ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES

DNA Methylation–Based Classification for Central Nervous System Tumours

A Health Technology Assessment

NOVEMBER 2025

Ontario Health

Key Messages

What Is This Health Technology Assessment About?

Central nervous system tumours occur when abnormal cells form in the brain and/or spinal cord. Treatment strategy starts with classifying the tumour according to its characteristics – including size and malignancy (tendency to grow and spread). Recently, a test called the DNA methylation–based classifier test has been used in addition to established tests to help with tumour classification, especially tumours that have been difficult to classify using other methods.

This health technology assessment looked at how safe, effective, and cost-effective DNA methylation–based classifier testing is for central nervous system tumour classification. It also looked at the budget impact of publicly funding DNA methylation–based classifier tests.

What Did This Health Technology Assessment Find?

Compared with conventional testing alone, adding the use of a DNA methylation–based classifier test may improve tumour classification and patient outcomes.

There is not enough data to determine the cost-effectiveness of DNA methylation–based classifier testing. We estimate that about 716 people in Ontario each year have primary tumours that are challenging to classify and the estimated cost of DNA methylation profiling for central nervous system tumours is $1,500 per patient. Based on these estimates, the cost increase would be around $5.4 million over the next 5 years for cases that are challenging to classify through conventional testing. The cost increase would be about $21 million over 5 years to test all newly diagnosed primary tumours.

Patient engagement was not conducted because we concluded that direct engagement would provide limited additional evidence to guide decision-making.

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Abstract

Background

Central nervous system (CNS) tumours occur when abnormal cells form in the tissues of the brain and/or spinal cord. Conventional testing for CNS tumour classification involves histopathological evaluation and molecular markers. More recently, DNA methylation–based classifier tests are being used as an adjunct tool in addition to conventional tests to help with CNS tumour classification. We conducted a health technology assessment of DNA methylation–based classifier tests for CNS tumours, which included an evaluation of effectiveness, cost-effectiveness, and budget impact of publicly funding DNA methylation–based classifier tests for CNS tumours. After considering the likely effects of testing on the patient experience, we determined not to perform an analysis of patient preferences and values.

Methods

We 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 Nonrandomized 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 performed a systematic economic literature search and developed a decision-analytic model to evaluate the cost-effectiveness of using DNA methylation–based classifier tests. We also analyzed the budget impact of publicly funding DNA methylation–based classifier tests. All costs were expressed in 2024 CAD.

Results

We included 38 studies in the clinical evidence review. Compared with conventional testing alone, DNA methylation–based classifier tests are an adjunct tool that may improve CNS tumour classification (GRADE: Moderate). The tests may improve downstream patient outcomes, although the evidence is very uncertain (GRADE: Very low). Unclassifiable test results may increase time to treatment, but the evidence is very uncertain (GRADE: Very low).

We did not identify any studies that met the inclusion criteria for our economic literature review. We estimated that there were about 716 patients with challenging diagnostic primary CNS tumours in Ontario each year. The cost of clinical-based DNA methylation profiling for CNS tumours was $1,500 per patient. The annual incremental costs of second-tier DNA methylation classifier tests (after the use of conventional test) would be $1,074,738 for all challenging diagnostic cases, and DNA methylation–based classifier tests improved the diagnosis for 195 patients. The incremental cost-effectiveness ratio (ICER; i.e., the incremental cost per case with an improvement in primary CNS tumour classification) was $5,521. Scenario analyses showed that for children aged 0 to 14 years, the ICER was reduced to $2,683. Publicly funding second-tier DNA methylation–based classifier testing for challenging diagnostic cases of primary CNS tumours would result in a budget increase of about $1 million per year, with total additional costs of about $5.4 million over 5 years to test 3,600 patients. The budget increase for funding subgroup populations (e.g., children, patients with malignant tumours) would be smaller. If DNA methylation–based classifiers are used as first-tier tests for all patients with newly diagnosed primary

CNS tumours, the additional funding costs would be about $4 million per year, with total additional funding costs of about $21 million over the initial 5-year period.

Conclusions

DNA methylation–based classifier tests are an adjunct tool that may improve CNS tumour classification compared with conventional testing alone. Given that there are no empirical willingness-to-pay thresholds for an improvement in primary CNS tumour classification, the cost-effectiveness of DNA methylation–based classifier cannot be determined. Publicly funding second-tier DNA methylation–based classifier tests for challenging diagnostic primary CNS tumours would result in a total budget increase of about $5.4 million over 5 years. Public funding DNA methylation-based classifiers as first-tier tests for all patients with newly diagnosed primary CNS tumours would result in total budget increase of around $21 million over the next 5 years.

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Objective

This health technology assessment evaluates the effectiveness and cost-effectiveness of DNA methylation–based classifier tests for the classification of central nervous system (CNS) tumours. It also evaluates the budget impact of publicly funding DNA methylation–based classifier tests.

Background

Health Condition

Central nervous system (CNS) tumours occur when abnormal cells form in the tissues of the brain and/or spinal cord. Tumours that start in the CNS are known as primary CNS tumours, which may spread to other parts of the CNS, but rarely to other parts of the body.[1] More often, CNS tumours are due to cancer from elsewhere in the body spreading to the CNS (these are known as metastatic or secondary CNS tumours).[2] The most common cancers that spread to the CNS are lung (up to 50%), colon, breast, kidney, and skin (melanoma) cancer.[2]

The World Health Organization (WHO) classification for CNS tumours is the international standard system, which presents definitions of CNS tumour types and subtypes and provides guidance for their recognition.[3] There are more than 100 types and subtypes of CNS tumours, which are generally named by their location or cell of origin. However, tumours within a WHO class may still be clinically heterogeneous.

Central nervous system tumours may be benign or malignant (cancerous); either can cause symptoms and require treatment. Symptoms of CNS tumours may include headaches, seizures or convulsions, nausea and vomiting, personality or behavioural changes, and issues with vision, speech, hearing, or coordination.[4] The most common brain tumour is meningioma (about 30% of brain tumours), of which about 80% are benign (noncancerous).[5,6] The most common malignant (cancerous) brain tumour in adults is glioblastoma (about 50% of brain tumours).[7]

The causes of most CNS tumours are unknown, but risk factors may include radiation exposure, family history, certain genetic conditions (e.g., neurofibromatosis type 1 and type 2, tuberous sclerosis, Li–Fraumeni syndrome, Von Hippel–Lindau syndrome, Turcot syndrome), and a weakened immune system.[8] Tumours are typically diagnosed by neurological exam, imaging (e.g., computed tomography [CT], magnetic resonance imaging [MRI], positron emission tomography [PET]), and biopsy.[9]

Treatment for CNS tumours depends on the type of diagnosed tumour and its characteristics (e.g., grade, location, size), along with patient factors (e.g., neurological function, previous treatment, age, overall health).[10] Most tumours are treated with surgery, radiation, or chemotherapy (alone or in combination).[10] Surgical treatment of CNS tumours aims for complete tumour removal, or removal of as much of the tumour as possible (known as debulking) to relieve symptoms and improve the response to radiation therapy or chemotherapy. Radiation therapy may be used when surgery is not possible, or after surgery (adjuvant radiation therapy) to reduce the chance of recurrence. Chemotherapy may be used after or in combination with radiation therapy, before and after surgery to reduce the chance of recurrence (neoadjuvant and adjuvant chemotherapy, respectively), or for recurrent tumours. Targeted (or molecular) therapies (e.g., monoclonal antibodies) exist for some CNS tumours, which target specific

molecules (e.g., proteins) on or inside tumour cells. Gene therapy is also being studied for some types of CNS tumours.[11]

Clinical Need and Population of Interest

In Canada, the average annual age-standardized incidence rate (ASIR) of primary CNS tumours (malignant, benign, and uncertain) was estimated to be 21.48 per 100,000 person-years (95% CI: 21.28–21.67). Around one-third of CNS tumours are malignant (i.e., CNS cancer). In 2023, there were an estimated 3,200 new cases of CNS cancers and 2,500 deaths due to CNS cancers.[12] In Ontario in 2022, there were an estimated 1,216 new cases and 901 deaths.[13,14] Based on Ontario data, the estimated 5-year relative survival ratio (RSR) was 28.6% for malignant CNS tumours and 85.7% for benign CNS tumours.[15] The RSR is the ratio of the observed survival in people with cancer to the expected survival of a group of similar people without cancer (in practice, the general population).

Tumours within the same type or subtype classified by the WHO system may still be biologically and clinically diverse, which may lead to diagnostic discordance and difficulties in clinical decision-making. Experts estimated that about 20% to 25% of CNS tumours are challenging to classify and diagnose (Andrew Gao, MD, personal communication, February 12, 2025). Improved classification of CNS tumours through molecular testing such as DNA methylation may result in more precise diagnosis and prognosis and more specific treatment. The more accurate a diagnosis, the more targeted and specific patient management can be, which ensures appropriate treatment choices that address the unique biology of each tumour.

Current Testing Options

Conventional Tests

Conventional testing for CNS tumour classification involves histopathological evaluation and molecular markers (i.e., changes in specific genes or proteins known to drive tumour growth) from tissue biopsy. Conventional tests on biopsied tissue include single- or multi-gene tests (e.g., fluorescence in situ hybridization [FISH], O^6-methylguanine-DNA methyltransferase [MGMT] promoter methylation, next-generation sequencing [NGS] panel, immunohistochemistry [IHC], or DNA sequencing for isocitrate dehydrogenase [IDH] mutation). Multiple tests may be performed for CNS tumour classification on a single patient biopsy sample. In addition, not all tests may be required for a single patient biopsy sample.

DNA Methylation Profiling

A more novel method to classify CNS tumours involves examining genome-wide (or whole genome) DNA methylation patterns of biopsied tumour tissue (sometimes referred to as the cancer methylome), known as DNA methylation (or methylome) profiling or analysis. DNA methylation is a naturally-occurring process where methyl groups (3 hydrogen atoms bonded to 1 central carbon atom) are added to the cytosine bases of DNA (1 of 4 nucleotide bases in DNA), resulting in 5-methylcytosine. DNA methylation regulates gene expression by recruiting proteins involved in gene repression (silencing) or by inhibiting the binding of transcription factors to DNA (proteins that bind to specific DNA sequences and control whether a gene is expressed). DNA methylation is a form of epigenetic change, where there are DNA changes that regulate gene expression without changes in the DNA sequence. This allows for genetically identical cells to establish distinct cellular phenotypes.

In the case of cancer and CNS tumours, disruption of DNA methylation control mechanisms occurs and may affect genes that are involved in tumour suppression, cell cycle regulation, and DNA repair.[16] Tumour cells have altered DNA methylation, and CNS tumour types or subtypes have distinct DNA methylation patterns. DNA methylation profiling also provides a surrogate marker for genetic mutations; however, in some cases it is more useful to understand the genetic mutations of certain tumours (e.g., for targeted therapy) and DNA sequencing is performed (Andrew Gao, MD, personal communication, February 12, 2025).

In 2021, the WHO updated their classification system for CNS tumours to improve upon previous versions that had primarily only considered histopathological evaluation (microscopic examination of tissue), which may suffer from interobserver variability and poor classification of tumours with diverse biologic behaviour.[17] This 5th edition update expanded the inclusion of DNA methylation information for classification and new tumour types and subtypes have been introduced as a result.[3] For example, a gain of chromosome 7 [Ch7] or loss of chromosome 10 [Ch10] in gliomas needs to be established for CNS tumour diagnosis, and cyclin-dependent kinase inhibitor 2A/2B [CDKN2A/B] loss in meningiomas needs to be established for CNS tumour grading. As a result, DNA methylation–based classification is now featured in the WHO system as an essential tool for some tumour diagnoses, and a relevant tool for many tumour diagnoses.[3]

Different methods exist for DNA methylation profiling, but sodium bisulfite conversion-based approaches are considered to be the gold standard, with the ability to detect 5-methylcytosine at a single nucleotide (base-pair) resolution.[18] Bisulfite treatment does not affect methylated cytosines, but converts unmethylated cytosines to uracil. The converted DNA can then be distinguished from unmethylated DNA using various methods to query methylation status. Typically fresh, frozen, or formalin-fixed paraffin-embedded (FFPE) tissue samples from biopsy may be used.

A popular bisulfite conversion-based high-throughput DNA methylation profiling platform is commercially available from Illumina, which uses its bead array technology (BeadChip) for DNA methylation profiling.[18] The array quantitatively interrogates methylation sites at the most biologically significant regions of the human methylome.[19] The current version, Infinium MethylationEPIC version 2 (930K array) was released in 2022 and measures more than 930,000 methylation sites. The previous version, Infinium MethylationEPIC version 1 (850K array), was released in 2016 and the version before that, the Infinium HumanMethylation 450 (450K array), was released in 2008.[20] Because of its time and cost efficiency, high-sample output, ease of use, and overall quantitative accuracy and reproducibility (including good agreement with DNA methylation measurements from other platforms), the Illumina platform has become the most widely used means of large-scale DNA methylation profiling of human samples in recent years.[21] For advanced downstream analysis, Illumina has noted that many free packages in the R software framework enable normalization and differential analysis of the methylation data.[19]

Health Technology Under Review

DNA methylation–based classifier tests for CNS tumours are machine learning algorithm-based tests that classify CNS tumours based on genome-wide DNA methylation profiling results as test input. These tests are most useful for challenging or uncertain cases of CNS tumours and may be used for primary, benign (e.g., meningiomas), or metastatic tumours or tumours of unknown origin.[22] In addition, since DNA methylation profiling requires only a small amount of biopsied tissue, DNA methylation–based classifier tests may be useful in instances where there are limited tissue samples (e.g., tumours not easily accessible for biopsy) and when multiple single gene tests are not possible for tumour classification.[22]

The use of DNA methylation–based classifier tests may result in new diagnoses for CNS tumours or changes in the WHO grading of tumours (both down- and upgrading).[23] The tests may also subclassify CNS tumours previously thought to be homogenous and may replace some conventional tests for tumour classification (e.g., FISH, or any conventional tests that assess DNA copy number variation). Unresolvable discrepant results are possible but rare (e.g., < 1% to 2%); in such cases, the histopathological diagnosis is retained.[23] Unclassifiable results (no classification) are also possible.

