNA methylation–based classifier tests to enhance CNS tumour classification. The committee agreed that these tests provide additional insights beyond what is available through conventional testing, potentially improving CNS tumour classification (new or refined classification or changes in tumour grade). This may result in more appropriate or specialized treatment decisions for patients and possible avoidance of unnecessary invasive procedures, which has the potential to improve downstream patient outcomes.

The committee was concerned about the wide variability in the classifier test results compared with conventional testing – which can include concordant, discordant, and unclassifiable results. However, the committee acknowledged that the results may be influenced by several factors, including the number of study participants, the specific CNS tumour or subtype being tested, the indication for testing, and clinical and pathology expertise. For example, novel, rare, or challenging cases of CNS tumours are difficult to classify and may lead to discordant results compared with conventional testing. The committee also noted that there is limited data on how the classifier test may impact long-term and direct patient outcomes.

The committee recognized that DNA methylation–based classifier tests may produce misleading classification results, but discussed how the risk was reduced due to the use of these tests as an adjunct to conventional testing. Classifier test results are always integrated and interpreted alongside conventional test results. If the classifier test results are misleading or unresolvable, CNS tumour classification determined by conventional testing prevails.

Another consideration discussed by the committee was the machine learning (type of artificial intelligence [AI]) component of the classifier tests and the importance of explainability and transparency for AI-based technologies. The committee acknowledged that the random forest algorithm used in the development of the classifier test is a commonly used, supervised (requiring human labelling of data)

form of machine learning, and there are likely low AI-related risks associated with the classifier tests. The development and training process for the classifier test has also been published in detail.

Although patients are not directly involved in the CNS tumour classification testing process, the committee discussed potential concerns regarding patient privacy and consent. Patient information is de-identified and secondary findings are also not possible with the classifier test. The consent and collection process for DNA methylation profiling data that is required for the classifier tests is also similar to that of other clinical and genetic testing and information.

The committee discussed the economic implications of DNA methylation–based classifier tests for CNS tumours. While the economic evaluation considered only the short-term costs, the committee acknowledged that improved CNS tumour classification may lead to better treatment outcomes or avoidance of unnecessary invasive procedures, which were not modelled due to a lack of data. The budget impact of using DNA methylation–based classifier tests for challenging diagnostic CNS tumour cases is considered reasonable compared with the cost of CNS tumour management and treatment. However, using the classifier tests for all newly diagnosed CNS tumours would significantly increase the budge impact.

The committee also discussed the role of centralized testing in the implementation of DNA methylation–based classifier tests for CNS tumours. Centralized testing may increase test efficiency and reduce test turnaround times and streamline the testing process. Increased testing volumes allows for more frequent batch testing and classifier tests have the potential to replace some conventional tests, possibly reducing the overall number of tests needed for CNS tumour classification.

In making their recommendation, the committee acknowledged that most of the evidence is from studies of primary CNS tumours. However, there may be cases of secondary (metastatic) CNS tumours where DNA methylation–based classifier tests may be useful.

The committee is aware that DNA methylation profiling and DNA methylation–based classifier tests for CNS tumours may evolve in the future and noted that the current funding recommendation is based on the evidence included in the accompanying HTA.[1] The committee may need to revisit the funding recommendation in the future if the technology substantially changes.

Decision Determinants for DNA Methylation–Based Classification for Central Nervous System Tumours

Overall Clinical Benefit

Effectiveness

How effective is the health technology/intervention likely to be (taking into account any variability)?

Compared with conventional testing alone for CNS tumours, DNA methylation–based classifier tests are an adjunct tool that may improve CNS tumour classification (Grading of Recommendations, Assessment, Development and Evaluations [GRADE]: Moderate). The test may also improve downstream patient outcomes, although the evidence is very uncertain (GRADE: Very low). Unclassifiable test results may increase time to treatment, although the evidence is very uncertain (GRADE: Very low).

Safety

How safe is the health technology/intervention likely to be?

There are no direct safety concerns. DNA methylation–based classifier tests use tissue biopsy material that is also needed for CNS tumour diagnosis. However, test results may have downstream impacts on patient treatment and outcomes.

Burden of Illness

What is the likely size of the burden of illness pertaining to this health technology/intervention?

In Ontario in 2022, there were an estimated 1,216 new malignant CNS tumour cases and 901 deaths. According to experts, about 20% to 25% of CNS tumours are difficult to classify. The 5-year survival rate is 28.6% and 85.7% for malignant and benign CNS tumours, respectively.

Need

How large is the need for this health technology/intervention?

DNA methylation–based classifier tests provide additional DNA methylation data that may improve CNS tumour classification and have the potential to replace some conventional tests.

Patient Preferences and Privacy

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?

Patients are not involved in the decision or use of DNA methylation–based classifier tests for CNS tumours. The tests are an adjunct tool that may be used within the conventional CNS tumour classification pathway.

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?

Patient data is de-identified and secondary findings are not possible. DNA methylation–based classifier tests may use machine learning-based algorithms, which is a form of AI. However, these types of algorithms are widely used and the risks are likely low for this type of AI use.

Equity and 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?

Currently, DNA methylation–based classifier tests for CNS tumour classification are available at only 2 hospitals in Ontario.

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?

Improved CNS tumour classification may lead to more tailored patient treatment and improved patient outcomes.

Cost-Effectiveness

Economic Evaluation

How efficient is the health technology/intervention likely to be?

Using DNA methylation–based classifier testing for challenging diagnostic cases improves CNS tumour classification with a moderate increase in costs, and an associated incremental cost-effectiveness ratio of $5,521 per case with improved CNS tumour classification. Given that there are no empirical willingness-to-pay thresholds for an improvement in primary CNS tumour classification, the cost-effectiveness of the DNA methylation–based classifier test cannot be determined.

Feasibility of Adoption Into Health System

Economic Feasibility

How economically feasible is the health technology/intervention?

Publicly funding second-tier DNA methylation–based classifier tests (after the use of conventional testing) for patients with primary CNS tumours that are difficult to classify based on conventional testing would result in a total budget increase of around $5.4 million to test 3,600 patients over 5 years. The cost increase would be about $21 million over 5 years to test all newly diagnosed primary CNS tumours.

Organizational Feasibility

How organizationally feasible is it to implement the health technology/intervention?

Facilities in Ontario are well positioned to support the implementation of second-tier DNA methylation–based classifier tests for CNS tumour classification.

Reference

1) TBD

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