DNA methylation–based classifier tests are adjunct tests that require histopathological context and are not interpreted in isolation; test results are integrated with the pathology report for a combined CNS tumour diagnosis. The testing process involves personnel with expertise in laboratory medicine, clinical molecular genetics, bioinformatics, neuropathology, and neuro-oncology.

As of the time of writing, the most widely used DNA methylation–based classifier test for CNS tumours internationally was developed by a group at the German Cancer Research Center (Deutsches Krebsforschungszentrum, or DKFZ).

DKFZ Classifier Test for Central Nervous System Tumours

Scientific background and data interpretation for the DKFZ classifier test was first published in 2018.[23] Initial data for the test was generated at the Genomics and Proteomics Core Facility of the DKFZ and the New York University Langone Medical Center; however, newer versions of the test have incorporated data from the international neuro-oncology community.[23] As of March 2024, there have been over 140,000 tumours tested and, of those, over 100,000 have been used for test development, with test version 12.8 being the latest.[24] Licensing and material transfer agreements may be necessary for institutions to use the test, in particular for clinical test use.

The DKFZ classifier test uses a random forest algorithm, which is a type of supervised machine learning model based on binary decision trees used to make predictions or classifications. Supervised machine learning uses labelled datasets to train algorithms to predict outcomes and recognize patterns, compared with unsupervised learning that occurs without human supervision. For the DKFZ classifier test, the random forest is used to classify a CNS tumour into tumour types and subtypes based on the methylation level at different DNA sites. Random forest algorithms use many decision trees (a “forest”), each of which evaluates a random part of the DNA methylation profiling data to make its own prediction about CNS tumour classification. The CNS tumour classification that is predicted by the largest number of decision trees is the final classification. Cross-validation is performed to address overfitting (when results follow too closely to the training data), which typically occurs for high-dimensional data.

Through the random forest algorithm method, the DKFZ classifier test generates a calibrated score that corresponds to CNS tumour types and subtypes.[23] The calibrated score allows for the comparison of results between different tumour types. Classifier test performance was then assessed and threshold analysis was conducted to establish a common classification threshold between tumour types. Developers of the DKFZ classifier test considered a balance between sensitivity and specificity, and chose a calibrated threshold score of 0.9 or higher (possible scores are between 0 and 1).

A calibrated score of 0.9 or higher indicates a valid prediction or successful tumour classification. Calibrated scores between 0.3 and 0.9 are often encountered, which indicate less accurate predictions or tumour classifications. However, classification results with these scores may still be clinically informative and the results may sometimes be used, especially in tumours with a low tumour cell count or when the tumour DNA methylation signature may be diluted by normal brain or inflammatory cells.

In addition, rare or novel CNS tumours may also be misclassified or unclassifiable due the lack of knowledge or characterization of these tumours. A calibrated score of less than 0.3 is considered negative (unclassifiable), suggesting that DNA methylation is not a useful diagnostic tool and results should not be reported.[25] Calibrated scores less than 0.5 are generally discarded.[26]

The current version of the DKFZ classifier test requires DNA methylation profiling data (in the IDAT [intensity data file] format) from Illumina's MethylationEPIC BeadChip. The unprocessed IDAT files are automatically compared with the DNA methylation data of a reference cohort, which in 2018 was comprised of over 2,800 CNS tumours of almost all known types (80 tumour types or subtypes at the time).[24] The accuracy of classification depends on the diversity, number, range, and complexity of CNS tumours included in the reference cohort. A DNA methylation profiling report is generated for tumour classification, and DNA copy number profiles and MGMT promoter methylation status are also included.

The DKFZ classifier test has been developed iteratively and is occasionally updated to incorporate either the inclusion of new tumour types or subtypes or changes in Illumina's DNA methylation profiling methods.[24] For example, the DKFZ classifier test previously used data from Illumina's Infinium HumanMethylation 450, the predecessor to the Infinium MethylationEPIC version 1 (850K array). Recalibration was required for the change from the 450K array to 850K array to ensure results were concordant where applicable (Andrew Gao, MD, personal communication, February 12, 2025). Re-validation and new licensing agreements are also required for new versions of the DKFZ classifier test. The most recent 12.8 version of the DKFZ classifier test is currently only compatible with results from EPIC version 1; however, older versions of the test remain available.[24]

Regulatory Information

DNA methylation–based classifier tests are machine learning–based algorithms and therefore do not require Health Canada approval. The tests require DNA methylation profiling results, which are considered laboratory-developed tests and also do not require Health Canada approval.

Ontario, Canadian, and International Context

Ontario and Canadian Context

In Canada, DNA methylation–based classifier tests for CNS tumours are used only at University Health Network (UHN) and the Hospital for Sick Children (SickKids) in Toronto. Both centres use the DKFZ classifier test with Illumina's MethylationEPIC platform, with no specific funding for testing. Both centres also have licensing agreements to use the DKFZ classifier test, but are currently not paying any licensing fees. However, licensing fees may be possible in the future.

Testing is selective at UHN and dependent on the availability of research funds. There were about 100 CNS tumours tested per year using the DKFZ classifier test. Testing was put on hold starting in January 2025 (Andrew Gao, MD, personal communication, February 12, 2025). The test is primarily used for challenging diagnostic cases in a research capacity. SickKids uses the DKFZ classifier test clinically for CNS tumours as well as DKFZ's more recent sarcoma classifier test[27] and currently tests about 24 cases per month (primarily CNS tumours, but also some sarcomas; Cynthia Hawkins, MD, personal communication, August 1, 2024). Test use at SickKids is more routine than at UHN; however, the decision to test is still very tumour-dependent and based on expertise (e.g., whether DNA sequencing or DNA methylation profiling is more appropriate as the first test; Cynthia Hawkins, MD, personal

communication, August 1, 2024). SickKids also uses the US NIH Bethesda classifier for CNS tumours and compares the results with the DKFZ classifier test. The results are typically concordant; however, the US NIH test includes some additional classifications (Cynthia Hawkins, MD, personal communication, August 1, 2024).

Since UHN and SickKids are the only centres in Canada that use the test, both centres receive out-of-province and out-of-country requests. Sometimes requests are for the DKFZ classifier test only and the results are returned to the requesting pathology laboratory; other times it may be referrals for a full consultation. SickKids also sometimes receives referrals from UHN for pediatric tumours.

In Ontario, access to DNA methylation–based classifier tests for CNS tumours is currently limited due to funding and insufficient personnel and expertise required for the testing process. However, additional testing centres are likely unnecessary as existing centres are expected to be able to increase testing capacity to accommodate increased testing demand. Increased test volumes at centralized centres would also increase testing efficiency, (e.g., through batching of samples for testing). In addition, test turnaround time could be reduced by replacing some conventional tests, resulting in a more streamlined testing process with fewer overall tests needed for CNS tumour classification.

International Context

The DKFZ classifier test is the main test used internationally for DNA methylation–based classification of CNS tumours. In parts of the United States, Germany, the United Kingdom, the Netherlands, and other places in Europe, the DKFZ classifier test is commonly used as a routine test for CNS tumour classification.

In the United States, the NIH Bethesda classifier test is widely used for CNS tumour classification. Some institutions also use their own DNA methylation–based classifier tests that were developed in-house, such as St. Jude Children's Research Hospital and Northwestern Medicine.

Equity Context

We use the PROGRESS-Plus framework[28] to help explicitly consider health equity in our health technology assessments. PROGRESS-Plus is a health equity framework used to identify population and individual characteristics across which health inequities may exist. These characteristics include place of residence; race or ethnicity, culture, or language; gender or sex; disability; occupation; religion; education; socioeconomic status; social capital; and other key characteristics that stratify health opportunities and outcomes.

Expert Consultation

We engaged with experts in the specialty areas of neuro-oncology, pathology, molecular genetics, laboratory medicine, and laboratory medicine to help inform our understanding of aspects of the health technology and our methodologies, and to contextualize the evidence.

PROSPERO Registration

This health technology assessment has been registered in PROSPERO, the international prospective register of systematic reviews (CRD42024551580), available at crd.york.ac.uk/PROSPERO.

Clinical Evidence

Research Question

What is the effectiveness (clinical utility) of DNA methylation–based classifier tests compared with conventional tests for the classification of central nervous system (CNS) tumours?

Methods

Clinical Literature Search

We performed a clinical literature search on May 10, 2024, to retrieve studies published from January 1, 2018, until the search date. The year 2018 was used because it was the year the first main DNA methylation–based classifier test for CNS tumours was published (DKFZ classifier test; Capper et al, 2018[23]). We used the Ovid interface in the following databases: MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and the National Health Service Economic Evaluation Database (NHS EED).

A medical librarian developed the search strategies using controlled vocabulary (e.g., Medical Subject Headings) and relevant keywords. When designing the population search terms, we sought expert advice on commonly used CNS tumour types in DNA methylation classification in addition to consulting the list of World Health Organization (WHO) classification for CNS tumours. To capture the intervention, we used a combination of terms representing DNA methylation profiling, since it is needed as an input for the classifier test, and classification testing keywords.[3] The final search strategy was peer-reviewed using the PRESS Checklist.[29]

We created database auto-alerts in MEDLINE and Embase and monitored them until November 2024. We also performed a targeted grey literature search of the International HTA Database, the websites of health technology assessment organizations and regulatory agencies, and clinical trial and systematic review registries, following a standard list of sites developed internally. See Appendix 1 for our literature search strategies, including all search terms.

Eligibility Criteria

Studies

Inclusion Criteria

- English-language full-text publications
- Studies published since January 1, 2018
- Randomized controlled trials (RCTs), observational studies, health technology assessments (HTAs), systematic reviews

Exclusion Criteria

- Nonsystematic reviews, narrative reviews, conference abstracts, editorials, letters, case reports, and commentaries
- Animal and in vitro studies

Participants

Inclusion Criteria

- Adults and children with CNS tumours (as defined within the studies)
  - CNS tumours of any origin (e.g., primary, metastatic, unknown)
  - Prospective or retrospective CNS tumour samples
  - Any clinical indication (e.g., routine testing or primarily only for challenging diagnostic cases)

Exclusion Criteria

- Tumours not of the CNS

Interventions

Inclusion Criteria

- DNA methylation–based classifier test for CNS tumours (e.g., DKFZ classifier test, NIH Bethesda classifier test)
  - Clinically validated tests that use genome-wide DNA methylation profiling results
  - Tests used in Canada or that are widely accepted/adopted within the international clinical community

Exclusion Criteria

- DNA methylation–based classifier tests for CNS tumours that are not widely available or adopted (e.g., research, used only in select centres)

Comparators

Inclusion Criteria

- Conventional testing (i.e., not genome-wide DNA methylation–based tests) for CNS tumour classification
  - Single or multi-gene tests (e.g., FISH, MGMT promoter methylation, IHC, or DNA sequencing for IDH mutation)
  - Histopathology

- Another (different) DNA methylation–based classifier test that also uses genome-wide DNA methylation profiling (i.e., head-to-head comparisons of different DNA methylation–based classifier tests)

Exclusion Criteria

- Different version or iteration of the same DNA methylation–based classifier test

Outcome Measures

- Classification results
  - Concordant with conventional testing (i.e., no changes in classification)
  - Discordant diagnosis
    - Improved (more precise) diagnosis (e.g., new or refined diagnosis, different tumour grade)
    - Misleading or disregarded diagnosis (e.g., misleading, non-contributory, unresolvable)
  - Unclassifiable results (e.g., calibrated score < 0.3)
- Downstream impact of testing (e.g., treatment, subsequent patient outcomes such as survival, recurrence, frequency of follow-up imaging)
- Time to diagnosis or time to treat
- Test turnaround time
- Replacement of conventional tests for classification (e.g., decrease in overall number of tests needed for CNS tumour classification)

Literature Screening

Two reviewers screened titles and abstracts to assess the eligibility of a sample of 100 citations to validate the inclusion and exclusion criteria. A single reviewer then screened all remaining citations using Covidence[30] and 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 and consulted content experts for any additional relevant studies not identified through the search.

Data Extraction

We extracted relevant data on study characteristics and risk-of-bias items using a data form to collect information on the following:

- Source (e.g., citation information, study type)
- Methods (e.g., study design, study duration and years, participant allocation, allocation sequence concealment, blinding, reporting of missing data, reporting of outcomes, whether the study compared 2 or more groups)
- Outcomes (e.g., outcomes measured, number of participants for each outcome, number of participants missing for each outcome, outcome definition and source of information, unit of

measurement, upper and lower limits [for scales], time points at which the outcomes were assessed)

Equity Considerations

There is currently inequitable access to DNA methylation–based classifier tests in Ontario due to limited funding and experienced personnel for testing. Other potential equity issues related to the research question were not evident during scoping.

Statistical Analysis

We did not conduct a meta-analysis due to the clinical heterogeneity of the studies. Many different types of CNS tumours were often included within the studies. We summarized the results narratively and in tabular form.

Critical Appraisal of Evidence

We assessed risk of bias of randomized controlled trials using the Cochrane Risk of Bias tool for RCTs (version 1),[31] and observational studies using RoBANS[32] (Appendix 2).

We evaluated the quality of the body of evidence for each outcome according to the *Grading of Recommendations Assessment, Development, and Evaluation* (GRADE) *Handbook*.[33] The body of evidence was assessed based on 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 clinical literature search yielded 1,489 citations, including grey literature results and after removing duplicates, published between January 1, 2018, and May 10, 2024. We did not identify any additional eligible studies from other sources, including database alerts (monitored until November 2024). In total, we identified 38 observational studies that met our inclusion criteria. Figure 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the clinical literature search.

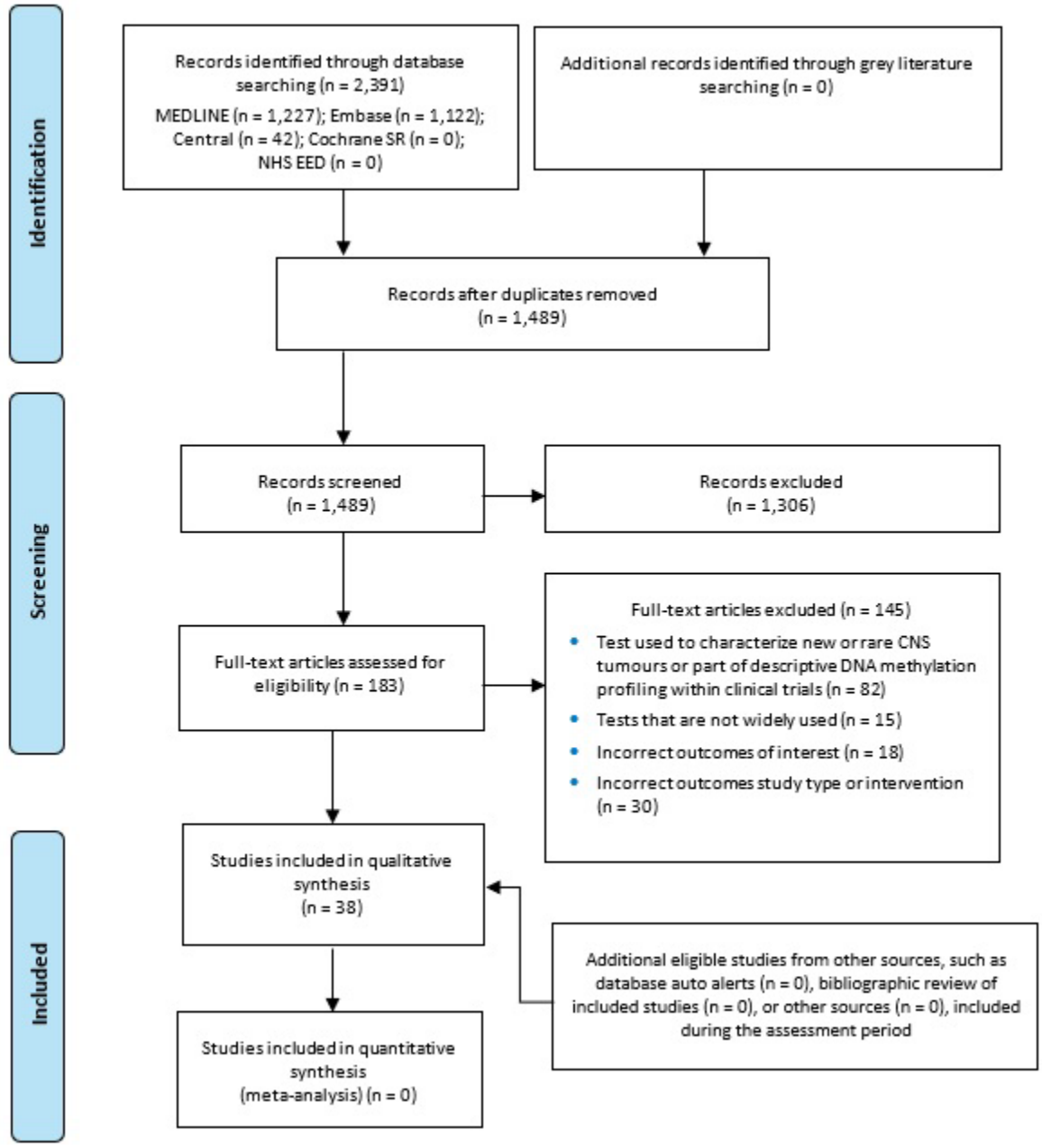

Figure 1: PRISMA Flow Diagram – Clinical Systematic Review

PRISMA flow diagram showing the clinical systematic review. The clinical literature search yielded 1,489 citations, including grey literature results and after removing duplicates, published between January 1, 2018 and May 10, 2024. We screened the abstracts of the 1,489 identified studies and excluded 1,306. We assessed the full text of 183 articles and excluded a further 145. In the end, we included 38 articles in the qualitative synthesis.

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

Source: Adapted from Page et al.[34]

Characteristics of Included Studies

We found 38 studies that evaluated DNA methylation–based classifier tests for the classification of CNS tumours from Australia and New Zealand, Austria, Hong Kong, India, France, Germany, Malaysia, Netherlands, Norway, South Africa, Sweden, United States, and Canada.

Studies that reported on the development of in-house classifier tests were not considered widely used tests and were thus excluded based on our inclusion criteria (e.g., Northwestern and St. Jude classifier tests for CNS tumours in the United States). As such, all included studies reported on the use of the DKFZ classifier tests. Studies that primarily used DNA methylation–based classifier tests for exploratory purposes to characterize rare tumour epigenetic signatures and as part of descriptive DNA methylation profiling within clinical trials were excluded. We also excluded studies that used DNA methylation profiling results as one component of a tool to help determine the prognosis of some CNS tumours. We did not find any head-to-head comparisons of different DNA methylation–based classifier tests based on our inclusion criteria.

The included studies varied in tumour types, patient characteristics, number of patients, classifier version, and score thresholds (for determining classification certainty). The most evaluated DKFZ classifier test versions were 11b2, 11b4, and 12.5 and all studies reported using calibration score thresholds of ≥ 0.9, 0.3–0.9, and < 0.3 or ≥ 0.84, 0.3–0.84, and < 0.3 for categorizing test results as having high confidence, possible confidence, or unclassifiable, respectively.

Studies also did not consistently report detailed patient and CNS tumour characteristics, such as tumour status (e.g., primary, recurrent, metastatic), tumour subtypes, patient demographics, initial WHO tumour grade, follow-up time since surgery, or prior use of radio- or chemotherapy. Most studies focused on the adult population; however, a few studies combined both adult and pediatric populations in their analysis.

Reported indications for DNA methylation–based classifier tests included challenging diagnostic CNS tumour cases, final determination of specific tumour biomarkers, molecular subtyping, and cases with discrepant clinical and pathological diagnosis. Most studies were retrospective and used previously collected tumour samples and data from hospital records. The most common comparator was histopathology, but some studies also explicitly noted using DNA or RNA sequencing, single-gene tests, or FISH analysis. Almost all studies referenced the article by Capper et al[23] for additional details of the DKFZ classifier test.

All studies reported on classification results of DNA methylation–based classifier tests, but only a few studies reported additional outcomes other than classification results (e.g., downstream impact on patient outcomes, time to diagnosis or treatment, test turnaround time).

Additional details of the included studies can be found in Appendix 2.

Risk of Bias in the Included Studies

The included studies generally had moderate risk of bias. Studies were mostly retrospective, using previous tumour samples and hospital records. Patient selection was often not described in detail or unclear, resulting in uncertainty about potential underlying differences between cases that were or were not tested or classified. We assessed low risk of bias for the DNA methylation–based classifier test as an intervention given the existing published and validated information about its development and use. The classifier test also uses DNA methylation profiling only as a test input and does not factor in any additional patient characteristics. Blinding is not possible with DNA methylation–based classifier tests, but we assessed that this does not impact testing or the results. However, there were selective reporting concerns among studies. Additional details about classification results were often not reported.

Details of the risk of bias of the included studies can be found in Appendix 3.

Classification Results

Table 1 presents the classification results from included studies for DNA methylation–based classifier tests for CNS tumours. Concordant results indicate no changes in classification. Discordant results may either lead to an improved (e.g., more precise or refined) diagnosis, or a misleading or disregarded diagnosis (e.g., non-contributory, unresolvable). Results may also be unclassifiable when the test does not indicate any type of CNS tumour (i.e., no result). For studies that did not report specific information on discordant cases (e.g., whether changes improved classification or not), the overall discordant data are presented.

In general, studies found that DNA methylation–based classifier tests had the potential to provide a new alternative diagnosis and revise/refine a diagnosis or WHO tumour grade. However, concordance and discordance rates varied widely and were impacted by CNS tumour type and sample size. DNA methylation–based classifier tests were used for multiple CNS tumour types (specific tumour types were often not specified within study methods), or to classify specific tumour types or subtypes (e.g., glioma, meningioma, ependymoma). Studies found that increased discordant results were often related to CNS tumour types with previously poorly categorized or rare DNA methylation characteristics, which may not yet be represented within the reference database of classifier tests.

Multiple studies also noted that discordant or unclassifiable results were primarily observed in challenging diagnostic cases or cases with low tumour cell content. Studies found that a younger age of the person at time of tumour sample collection ($P < .03$) and lower purity of the tumour ($P < .01$) also lowered classification certainty. Similarly, a study found that tumour purity was significantly lower within the unclassifiable group.[35] Prior radiotherapy was also suggested to potentially impact classification accuracy, but the location of the resected tumour sample and MGMT promoter methylation status was found to not influence scores in one study ($P = .009$).

Drexler et al[35] found that newer versions of the DKFZ classifier test improve classification results in subgroup analysis. Version 12.5 (2022) of the DKFZ classifier test was able to classify an additional 46 of 69 (66.7%) tumours that were originally classified as unclassifiable in the earlier version 11b4. Similarly, Reinhardt et al[36] found improved concordance rates and reduced low-confidence classification rates for version 12.5 compared with earlier versions.

The GRADE certainty for classification results for DNA methylation–based classifier tests compared with conventional tests was Moderate, downgrading for inconsistency but upgrading for the large magnitude of effect; Table A3).

Table 1: Classification Results for DNA Methylation–Based Classifier Tests

Author, year	Test, version	Concordant	Discordant – improved or refined	Discordant – misleading or disregarded	Unclassifiable
Abe et al, 2024[37]	DKFZ, version NR	11/15 (73.3%)	2/15 (13.3%)	Low uncertainty: 2/15 (13.3%)	NR
Alharbi et al, 2020[38]	DKFZ, version NR	39/41 (95.1%)	NR	NR	Insufficient tumour cells: 8/49 (16.3%)
Bode et al, 2023[39]	DKFZ, v12.5	39% Using lower score threshold: 49/79 (61%)	Matched different tumour type: 16%	Using lower score threshold: 10/79 (13%)	NR
Capper et al, 2018[23]	DKFZ, initial version	838/1,104 (75.9%)	Additional molecular subgroup: 171/1,104 (15.5%) Overall revised classification: 129/1,104 (11.7%) **Among discrepant cases** Revised classification: 129/139 (92.8%) WHO tumour grade: 92/129 (71%) Upgraded: 53/129 (41%) Downgraded: 39/129 (30%) Data from 5 external centres New diagnosis: 50/401 (12%)	Overall discrepant but unresolved: 10/1,104 (0.9%) **Among discrepant cases** 10/139 (7.2%)	Low certainty, not assigned: 127/1,104 (11.5%)
Chiang et al, 2024[40]	DKFZ, version NR	34/51 (61%)	NR	Low certainty: 17/51 (33%)	NR
Diaz de Stahl et al, 2023[41]	DKFZ v11b2	3/73 (4.1%)	Refined diagnosis: 57/73 (78.1%)	Low certainty: 6/73 (8.2%)	Unclassifiable or scored poorly: 7/73 (9.6%)
Drexler et al, 2024[35]	DKFZ v11.b4 and v12.8	NR	Reclassification with v12.8 (initial classification with v11b4 resulted in "unclassifiable" determination): 46/69 (66.7%)	NR	Unclassifiable with v11.b4: 69/1,481 (4.6%) Reclassification with v12.8: 23/69 (33.3%) remained unclassifiable
Djirackor et al, 2021[42]	DKFZ, version NR	Overall: 93/105 (89%)	Overall: 12/105 (11%) Adult: 4/55 (7.3%) Pediatric: 8/50 (16%)	Overall: 4/105 (3.8%)	Overall: 3/105 (2.8%)
Ebrahimi et al, 2022[43]	DKFZ, version NR	79/144 (54.9%)	NR	NR	17/144 (11.8%)
Fukuoka et al, 2020[44]	DKFZ, version NR	NR	NR	Low certainty: 44%	NR

Author, year	Test, version	Concordant	Discordant – improved or refined	Discordant – misleading or disregarded	Unclassifiable
Galbraith et al, 2023[45]	DKFZ, version NR	1,189/1,602 (74%)	New diagnosis: 225/1,602 (14%) WHO tumour grade: 58/1,602 (3.6%) Confirmed diagnosis and provided additional prognostic information: 110/1,602 (7%)	6/1,602 (0.3%)	78/1,602 (5%)
Hasselblatt et al, 2018[46]	DKFZ, v11b2	8/25 (32%)	New diagnosis: 10/25 (40%)	Could not be classified, but showed characteristics of certain tumour types: 7/25 (28%)	NR
Jaunmuktane et al, 2019[47]	DKFZ, version NR	Tumours with calibrated score > 0.84: 179/325 (56%) Confirmed diagnosis: 44/325 (14%)	New diagnosis: 45/325 (14%) Refined diagnosis: 86/325 (26%)	Non-contributory: 4/325 (1%)	NR
Karimi et al, 2019[22]	DKFZ, 11b2 or 11b4	9/55 (16%) WHO grade: 40/55 (73%)	Tumour entity: 13/55 (24%) Resolved differential diagnosis: 17/55 (31%) WHO tumour grade: 15/55 (27%) Refined diagnosis: 16/55 (29%)	NR	NR
Kalawi et al, 2022[48]	DKFZ, v11b and v12	1/4 (25%)	New diagnosis: 1/4 (25%)	Neither affirmed nor altered diagnosis: 1/4 (25%)	NA
Lebrun et al, 2021[49]	DKFZ, version NR	3/16 (18.8%)	NR	Low confidence: 6/16 (37.5%)	7/16 (43.8%)
Mortensen et al, 2022[50]	DKFZ, version NR	NR	19/29 (65.5%)	NR	NR
Pages et al, 2019[51]	DKFZ, version NR	28/38 (74%)	NA	Undetermined: 10/38 (26%)	NR
Pages et al, 2021[52]	DKFZ, v11b4	Confirmed initially proposed diagnosis: 15/62 (24.2%) Precisely confirmed: 8/62 (12.9%)	New diagnosis: 10/62 (16.1%) Refined diagnosis: 8/62 (12.9%)	Noninformative: 26/62 (41.9%)	3/62 (4.8%)
Price et al, 2024[53]	DKFZ, v11b4	7/8 (87.5%)	WHO tumour grade: 2/7 (28.6%)	Could not be classified: 1/8 (12.5%) (Was able to classify using the US Cancer Genome Atlas glioma classifier test)	NR

Author, year	Test, version	Concordant	Discordant – improved or refined	Discordant – misleading or disregarded	Unclassifiable
Priesterbach-Ackley et al, 2020[54]	DKFZ, 11b2 and 11b4	273/502 (54.4%)	Refined diagnosis: 67/502 (13.3%) New diagnosis: 49/502 (9.8%) WHO tumour grade change among new diagnosis cases: 35/49 (71.4%)	Misleading or disregarded: 5/502 (1%) Not contributory: 6/502 (1.2%) Low certainty: 130/502 (25.9%)	39/502 (7.8%)
Shen et al, 2023[55]	DKFZ v12.5 and v12.6	NR	Improved diagnosis: 17/17 (100%)	NR	NR
Rajagopal et al, 2023[56]	DKFZ, version NR	41/50 (85%)	None	7/50 (15%)	None
Reinhardt et al, 2022[36]	DKFZ, v11b4, v12.3, and v12.5	V11b4: 29/56 (51.8%) V12.3: 32/56 (57.1%) V12.5: 36/56 (64.2%)	None	Low certainty: V11b4: 27/56 (48.2%) V12.3: 24/56 (42.9%) V12.5: 20/56 (35.7%)	NR
Rohrich et al, 2018[57] Germany	DKFZ, version NR	35/44 (79.5%)	New diagnosis: 9/44 (20.5%)	NA	NA
Singh et al, 2023[58]	DKFZ, v11b4, meningioma classifier v2.4	20/35 (57%)	Refined diagnosis: 5/35 (14.2%)	Could not be accurately classified: 10/35 (28.6%)	NR
Schepke et al, 2023[59]	DKFZ, 12.5	Successful match: 60/71 (85%)	NR	Classified as 'other' tumour type: 14/71 (19.7%)	5/71 (7%)
Tam et al, 2023[60]	DKFZ, 11b4	73/97 (75%)	Alternative diagnosis: 12/97 (12%)	None	None
Tauziede-Espariat et al, 2022[61]	DKFZ v11b4 and 12.2	0/10	0/10	Showed no to little relation to other tumour types: 6/10 (60%)	None
Trager et al, 2023[62]	DRKFZ version NR	125/170 (73.5%)	New diagnosis: 18/170 (10.6%)	NR	27/170 tumours (15.9%)
Wenger et al, 2022[63]	DKFZ v12.5	Matched: 102/121 (84%)	NA	Low certainty with no certain match: 19/121 (15.7%)	None
White et al, 2023[64]	DKFZ v11b4 and v12.5	162/176 (92%)	Refined diagnosis: 130/176 (74%) New diagnosis: 7/176 (4.0%)	NR	25/265 (9.4%)
Witt et al, 2018[65]	DKFZ version NR	122/122 (100%)	NR	NA	NA
Wood et al, 2023[66]	DKFZ v12.5	7/10 (70%)	NR	Low certainty: 3/10 (30%)	NR
Wu et al, 2021[67]	DKFZ version NR	53.2%	Refined diagnosis: 19.6% New diagnosis: 26.9%	Disregarded: 0.3%	12.9%
Vega et al, 2021[68]	DKFZ version NR	126/166 (76%)	NR	Low certainty or unclassifiable: (35/166) 21%	NR

Author, year	Test, version	Concordant	Discordant – improved or refined	Discordant – misleading or disregarded	Unclassifiable
Zschernack et al, 2021[69]	DKFZ v11b4	3/18	None	No match: 15/18 (83.3%)	NR

Abbreviations: DKFZ, Deutsches Krebsforschungszentrum (German Cancer Research Center); NA, not applicable; NR, not reported; v, version; WHO, World Health Organization.
Note: Some studies defined improved or refined diagnoses as discordant cases. Previously unclassifiable samples (using DKFZ classifier test v11.4) were reclassified using v12.8.

Downstream Impact of Testing

Table 2 presents the results of the downstream impact of DNA methylation–based classifier tests. Although studies reported different downstream impacts, DNA methylation–based classifier tests may have the potential to positively impact patient care and treatment management (e.g., changes in intraoperative surgical strategy, avoidance of unnecessary treatment or invasive biopsy, longer overall survival).

The GRADE certainty for the downstream impact of DNA methylation–based classifier tests for observational studies compared with conventional tests was Very low (downgrading for imprecision; Table A3).

Table 2: Downstream Impact of DNA Methylation–Based Classifier Tests

Author, year	Test, version, score thresholds[a]	Downstream impact
Drexler et al, 2024[35]	DKFZ v11.b4 and v12.8 > 0.84, 0.3–0.8, < 0.3	Unclassifiable CNS tumours showed a significantly shorter overall survival compared with classifiable tumours (P = .025), but progression-free survival did not differ significantly between the groups (P = .33)
Djirackor et al, 2021[42]	DKFZ version: NR Score thresholds: NR	Precise classification of the CNS tumour entity and subtype would have supported modification of the surgical strategy in 12/20 (60%) patients evaluated intraoperatively
Karimi et al, 2019[22]	DKFZ, 11b2 or 11b4 > 0.9, 0.3–0.9, < 0.3	7/55 (12.7%) of cases with significant impact on patient care: 3/7 avoided unnecessary treatment 3/7 avoided/received potentially insufficient initial treatment 2/7 resolved depression/anxiety due to initial diagnosis/treatment 1/7 may have avoided unnecessary invasive biopsy 1/7 may have avoided potential medical-assisted death due to diagnosis given

Abbreviations: CNS, central nervous system; DKFZ, Deutsches Krebsforschungszentrum (German Cancer Research Center); NR, not reported; v, version.
[a]Score thresholds are presented from greatest certainty to least certainty.

Time to Diagnosis or Treatment

Drexler et al[35] found that unclassifiable results had a longer time to treatment decision (P < .0001) and, in a subset of glioblastomas, led to an increased time to the start of adjuvant treatment (P < .001) and unfavourable survival (P < .001).

The GRADE certainty for time to treatment of DNA methylation–based classifier tests for observational studies compared with conventional tests was Very low (downgrading for imprecision; Table A3).

Test Turnaround Time

No studies directly compared test turnaround time between DNA methylation–based classifier tests and conventional tests. However, 3 studies reported or noted the test turnaround time for DNA methylation–based classifier tests. Djirackor et al[42] evaluated the intraoperative use of the DKFZ classifier test and found that results could be returned to the operating room at a median of 97 minutes (range 91–161 min). Pages et al[52] reported a mean turnaround time of 25 days, between DNA extraction and submission to use of the classifier test. Finally, Capper et al[23] presented a suggested workflow for the DKFZ classifier test, which included 8 working days from tumour content assessment (for tumour cell content and determining the optimal area for DNA extraction for DNA methylation profiling) to integrating the classifier test results with pathological findings.

Replacement of Conventional Tests

No studies directly compared whether DNA methylation–based classifier tests can replace certain conventional tests. However, DNA methylation–based classification and copy number plotting may be done with 1 array and can also obtain results for IDH status, 1p/19q codeletion status, and MGMT methylation status, as the results between tests for these molecular features and the results by methylation profiling are highly concordant.[22] In diagnostically challenging cases, a subset of these results may also be obtained prior to pursuing DNA methylation profiling. In addition, authors noted that DNA methylation–based classifier tests may benefit cases where multiple single conventional tests may not be possible due to limited tumour sample or cell content. Studies also noted that reconsideration of histology and additional molecular testing may be required even after DNA methylation–based classifier tests.

Ongoing Studies

We are not aware of any ongoing clinical studies that specifically evaluate DNA methylation–based classifier tests for CNS tumours. However, we found 1 ongoing systematic review in PROSPERO that is evaluating the use of molecular diagnostics and artificial intelligence in the classification and prognosis of gliomas (CRD42023408849). We also found that the Children's National Research Institute in the United States is creating an international rare brain tumour registry and will be performing DNA methylation profiling as part of the molecular characterization of the tumours (NCT05697874).

Discussion

Our results show that DNA methylation–based classifier tests have the potential to improve CNS tumour classification through new or revised classifications or changes in tumour grade, although concordance and discordance compared with conventional tests may vary widely depending on the tumour type and may be impacted by the level of tumour cell content and tumour purity. In general, studies noted that optimal candidates for DNA methylation–based classifier tests are diagnostically challenging cases or cases with limited tissue after a small biopsy (e.g., CNS tumours that are difficult to remove or biopsy due to their location), which precludes the application of multiple single tests.

We found that all included studies used established score thresholds for the DKFZ classifier test, but a few studies also explored and used a lower threshold for improved CNS tumour classification. In addition, exceptions to recommended score thresholds may be made depending on the specific CNS tumour case, and the determination is also dependent on clinical and pathology expertise.

DNA methylation–based classifier tests were also found to have the potential to impact downstream patient outcomes, such as the avoidance of unnecessary treatment (e.g., radio- or chemotherapy and its associated risks and side effects) and possibly even longer overall survival. In contrast, malignant CNS tumours typically require adjuvant radio- or chemotherapy, and delays in treatment initiation due to continued diagnostic investigation may potentially impact patient outcomes.[70]

Studies iterated that DNA methylation–based classifier tests are a complementary tool to conventional tests and may help streamline the tumour classification testing process; its use remains as an adjunct test to clinical and pathological expertise. Neuropathologists can integrate the interpretation of clinical information, histomorphology, IHC profiles, and other targeted molecular data. Sometimes the use of DNA methylation–based classifier tests may also lead to additional conventional testing (e.g., DNA sequencing).

A strength of our review is its comprehensive inclusion of studies evaluating DNA methylation–based classifier tests for CNS tumours. However, we focused only on widely-used classifier tests, which, based on the published literature, were found to be limited to the DKFZ classifier test. We found some studies on DNA methylation–based classifier tests that were developed in-house and used at specific institutions, but we excluded them based on our inclusion criteria. These in-house classifier tests may be developed using different machine learning or algorithmic methods and we were unable to determine how their performance compares with the DKFZ classifier test or other similar classifier tests. However, in-house classifier tests may better suit the individual institution's needs, and development of one's own DNA methylation–based classifier test would also ensure ownership of the test and remove the need for licensing and permissions from the use of a third-party classifier test.

Future use of the DKFZ classifier test may also be unclear. New licensing agreements may be needed for future versions of the DKFZ test. Currently, the classifier test uses the Illumina Infinium MethylationEPIC v2 system for DNA methylation profiling. Newer versions of the Infinium MethylationEPIC system are more sensitive (i.e., include more probe sites), but updates have required re-validation against the previous version.

While we did not set out to compare different versions of the same DNA methylation-classifier test, subgroup analyses from included studies have shown that newer versions may improve classification, even cases that were deemed unclassifiable based on earlier test versions. DNA methylation–based classifier tests evolve over time as additional CNS tumour samples are included in the test's reference cohort. Classification accuracy is dependent on the quality, size, and complexity of the reference cohort. The WHO CNS tumour classification (now in its 5th edition) continues to evolve, as shown by certain new CNS tumour classifications requiring DNA methylation profiling information in its newest version. These factors make comparability and generalization difficult between DNA methylation–based classifier tests and over time.

The DKFZ classifier test is based on a random forest algorithm, which is a type of supervised machine learning model based on binary decision trees that may be used for classification.[23] Machine learning is a subset of artificial intelligence (AI), and its use warrants additional considerations. According to Canada Health Infoway's toolkit for the implementers of AI in health care,[71] the key risks of AI systems are: bias and non-discrimination, privacy, explainability, safety and unintended consequences, security, robustness, and lack of regulatory clarity.

There is likely low bias and discrimination with the DKFZ classifier test. International collaboration occurred during its development and refinement and, as the test's reference cohort grew (with CNS tumour samples from different countries and patients), newer versions were released.[23] The collaborative development of the DKFZ classifier test strengthens the test's ability for CNS tumour classification. In terms of explainability and robustness, Capper et al[23] reported the development process and the reasoning behind the values and thresholds that were used for creating and training the algorithm, as well as the clinical implementation results in a cohort of patients that were not used for algorithm training.

There are no specific privacy or security concerns for DNA methylation–based classifier tests since all patient data is de-identified, and only DNA methylation profiling results are used as test input. In addition, CNS tumour samples and test results would be handled in the same manner as other patient samples or clinical or genetic data. As with any diagnostic or classification test, there is always the risk of inaccurate or misleading results. However, this is mitigated by the use of DNA methylation–based classifier test results as an adjunct to conventional tests and the fact that clinical expertise always determines the final classification result from an integrated report. In terms of regulation, Health Canada has begun to regulate AI-enabled medical devices and software as medical devices; however, the classifier test is more akin to laboratory-developed tests, which are also not approved by Health Canada.

DNA methylation profiling for CNS tumours is also extending beyond tumour classification. Nomograms are now being developed that consider patient characteristics (e.g., age) and tumour molecular features (e.g., DNA methylation profiling) to predict CNS tumour type and overall survival for more personalized risk assessment and prediction for patients. Research is also ongoing for DNA methylation–based testing of circulating tumour DNA in the blood (liquid biopsy) for CNS tumour classification. Beyond CNS tumours, DNA methylation–based classifier tests are also being developed and used for other conditions (e.g., solid tumours, skin cancer, sarcoma, hematological cancers, rare disorders).

Conclusions

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

Economic Evidence

Research Question

What is the cost-effectiveness of DNA methylation–based classifier tests compared with conventional tests for the classification of central nervous system (CNS) tumours?

Methods

Economic Literature Search

We performed an economic literature search on May 14, 2024, to retrieve studies published from January 1, 2018, until the search date. To retrieve relevant studies, we developed a search using the clinical search strategy with an economic and costing filter applied.

We created database auto-alerts in MEDLINE and Embase, and monitored them until October 31, 2024. We also performed a targeted grey literature search following a standard list of websites developed internally, which includes the International HTA Database and the Tufts Cost-Effectiveness Analysis Registry. See Clinical Literature Search, above, for further details on methods used. See Appendix 1 for our literature search strategies, including all search terms.

Eligibility Criteria

Studies

Inclusion Criteria

- English-language full-text publications
- Studies published since January 1, 2018
- Cost–benefit analyses, cost–effectiveness analyses, cost–minimization analyses, or cost–utility analyses

Exclusion Criteria

- Narrative reviews, editorials, case reports, commentaries, and abstracts

Participants

Inclusion Criteria

- Adults and children with CNS tumours (as defined within the studies)
  - CNS tumours of any origin (e.g., primary, metastatic, unknown)
  - Prospective or retrospective CNS tumour samples
  - Any clinical indication (e.g., routine testing or primarily only for challenging diagnostic cases)

Exclusion Criteria

- Tumours not of the CNS

Interventions

Inclusion Criteria

- DNA methylation–based classifier test for CNS tumours (e.g., the Deutsches Krebsforschungszentrum [DKFZ] classifier test, NIH Bethesda classifier test)
  - Clinically validated test that uses genome-wide DNA methylation profiling results
  - Tests used in Canada or are widely accepted/adopted within the international clinical community

Exclusion Criteria

- DNA methylation–based classifier tests for CNS tumours that are not widely available or adopted (e.g., research, used only in select centres)

Comparators

Inclusion Criteria

- Conventional testing (i.e., not genome-wide DNA methylation–based tests) for CNS tumour classification
  - Single or multi-gene tests (e.g., FISH, MGMT promoter methylation, IHC, or DNA sequencing for IDH mutation)
  - Histopathology
- Another different DNA methylation–based classifier test that also uses genome-wide DNA methylation profiling (i.e., head-to-head comparisons of different DNA methylation–based classifier tests)

Exclusion Criteria

- Different version or iteration of the same DNA methylation–based classifier test

Outcome Measures

- Costs
- Health outcomes (e.g., quality-adjusted life-years, or classification results)
- Incremental costs
- Incremental effectiveness
- Incremental cost-effectiveness ratios

Literature Screening

A single reviewer conducted an initial screening of titles and abstracts using Covidence[30] 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 and consulted content experts for any additional 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, intervention[s], comparator[s])
- Outcomes (e.g., health outcomes, costs, incremental cost-effectiveness ratios)

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.[72] The NICE checklist has 2 sections: the first is for assessing study applicability, and the second is for assessing study limitations. We modified the wording of the questions of the first section to make it specific to Ontario. Using this checklist, we assessed the applicability of each study to the research question (directly, partially, or not applicable). Next, we assessed the limitations (minor, potentially serious, or very serious) of the studies that we found to be applicable.

Results

Economic Literature Search

The economic literature search yielded 31 citations, including grey literature results and after removing duplicates, published between January 1, 2018, and May 14, 2024. We did not identify any additional eligible studies from other sources, including database alerts (monitored until October 31, 2024). We identified no studies that met our inclusion criteria. Figure 2 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the economic literature search.

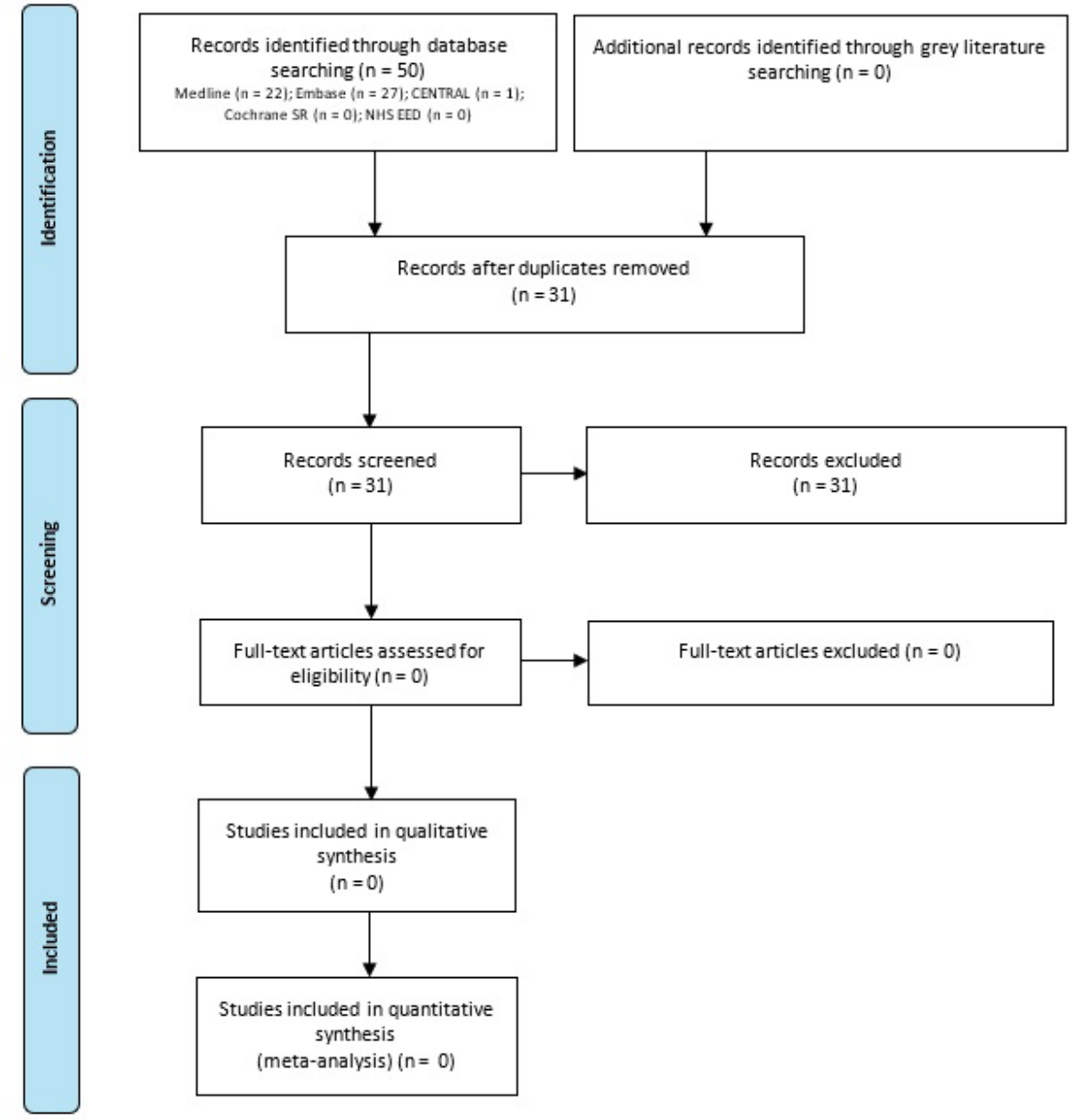

Figure 2: PRISMA Flow Diagram – Economic Systematic Review

PRISMA flow diagram showing the economic systematic review. The economic literature search yielded 31 citations, including grey literature results and after removing duplicates, published between January 1, 2018, and May 14, 2024. We screened the abstracts of the 31 identified studies and excluded all of them.
Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.
Source: Adapted from Page et al.[34]

Conclusions

We did not identify any studies that evaluated the cost-effectiveness of DNA methylation–based classifier tests for CNS tumour classification. Based on our literature search, the cost-effectiveness of DNA methylation–based classifier tests is unknown.

Primary Economic Evaluation

No published economic evaluations were identified in the economic literature review. We therefore conducted a primary economic evaluation.

Research Question

What is the cost-effectiveness of second-tier DNA methylation–based classifier tests (following the use of conventional testing) for the classification of challenging diagnostic cases of CNS tumours compared with conventional tests alone 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.[73] The content of this report is based on a previously developed economic project plan.

Given that a random forest algorithm (a type of machine learning algorithm) was used to develop DNA methylation–based classifier tests, we followed the artificial intelligence (AI) extension of CHEERS (CHEERS-AI) to present relevant AI information.[74] Items in the "AI elaboration" section added AI-specific context to the existing CHEERS item, while items in the "AI extension" section were new reporting items that were not included in the standard CHEERS 2022 checklist. See Table A4 in Appendix 4.

Type of Analysis

We conducted a cost-effectiveness analysis to evaluate the use of DNA methylation–based classifier testing as a second-tier test following conventional testing for the classification of challenging diagnostic cases of CNS tumours. The number of patients with an improved CNS tumour classification was our measure of clinical effectiveness. Improved diagnosis is defined as test results that lead to establishing a new diagnosis (including revising a previous classification) or refining an existing classification (e.g., tumour subtype).

Quality-adjusted life-year (QALY) is the recommended measure of effectiveness for economic evaluations. However, it was not feasible to estimate QALYs for this economic evaluation because there are over 100 subtypes of CNS tumours,[3] each associated with varying patient treatment and health outcomes. While numerous publications have reported on the benefits of DNA methylation–based classifier tests for the classification of CNS tumours, fewer studies report the downstream impact on patient treatment and health outcomes, which includes health-related quality-of-life outcomes.

Population of Interest

Our DNA methylation–based population of interest includes newly diagnosed primary CNS tumours that have undergone some conventional testing, but may still have some uncertainty surrounding their diagnosis. DNA methylation–based classifier tests are expected to be most useful for newly diagnostic cases, although they may be used in other clinical situations. We assumed that any previously diagnosed CNS tumours have already resulted in patient management and treatment plans. As conventional testing may be sufficient for the majority of newly diagnosed CNS tumours (see Background, above), the

added use of DNA methylation–based classifier testing would therefore have limited impact on patient management for most patients with CNS tumours. In contrast, a proportion of newly diagnosed CNS tumours may be challenging to classify for various reasons (termed as "challenging diagnoses;" see Table A1, Appendix 2).

Deciding which cases are "challenging" is dependent on clinical and pathology experience and may therefore be subjective and vary between clinical studies. One Ontario study described the following challenging situations where DNA methylation–based classifier tests may be useful after conventional testing: 1) there are uncertain histopathological results after assessment by 2 independent neuropathologists, 2) there are indeterminant results from conventional tests, 3) molecular subtyping is required, and 4) there are discrepancies between clinical or imaging features and histopathological diagnoses.[22] In another study, Capper et al[23] provided reasons for using DNA methylation–based classifier tests for CNS tumours from external centres in their supplementary materials. In addition to listing similar reasons as the Ontario study, other reasons for using DNA methylation–based classifier tests also included resolving: 1) nonrepresentative biopsy samples, 2) unusual histology findings, 3) rare tumour class diagnoses, and 4) ambiguous findings in immunohistochemistry (IHC) or molecular tests. However, overall, many studies did not provide the exact reasons for using DNA methylation–based classifier tests. For example, an institution in the United States reported that they conducted 1,045 DNA methylation–based classifier tests requested by outside institutions, and 213 cases underwent internal consultation, but no reasons for testing were specified.[67] For our analysis, we considered challenging CNS tumour diagnostic cases to be those that still have uncertain classification after conventional testing and whose classification may be improved by the addition of DNA methylation–based classifier tests as a second-tier test. In 1 of our scenario analyses, we considered using DNA methylation–based classifier tests as a first-tier test for all newly diagnosed primary CNS tumour cases.

We estimated that the annual incidence of people with CNS tumours will be around 3,580 (ranging from 3,525 to 3,634 children and adults) over the next 5 years in Ontario, based on the annual age-standardized incidence rate in Canada[75] multiplied by the population size in Ontario[76] (for details, please see Population of Interest in the Budget Impact Analysis, below). Of these new CNS tumours, around 1,280 (35.7%[75]) are estimated to be malignant and the remaining are non-malignant (benign or uncertain). We estimated that around 20% to 25% of all CNS tumours are considered challenging diagnostic cases (Andrew Gao, MD, written communication, February 2025). As such, we estimated that each year, around 716 Ontarians with CNS tumours (20%, or 716) would receive DNA methylation–based classifier tests as a second-tier test.

Subgroup Analysis

We projected that for children (aged 0 to 14 years), there will be around 125 newly diagnosed CNS tumours per year in the next 5 years. Although the incidence rate of CNS tumours was found to be much lower in children than in adults, the percentage of malignant CNS tumours was greater in children than in adults (percentages of malignant CNS tumours for people aged 0–14, 15–39, and 40+ were 67.1%, 34.2%, and 34.4%, respectively).[75] We assumed that 20% of children with CNS tumours would receive DNA methylation–based classifier tests as a second-tier test, corresponding to 25 children per year.

We also included glioblastoma (the most common type of malignant CNS tumour) in our scenario analysis. For details, please see Population of Interest in the Budget Impact Analysis, below, for both subgroups.

Perspective

We conducted this analysis from the perspective of the Ontario Ministry of Health.

Interventions and Comparators

We conducted evaluations of the addition of DNA methylation–based classifier testing as a second-tier test compared with conventional testing alone for classifying challenging diagnostic cases of newly diagnosed CNS tumours. Table 3 summarizes the interventions evaluated in the economic model.

Conventional testing for CNS tumour classification involves histopathology and molecular markers (i.e., changes in specific genes or proteins known to drive tumour growth). Conventional testing for CNS tumour classification includes immunohistochemistry (IHC) and single- or multi-gene tests (e.g., fluorescence in situ hybridization [FISH], O^6-methylguanine-DNA methyltransferase [MGMT] promoter methylation), and DNA sequencing. While not all of these conventional tests are required, multiple tests may be performed for a single patient sample.

A more novel method to classify CNS tumours examines genome-wide DNA methylation patterns of tumours, known as DNA methylation profiling or analysis. DNA methylation is a form of epigenetic change, where chemical changes to DNA regulate gene expression without changes in the DNA sequence. This allows for genetically identical cells to establish distinct cellular phenotypes. The DKFZ classifier test is the most commonly used DNA methylation–based classifier test internationally, but other similar tests also exist.[23] For additional details on conventional tests and DNA methylation–based classifier tests, please see Clinical Evidence, above.

Table 3 summarizes the interventions evaluated in our economic model.

Table 3: Interventions and Comparators Evaluated in the Primary Economic Model

Intervention	Comparator	Population	Outcome
DNA methylation–based classifier testing as a second-tier test, after conventional testing	Conventional testing alone (e.g., histopathology, single or multi-gene tests, DNA sequencing)	People (children and adults) with challenging diagnostic cases of CNS tumours	Incremental cost Number of people with an improved diagnosis Incremental costs per improved diagnosis case

Abbreviations: CNS, central nervous system; DNA, deoxyribonucleic acid.

Time Horizon and Discounting

We did not include any health outcomes or costs associated with patient management and treatment. Therefore, the time horizon was the duration of classifying or refining the type or subtype of CNS tumour, typically over several weeks. As a result, discounting was not applicable.

Main Assumptions

The model's main assumptions were as follows:

- For individual patients, CNS tumour classification may be unchanged or improved with the addition of a DNA methylation–based classifier test. Results from the DNA methylation–based classifier test will be combined with results from other conventional tests for clinical decision-making. Therefore, results of the DNA methylation–based classifier test may be discarded or disregarded for cases with low certainty scores or cases with misleading or unclassifiable results
- In our model, an unclassifiable result from DNA methylation–based classifier testing is not considered an improvement in diagnosis, although these findings may have value in clinical practice
- DNA methylation–based classifier testing may include components of conventional testing (e.g., MGMT promoter methylation by PCR, CDKN2A gene deletion by micro-array, 1p/19q co-deletion by FISH in a single assay; Cynthia Hawkins, MD, Aaron Pollett, MD, and Andrew Gao, MD, written communications, December 2024 to February 2025). Thus, when used as a first-tier test, DNA methylation–based classifier testing may be able to replace some conventional tests

Model Structure

We developed a model to evaluate the cost-effectiveness of using DNA methylation–based classifier testing as a second-tier test (Figure 3). In the conventional testing alone arm, classification is uncertain for challenging diagnostic cases. In the intervention arm, DNA methylation–based classifier test results may be concordant or discordant with conventional testing results.

Concordant results were defined as no changes in classification, which applies to the majority of cases. However, there are instances where DNA methylation–based classifier testing can provide additional information that allows for tumour subtyping. We termed these cases "refined diagnosis"; they were considered an improvement in classification.[23]

DNA methylation–based classifier test results may also be discordant with results from conventional testing. Conventional test results may be re-evaluated for these cases and additional tests may be conducted (this scenario is not incorporated into our model). This may result in establishing a new classification (or a revision of a previous classification), which was considered an improvement in classification.[23] Less commonly, discordant DNA methylation–based classifier test results may be misleading or discarded, and the final classification would then still be based on conventional testing results alone.

Some CNS tumour cases are unclassifiable (i.e., scores < 0.3) or may receive low certainty scores. These cases may represent rare, novel molecular tumour entities not previously recognized and, as such, results from DNA methylation–based classifier testing may still provide useful information.[23] However, given that it may be difficult to interpret scores with low certainty, we excluded possible classification improvement for these cases.

The diagnostic pathway of CNS tumours is complex and varies by CNS tumour type and patient characteristics. Although there are multiple conventional tests, a patient may only receive a subset of these tests. Sometimes, following DNA methylation–based classifier testing, additional molecular tests

may be further performed to help resolve discrepant cases (e.g., cases that are discordant or unclassifiable).[23,45] For some individuals, a definite diagnosis may still be unclear even after multiple tests.[77] However, because of the heterogeneity of CNS tumours, it is difficult to propose a clear diagnostic pathway for our population of interest. Further, some advanced tests being conducted for academic research purposes may not always be feasible or justifiable in the clinical setting. Given that the clinical impacts of further testing (after second-tier DNA methylation–based classifier testing) have not been widely discussed in the published literature and most cases in the clinical setting may not undergo further testing, we did not include these cases in our model.

According to the "User autonomy" item in the CHEERS-AI tool, the technology may be classified as "Leads to direct care action" (i.e., being used to definitive diagnosis, or being a treatment), "Drives clinical management" (i.e., aiding treatment, diagnosis, or decision making) and "Informs clinical management" (i.e., no direct care action used).[74] We judged that DNA methylation–based classification falls under the category of AI technologies that "drive clinical management" because patients with CNS tumours generally undergo a range of diagnostic tests. When DNA methylation–based classifier testing is included in the range of diagnostic tests being performed, its results will be evaluated together with the results of conventional testing by neuropathologists to classify CNS tumours, which will subsequently inform patient treatment and management. Overall, the machine learning (AI) aspect of DNA methylation–based classification did not influence our choice of economic model.

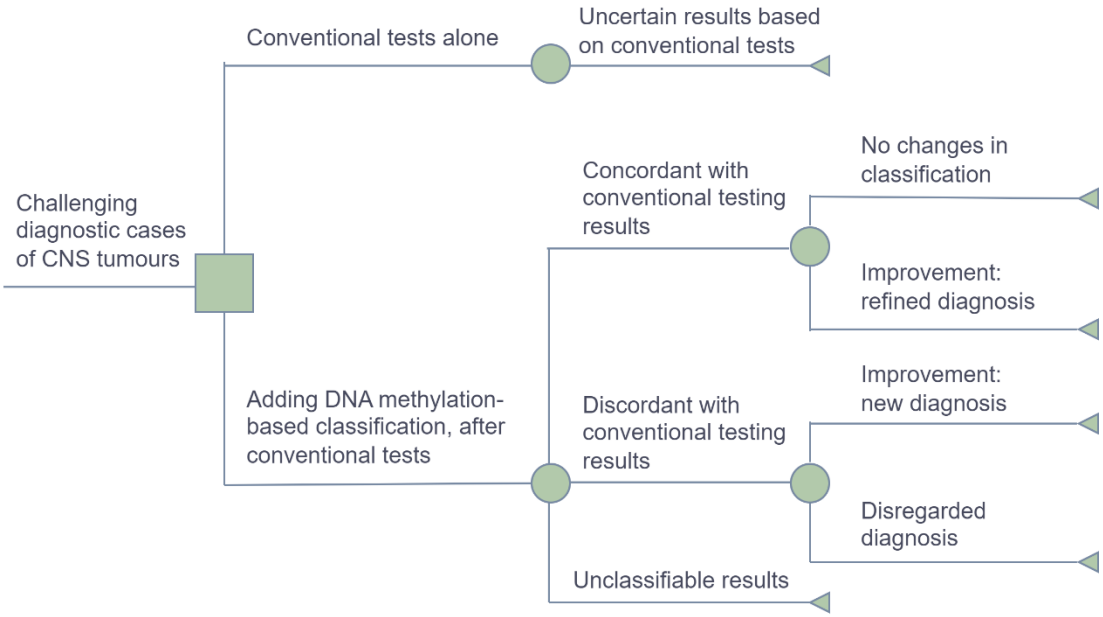

Figure 3: Model Structure of Second-Tier DNA Methylation–Based Classifier Tests for Challenging Diagnostic Cases of CNS Tumours

Decision-tree model of diagnostic pathway for CNS tumours showing conventional testing alone, which may lead to uncertain results, and conventional testing plus DNA methylation, which may lead to concordant, discordant, or unclassifiable results. Concordant results may lead to no changes in classification or a refined diagnosis. Discordant results may lead to a new diagnosis or a disregarded diagnosis.

Clinical Outcomes

We used several input parameters to populate the model (Table 4). The annual incidence of newly diagnosed CNS tumours and the percentage of challenging diagnostic cases are previously described (see "Population of Interest," above). The parameters for clinical utility (e.g., improvement in classification) for DNA methylation–based classification were obtained from Capper et al, 2018.[23] DNA methylation–based classifier testing may improve CNS tumour classification (refinement or establishment of a new classification), but there is also a chance of misleading or unclassifiable results. Multiple published studies have evaluated the clinical utility of DNA methylation–based classifier testing as a second-tier test. However, due to heterogeneity in CNS tumour types, patient population, and study design and methods, it was not suitable to pool the results. We chose Capper et al[23] as the main source of model parameters since it was the original publication that described the development and clinical validation of a widely-used DNA methylation–based classifier test (DKFZ classifier test), while also considering study quality, patient population, sample size.

Table 4: Clinical Inputs Used in the Economic Model

Model parameter	Mean	Distribution (parameters)	Reference
DNA methylation–based classifier test as a second-tier test			
Annual incidence of newly diagnosed CNS tumours in Ontario, N	3,580	Fixed	Walker et al, 2023[75]; MOF, 2024[76]
Percentage of patients with CNS tumours who are challenging to diagnose, %	20	Uniform (0.15, 0.25)	Expert consultation[a]
DNA methylation–based classification results			
Concordant with conventional testing, %	75.9	Dirichlet (838;139;127)-1	Capper et al, 2018[23]
Percentage with refinement of diagnosis (improvement), %	20.4	Beta (171, 667)	Capper et al, 2018[23]
Percentage with no changes in classification, %	79.6	1 – Beta (171, 667)	Capper et al, 2018[23]
Discordant with conventional testing, %	12.6	Dirichlet (838;139;127)-2	Capper et al, 2018[23]
Percentage establishing new diagnosis (improvement), %	92.8	Beta (129, 10)	Capper et al, 2018[23]
Percentage disregarded diagnosis (misleading), %	7.2	1 – Beta (129, 10)	Capper et al, 2018[23]
Unclassifiable results, %	11.5	Dirichlet (838;139;127)-3	Capper et al, 2018[23]

Abbreviations: CNS, central nervous system; DNA, deoxyribonucleic acid; MOF, Ontario Ministry of Finance; N, number.
[a]Andrew Gao, MD, written communication, January 2025.

Cost Parameters

The costs of DNA methylation–based classifier testing and conventional tests are presented in Table 5. All costs are presented in 2024 CAD.[78]

There are challenges to estimating the average cost of conventional testing for CNS tumour classification. For instance, histopathology is conducted for all patients, but other conventional tests may be conducted for only select patients. The number of histopathological and IHC tests performed also varies depending on the CNS tumour case. In addition, DNA sequencing has become more widely available and has gradually replaced single-gene tests in Ontario. DNA sequencing is also typically performed only for some CNS tumour cases. We therefore estimated the average total cost of conventional testing based on the total cost of the most common tests performed for CNS tumour classification: histology, IHC, FISH, and DNA sequencing. The estimated average total cost was $1,981.73 per patient for conventional testing (Table 5). Because DNA methylation–based classifier testing as a second-tier test is intended to be conducted after completing the routine conventional tests, it would not replace any existing conventional tests. Therefore, any variation in the average total costs of conventional testing would not impact the incremental costs of adding DNA methylation–based classifier tests as a second-tier test. As such, we excluded the costs of conventional tests in the reference case analysis. We considered DNA methylation–based classifier tests as a first-tier test in 1 of our scenario analyses and included the costs of conventional tests (scenario analysis 3, below).

We did not identify any published data on costs associated with the classification of CNS tumours in Ontario in a targeted search. As such, we consulted with experts to estimate the cost of testing from hospital laboratories in Ontario. We considered that DNA methylation–based classifier tests would be performed at hospitals already equipped with the existing infrastructure required for this test (i.e., a laboratory with advanced molecular technologies and professionals). We did not include the additional capital investment or staff hiring. The actual costs of DNA methylation–based classifier testing depends on the volume of tests. Illumina's MethylationEPIC system has the capacity to run 8 samples at a time. If publicly funded, we considered that all samples across Ontario would be conducted at a select number of hospital laboratories for DNA methylation–based classifier testing. As such, if publicly funded, we anticipate a sizable volume of DNA methylation–based classifier testing for each of these hospital laboratories. It was estimated that the cost of supplies (e.g., Illumina MethylationEPIC Kit, Illumina FFPE DNA Restore Kit) was $1,297.68 per test for running a batch of 6 samples (Wes Morrison, written communication, January 2025). Assuming that the cost of labour is around 10% of supply costs and that only a small proportion of all testing will be conducted in a batch of less than 6 samples, we estimated that the average cost of DNA methylation–based classifier testing per patient is about $1,500 per test, including supplies and labour.

There are a number of factors that may impact the cost estimates for this test. For example, DNA methylation–based classifier tests at some hospitals in Ontario have been largely funded by research grants. However, research laboratories may have lower overall costs compared with clinical laboratories (Cynthia Hawkins, MD, written communication, December 2024; Aaron Pollett, MD, written communication, January 2025). For example, compensation for laboratory technologists is typically higher at clinical laboratories, and clinical laboratories require more administrative work, overhead, and quality metrics (e.g., quality assurance and clinical validation). Additionally, if a laboratory has lower testing volumes, then there may be a higher proportion of tests where batches of fewer than 6 samples may need to be run to ensure reasonable test turnaround time (i.e., the time required to accumulate the ideal 6 to 8 samples would negatively impact timely clinical decision-making). Moreover, in clinical

practice, reagent wasting (e.g., contamination errors) may occur from time and time. On the other hand, hospitals may negotiate discounts for various testing components with manufacturers (e.g., price of reagents), particularly in the context of high testing volumes. Overall, it is therefore challenging to accurately account for all the factors that may impact the actual cost of DNA methylation–based classifier testing.

We did not include the following costs in our reference case analyses:

- *Capital costs of equipment:* DNA methylation–based classifier tests will be conducted using existing equipment, which is also used for other purposes. However, if we were to account for the per person capital cost of using existing equipment, the cost of DNA methylation–based classifier tests is expected to be higher
- *Licensing fees (e.g., DKFZ classifier test):* Currently, Ontario hospitals do not pay any licensing fees for using the DKFZ classifier test, but this may change in the future. Other DNA methylation–based classifier tests have also since been developed (e.g., NIH Bethesda classifier test). It remains uncertain which DNA methylation–based classifier test (and its associated possible licensing fees) will be used in Ontario over the long-term
- *Costs of physician fees:* DNA methylation–based classifier test analysis and interpretation are performed by existing laboratory technologists and neuropathologists. Costs are not directly associated with additional physician fees because the time required to analyze and interpret test results is variable, depending on whether these tests increase the overall time needed for CNS tumour classification (e.g., subsequent testing is indicated, resolving discordant results), or decreases the time (e.g., replacing some conventional tests)
- *Cost of sample collection*: We assume no costs for additional sample collection because DNA methylation–based classifier tests are conducted using the same tissue biopsy samples as conventional testing
- *Cost of treatments:* The impact of DNA methylation–based classifier test results on patient management and treatment is variable, and depends on the CNS tumour and patient characteristics
- *Cost of repeat testing:* No costs are expected to arise from repeat testing because, although discordance may exist between the results of DNA methylation–based classifier tests and conventional testing, typically earlier test results may be re-evaluated, but repeat testing is not performed

Table 5: Costs of DNA Methylation–Based Classifier Test and Conventional Tests

Model parameter	Mean	Range (lower – higher limit)	Distribution[a]	Reference
New test				
DNA methylation–based classifier test	$1,500	$1,000–$2,000	Gamma	Expert consultation[b]
Conventional tests				
Histology	$103.20	NA	Gamma	OHIP code: L865, surgical pathology, MOH[79]
Number of histology slides per patient	7.5	5–10	Uniform	Assumption
IHC	$51	NA	Gamma	Djalalov et al, 2014[80]
Number of IHC per patient	8.5	7–10	Uniform	Assumption
FISH	$581.73	NA	Gamma	Expert consultation[b]
DNA sequencing	$1,100	NA	Gamma	Makarem et al, 2021[81]
Percentage of patients tested	17.5	10–25	Uniform	Assumption
Average total cost per case[c,d]	$1,981.73	NA	NA	Calculated

Abbreviations: FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; MGMT, methylguanine methyltransferase; MOH, Ontario Ministry of Health; NA, not applicable; OHIP, Ontario Health Insurance Plan.

[a]A standard error of 10% of the mean value was assigned for the gamma distributions for the costs of conventional tests.[82] DNA methylation–based classifier test is a new test, and the uncertainty of costs is greater. We assumed that the range of $1,000 to $2,000 were the lower and upper limits of 95% confidence intervals for the costs of DNA methylation–based classifier testing, respectively, and the corresponding standard error was $255[($2,000 − $1,000) ÷ 3.92]. We assigned uniform distributions for the number of histology slides per patient, the number of IHC per patient, and percentage of patients tested.

[b]Wes Morrison, written communication, January 2025.

[c]The average total costs were calculated as the sum of the costs for histology, IHC, FISH, and DNA sequencing.

[d]The costs of conventional testing were included in the scenario analysis, but not the reference case analysis.

Internal Validation

The secondary health economist conducted formal internal validation. This process included testing the mathematical logic of the model, checking for errors, and ensuring the accuracy of parameter inputs and equations.

Equity Considerations

Economic evaluations inherently focus on horizontal equity (i.e., people with similar characteristics are treated in a similar way). Where possible, we conducted subgroup or scenario analyses to best address vertical equity (which allows for people with different characteristics to be treated differently according to their needs).

Analysis

Our reference case and sensitivity analyses adhere to Canada's Drug Agency (CDA, formerly Canadian Agency for Drugs and Technologies in Health [CADTH]) guidelines[83] when appropriate. Our reference case represents the analysis with the most likely set of input parameters and model assumptions.

We calculated the reference cases of our analyses by running 100,000 simulations (probabilistic analysis) to simultaneously capture the uncertainty in all parameters that are expected to vary. We used the

Monte Carlo standard error (MCSE) to evaluate the number of iterations required for the probabilistic analysis.[82] We set distributions for variables within the model. Tables 4 and 5 list the model variables and their corresponding distributions. We calculated the annual costs with credible intervals (CrI) and the number of people with improved classification (i.e., the effectiveness) with CrI for each intervention assessed. We also calculated the mean incremental costs and incremental effectiveness with CrI and incremental cost-effectiveness ratios (ICERs) for DNA methylation–based classifier tests in addition to conventional tests versus conventional tests alone.

We assessed variability and uncertainty in the model using probabilistic analyses.

Scenario Analyses

We conducted scenario analyses by modifying various parameter inputs and applying alternative assumptions.

- **Scenario 1, subgroup analysis, children (0–14 years old):** We projected that there will be 125 children aged 0 to 14 years with newly diagnosed primary CNS tumours per year in the next 5 years in Ontario.[75,76] For details, please see Population of Interest in the Budget Impact Analysis, below. We assumed that 25 (20%) of these newly diagnosed tumours are considered challenging diagnostic cases. Capper et al[23] presented individual-level data in their supplementary materials. We analyzed these data and presented the model parameters for children aged 0 to 14 years in Table 6
- **Scenario 2, subgroup analysis, glioblastoma** (the most common type of malignant CNS tumour)**:** The annual age-standardized incidence rate of glioblastomas was 4.01 per 100,000 person-years in Canada.[75] This translates to about 668 newly diagnosed patients annually in Ontario in the next 5 years.[75,76] For details, see Population of Interest in the Budget Impact Analysis, below. Capper et al[23] presented individual level-data in their supplementary materials. There were 316 patients classified as having glioblastoma from pathological classification prior to DNA methylation–based classification, including 283 with glioblastoma isocitrate dehydrogenase (IDH)-wildtype, 16 with glioblastoma IDH-mutant, and 17 with gliosarcoma IDH-wildtype. We extracted a subgroup of these patients and obtained model parameters (see Table 7)
- **Scenario 3, DNA methylation–based classifier test as a first-tier test:** This scenario evaluated DNA methylation–based classifier tests as a first-tier test in addition to conventional tests for all newly diagnosed CNS tumours. When the DNA methylation–based classifier test is used as a first-tier test, we assumed that it could replace some conventional tests, such as single- or multi-gene tests (replacing 60% of FISH and single-gene tests [e.g., MGMT promoter methylation], but not histopathology or DNA sequencing). As such, the total estimated cost of first tier testing with DNA methylation–based classification (at $1,500 per patient) and conventional tests (at $1,632.69 per patient) is $3,132.69. For this scenario, the incremental cost of DNA methylation–based classifier testing compared with conventional testing alone (at $1,981.73) decreases to $1,150.96 per patient. There were limited studies that evaluated DNA methylation–based classifier tests as a first-tier test. For instance, Galbraith et al[45] was a prospective study using DNA methylation analysis as a primary diagnostic method for 1,921 patients with CNS tumours. We developed the economic model and obtained the clinical model parameters based on this study (see Table 8)

- **Scenario 4: Higher and lower chances of an improvement in classification:** The performance of the DNA methylation–based classifier test may improve over time. For example, the DKFZ classifier has released multiple new versions as the reference cohort of CNS tumours has grown and more information is known about different CNS tumours.[84] In addition, some CNS tumour samples may not be suitable for DNA methylation profiling and "challenging diagnostic cases" is difficult to define accurately, so the percentage of patients with an improvement in classification may be smaller than that for the reference case based on Capper et al.[23] In this scenario, we assumed that, compared with the reference case, patients may have a 20% higher or lower chance to have an improved classification. Since 92.8% of patients established new classifications (i.e., improvement) when the results were discordant with conventional testing, and a 20% increase would lead a value greater than 100%, we set an upper bound of 100% for an improved classification for our simulations
- **Scenario 5: Higher and lower costs for the DNA methylation–based classifier test:** The cost of DNA methylation–based classifier testing may increase (e.g., due to licensing fees, the capital cost of molecular testing equipment, and potential costs of further testing for discordant or unclassifiable results) or decrease (e.g., due to more efficient or streamlined testing). In this scenario, we varied costs ± 20%

Table 6: Clinical Inputs Used in the Economic Model, Scenario 1 for Children Aged 0 to 14 Years

Model parameter	Mean	Distribution (parameters)	Reference
DNA methylation–based classifier test as a second-tier test			
Annual incidence of newly diagnosed CNS tumours	125	Fixed	Walker et al, 2023[75]; MOF, 2024[76]
Percentage of patients with CNS tumours who are challenging to diagnose	20	Uniform (0.15, 0.25)	Expert consultation[a]
DNA methylation–based classification results			
Concordant with conventional testing, %	70.5	Dirichlet (179;45;30) – 1	Clapper et al, 2018[23]
Percentage with refinement of diagnosis (improvement)	56.4	Beta (101, 78)	Clapper et al, 2018[23]
Percentage with no changes in classification	43.6	1 – Beta (101, 78)	Clapper et al, 2018[23]
Discordant with conventional testing, %	17.7	Dirichlet (179;45;30) – 2	Clapper et al, 2018[23]
Percentage with establishing new diagnosis (improvement)	91.1	Beta (41, 4)	Clapper et al, 2018[23]
Percentage with disregarded diagnosis (misleading)	8.9	1 – Beta (41, 4)	Clapper et al, 2018[23]
Unclassifiable results, %	11.8	Dirichlet (179;45;30) – 3	Clapper et al, 2018[23]

Abbreviations: CNS, central nervous system; DNA, deoxyribonucleic acid; MOF, Ontario Ministry of Finance.
[a]Andrew Gao, MD, written communication, January 2025.

Table 7: Clinical Inputs Used in the Economic Model, Scenario 2 for Patients With Glioblastoma

Model parameter	Mean	Distribution (parameters)	Reference
DNA methylation–based classifier test as a second-tier test			
Annual incidence of newly diagnosed glioblastoma	668	Fixed	Walker et al, 2023[75]; MOF, 2024[76]
Percentage of patients with glioblastoma who are challenging to diagnose	20	Uniform (0.15, 0.25)	Expert consultation[a]
DNA methylation–based classification results			
Concordant with conventional testing, %	81.6	Dirichlet (258;16;42) – 1	Clapper et al, 2018[23]
Percentage with refinement of diagnosis (improvement)	4.3	Beta (11, 247)	Clapper et al, 2018[23]
Percentage with no changes in classification	95.7	1 – Beta (11, 247)	Clapper et al, 2018[23]
Discordant with conventional testing, %	5.1	Dirichlet (258;16;42) – 2	Clapper et al, 2018[23]
Percentage with establishing new diagnosis(improvement)	87.5	Beta (14, 2)	Clapper et al, 2018[23]
Percentage with disregarded diagnosis (misleading)	12.5	1 – Beta (14, 2)	Clapper et al, 2018[23]
Unclassifiable results, %	13.3	Dirichlet (258;16;42) – 3	Clapper et al, 2018[23]

Abbreviations: CNS, central nervous system; DNA, deoxyribonucleic acid; MOF, Ontario Ministry of Finance.
[a]Andrew Gao, MD, written communication, January 2025.

Table 8: Clinical Inputs Used in the Economic Model, Scenario 3 for DNA Methylation–Based Classifier Tests as a First-Tier Test

Model Parameter	Mean	Distribution (parameters)	Reference
DNA methylation–based classifier test as a first-tier test			
Annual incidence of newly diagnosed CNS tumours	3,580	Fixed	Walker et al, 2023[75]; MOF, 2024[76]
DNA methylation–based classification results in patients with a recognized WHO histologic diagnosis, %	83.4	Beta (1602, 319)	Galbraith et al, 2023[45]
Complete diagnostic match, %	74.2	Dirichlet (1189; 225; 110; 78) – 1	Galbraith et al, 2023[45]
Diagnostic mismatch with discrepant tumour type and/or grade (improvement),[a] %	14.0	Dirichlet (1189; 225; 110; 78) – 2	Galbraith et al, 2023[45]
Adding additional prognostic information (improvement), %	0.069	Dirichlet (1189; 225; 110; 78)-3	Galbraith et al, 2023[45]
No match, %	0.049	Dirichlet (1189; 225; 110; 78) – 4	Galbraith et al, 2023[45]
DNA methylation–based classification results in patients with descriptive diagnoses (no WHO histologic diagnosis), %	16.6	1 – Beta (1602, 319)	Galbraith et al, 2023[45]
Providing a definitive diagnosis (improvement), %	85.6	Beta (273, 46)	Galbraith et al, 2023[45]
No match, %	14.4	1 – Beta (273, 46)	Galbraith et al, 2023[45]

Abbreviations: CNS, central nervous system; DNA, deoxyribonucleic acid; MOF, Ontario Ministry of Finance; WHO, World Health Organization.
[a]Galbraith et al used DNA methylation–based classifier test results to determine the final classification. We considered these cases as an improvement in classification.

Results

Reference Case Analysis

Using DNA methylation–based classifier tests as a second-tier test for newly diagnosed CNS tumours in Ontario would result in about 716 people receiving the test annually, with total test costs of $1,074,738 (95% CrI: $667,960–$1,595,901). It was expected that 195 (95% CrI: 145–248) patients would have an improved classification with DNA methylation–based classifier tests, including 111 (95% CrI: 81–145) people with a refined diagnosis (e.g., subclassification) and 84 (95%CrI: 60–111) with a new classification. The number needed to test (NNT)[85] is about 3.7 for the second-tier DNA methylation–based classifier tests. This suggests that, on average, 1 case with improved classification can be identified for every 3.7 people tested.

The ICER (i.e., incremental cost per case with improved CNS diagnosis) was $5,521 (Table 9). A definitive conclusion about the cost-effectiveness of DNA methylation–based classifier tests as a second-tier test is difficult to determine because there is no specific willingness-to-pay (WTP) value for 1 case with an improved diagnosis. However, given that the ICER was not high and the impact of DNA methylation–based classifier test results are long-term (e.g., patient management and treatment), it may be reasonable to consider that a second-tier DNA methylation–based classifier test is probably cost-effective for challenging diagnostic cases of CNS tumours (rationale provided in the Discussion).

Monte Carlo standard errors of incremental costs and the incremental number of CNS tumour cases with an improved classification were $763 and 0.09, respectively. Since the MCSEs were much smaller than the corresponding mean values and have minimal impact on the ICER, 100,000 iterations were likely adequate for the present probabilistic analysis.[82]

Table 9: Results for the Reference Case Analysis, Primary Economic Evaluation

Strategy	Average total costs (95% CrI)[a]	Incremental cost (95% CrI)[a,b]	Average total effects (95% CrI)[c]	Incremental effect (95% CrI)[b,c,d]	ICER[a,b,c]
Conventional tests	0	NA	0	NA	NA
DNA methylation–based classifier tests	1,074,738 (667,960–1,595,901)	1,074,738 (667,960–1,595,901)	195 (145–248)	195 (145–248)	5,521

Abbreviations: CrI, credible interval; ICER, incremental cost-effectiveness ratio; NA, not applicable.

[a]All costs in 2024 CAD. Incremental cost = average cost (strategy B) − average cost (strategy A).

[b]Results may appear inexact due to rounding.

[c]The effects were measured as the yearly number of patients with an improvement in diagnosis in Ontario when using second-tier DNA methylation–based classifier tests. The ICER was the incremental cost per CNS tumour case with an improved classification.

[d]Incremental effect = average effect (strategy B) − average effect (strategy A).

Scenario Analysis

We also conducted several scenario analyses (Table 10). For children aged 0 to 14 years with CNS tumours, the NNT was about 1.8 and the ICER was much lower, at $2,683 per case with an improved classification (Scenario 1). For glioblastoma, the ICER was much higher, at $19,286 per case with an improved classification (Scenario 2). Given that glioblastoma is the most common malignant CNS tumour, the implications of 1 case of glioblastoma with an improved diagnosis may not be the same as 1 case of benign CNS tumour with an improved diagnosis. When DNA methylation–based classifier tests are used as first-tier tests, more patients would receive the tests and the ICER was reduced to $3,634 (Scenario 3). The definitions of an improvement in diagnosis may vary across studies. The clinical data used for first- and second-tier DNA methylation–based classifier testing were based on different studies[23,45] and, as such, we cannot compare ICERs between them. For example, the majority of people with descriptive diagnoses (i.e., diagnosis not represented in the CNS WHO classification of tumours) were considered as the improvement in modelling the first-tier DNA methylation–based classifier test (based on Galbraith et al, 2023[45]), while the unclassifiable cases were not considered as the improvement in modelling the second-tier test (based on Capper et al, 2018[23]). Lastly, variations to the costs and effectiveness of DNA methylation–based classifier tests also impacted ICERs considerably (Scenarios 4 and 5).

The main uncertainty of the cost-effectiveness results was driven by the heterogeneity of CNS tumours. Different types and grades of CNS tumours have substantially different prognosis and patient management pathways. More recent and improved DKFZ classifier test versions released over the years may have more favorable cost-effectiveness results compared with our current estimates that are based on clinical data published in 2018.[23,84]

Table 10: Results for the Scenario Analysis, Primary Economic Evaluation

Strategy	Average total costs (95% CrI)[a]	Incremental cost (95% CrI)[a,b]	Average total effects (95% CrI)[c]	Incremental effect (95% CrI)[b,c,d]	ICER[a,b,c]
Reference case					
DNA methylation–based classifier test	1,074,738 (667,960–1,595,901)	1,074,738 (667,960–1,595,901)	195 (145–248)	195 (145–248)	5,521
Scenario 1, children (0–14 years)					
DNA methylation–based classifier test	37,521 (23,331–55,737)	37,521 (23,331–55,737)	14 (10–18)	14 (10–18)	2,683
Scenario 2, glioblastoma (most common type of malignant CNS tumour)					
DNA methylation–based classifier test	200,522 (124,770–297,812)	200,522 (124,770–297,812)	10 (6–16)	10 (6–16)	19,286
Scenario 3, DNA methylation–based classifier test as a first-tier test					
Conventional tests	7,091,315 (5,829,412–8,489,073)	NA	0	NA	NA
DNA methylation–based classifier test	11,208,673 (9,115,820–13,536,833)	4,117,358 (2,464,216–6,067,196)	1,133 (1,059–1,208)	1,133 (1,059–1,208)	3,634
Scenario 4-1: higher chance of an improved classification[e]					
DNA methylation–based classifier test	1,074,738 (667,960–1,595,901)	1,074,738 (667,960–1,595,901)	223 (166–285)	223 (166–285)	4,812
Scenario 4-2: lower chance of an improved classification					
DNA methylation–based classifier test	1,074,738 (667,960–1,595,901)	1,074,738 (667,960–1,595,901)	156 (116–199)	156 (116–199)	6,901
Scenario 5-1: higher cost for DNA methylation–based classifier tests					
DNA methylation–based classifier test	1,289,686 (801,552–1,915,081)	1,289,686 (801,552–1,915,081)	195 (145–248)	195 (145–248)	6,625
Scenario 5-2: lower cost for DNA methylation–based classifier tests					
DNA methylation–based classifier test	859,790 (534,368–1,276,721)	859,790 (534,368–1,276,721)	195 (145–248)	195 (145–248)	4,417

Abbreviations: CNS, central nervous system; CrI, credible interval; ICER, incremental cost-effectiveness ratio; NA, not applicable.

[a]All costs in 2024 CAD. Incremental cost = average cost (strategy B) − average cost (strategy A).

[b]Results may appear inexact due to rounding.

[c]The effects were measured as the yearly number of patients with an improved classification in Ontario when using first-tier (Scenario 3) and second-tier (other scenarios) DNA methylation–based classifier tests.

[d]Incremental effect = average effect (strategy B) − average effect (strategy A).

Discussion

Exploring the Cost-Effectiveness

Although the use of QALYs in cost-effectiveness analysis is generally preferred, it was not feasible to conduct a cost–utility analysis for DNA methylation–based classifier tests. There is a lack of data and methodology to quantify the health outcomes of improved classification that can be used for a cost effectiveness analysis. However, following Bayesian logic, we can apply new findings of a health technology into the context of existing health economic evidence.[86] A study on second-tier DNA methylation–based classifier tests based on 55 patients from Ontario showed that patient care was directly changed in 15% of all cases with major changes in clinical decision-making.[22] In addition, this study also found that when integrating second-tier DNA methylation–based classifier tests, unnecessary

treatment was avoided in 6.4% of patients, and insufficient treatment could be avoided in an additional 6.4% of patients.[22] DNA methylation–based classifier tests may have long-term downstream impacts on patient management and outcomes. Typically, long-term impact is associated with the potential of greater QALYs gained.[87] An Ontario population-based study that investigated the net cost for different types of cancer (i.e., cost attributable to cancer)[88] showed that the mean net costs of care for the initial 6 months of treatment after diagnosis were $33,241 and $30,683 (in 2009 CAD) for men and women with brain cancer, while the lifetime costs were $100,364 and $107,188, respectively. The literature on costs for patients with benign CNS tumours in Ontario is sparse. The costs of DNA methylation–based classifier tests are relatively low compared with CNS tumour treatment and care. Using DNA methylation–based classifier tests may help avoid other types of testing as well as unnecessary or inappropriate treatments for some patients. However, DNA methylation–based classifier tests may also be associated with additional treatments for patients who previously received inadequate or inappropriate treatments based on their conventional test results.[22] Given that the potential cost increase for adopting DNA methylation–based classification is relatively low, and there are potential long-term health benefits, it may be reasonable to consider that second-tier DNA methylation–based classifier tests are cost-effective for patients with challenging diagnostic cases of CNS tumours, compared with conventional testing alone.

DNA methylation–based classifier tests can be even more cost-effective for children. An Ontario population-based study showed that treating children with cancer was more costly than treating adults, and proper treatment may lead to greater health benefits.[89] Therefore, the relative cost of DNA methylation–based classifier tests versus cancer treatment would be even lower for children compared with adults. This is also reflected in our economic analysis, which showed that the cost for 1 improved CNS tumour classification for children ($2,683 per improved classification) was lower than that of the overall population in our reference case ($5,521 per improved classification).

Implementation Considerations

Similar to any diagnostic tool, DNA methylation–based classifier tests are not 100% accurate; however, they may provide more information than conventional testing alone. DNA methylation–based classifier tests are likely to continue to improve over time as more CNS tumours are classified and characterized. The DKFZ classifier test has been used in Ontario for several years at 2 hospitals, funded by research grants or hospital global budgets.

If DNA methylation–based classifier tests are publicly funded in Ontario, we anticipate that testing for all eligible CNS tumour cases will continue to be performed at a few hospitals that currently conduct testing. Furthermore, we do not anticipate any major barriers or risks to the implementation of public funding of second-tier DNA methylation–based classifier tests for CNS tumours, given the following considerations: 1) two Ontario hospital laboratories have already used DNA methylation–based classifier tests for several years and have the capacity to perform more tests; 2) while DNA methylation–based classifier tests may lead to misleading or unclassifiable results in a small number of cases, these results will likely be disregarded because test results are integrated with pathology results and the final classification is decided by physicians with clinical expertise; 3) DNA methylation–based classifier tests will likely not be overused due to their main role in challenging diagnostic CNS tumour cases; and 4) the total budget impact is moderate.

Equity Considerations

We included 1 scenario analysis for children and another for glioblastoma (the most common type of malignant primary CNS tumour). The greatest impact of improved classification may be for these subgroups. There are a number of requirements to perform DNA methylation–based classifier tests (e.g., highly skilled labors, high-tech laboratories, and high-cost equipment). As such, it is likely that only a small number of hospitals are well positioned to conduct this test in Ontario. If this test is funded publicly in Ontario, it is expected that all samples would need to be sent to these hospitals for testing.

Strengths and Limitations

Our study had the following strengths:

- Our key parameters, main model assumptions, and potential CNS tumour diagnostic pathways generally reflect the current clinical context in Ontario and were verified by clinical experts
- This study contributes to the economic analysis of CNS tumour classification and testing, an area that is currently sparse with limited published studies

The following limitations should be noted when interpreting the findings of this analysis:

- The clinical diagnostic pathway for CNS tumours may be more complex than what is reflected in our decision-analytic model structure. For example, DNA methylation–based classifier tests might not help resolve challenging or uncertain diagnostic cases of CNS tumours for a small number of patients and further testing may be warranted. There may also be additional tests conducted in the conventional testing strategy
- QALYs were not used as the health outcome of interest in our model due to a lack of data

Conclusions

Since there are no empirical willingness-to-pay thresholds for improvement in primary CNS tumour classification, the cost-effectiveness of DNA methylation–based classifier cannot be determined. However, given that second-tier DNA methylation–based classifier tests improve CNS tumour classification with moderate increased costs, second-tier DNA methylation–based classifier tests may be cost-effective for CNS tumour classification, and probably more cost-effective in children.

Budget Impact Analysis

Research Question

What is the potential 5-year budget impact for the Ontario Ministry of Health of publicly funding DNA methylation–based classifier tests as a second-tier test for challenging diagnostic cases of CNS tumours?

Methods

Analytic Framework

We estimated the budget impact of publicly funding DNA methylation–based classification using the cost difference between 2 scenarios: (1) current clinical practice without specific public funding for DNA methylation–based classification (the current scenario), and (2) anticipated clinical practice with public funding for DNA methylation–based classification as a second-tier test (the new scenario). Figure 4 presents the budget impact model schematic.

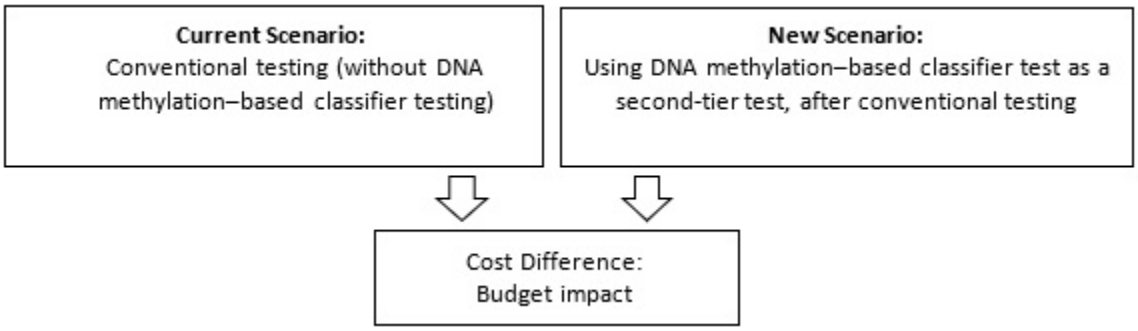

Figure 4: Schematic Model of Budget Impact

Flow chart describing the model for the budget impact analysis. The current scenario would explore resource use and total costs without public funding for DNA methylation–based classifier tests. The new scenario would explore resource use and total costs with public funding for second-tier DNA methylation–based classifier tests. The budget impact would represent the difference in costs between the two scenarios.

Key Assumptions

In addition to the assumptions made in our primary economic evaluation, our budget impact analysis included the following assumptions:

- Only people with newly diagnosed primary central nervous system (CNS) tumours receive a DNA methylation–based classifier test
- People receiving a DNA methylation–based classifier test generally do not need to undergo any repeat testing
- There are no licensing fees associated with using the DNA methylation–based classifier test

Population of Interest

There were 45,115 patients diagnosed with primary CNS tumours between 2010 and 2017 in Canada (excluding Quebec), and the average annual age-standardized incidence rate (ASIR) was 21.48 per 100,000 person-years (95% CI: 21.28–21.67).[75] Around 35.7% of these patients had malignant CNS tumours, and the remining were non-malignant (including benign and uncertain). Around 19% of these patients had unclassified CNS tumours, which are tumours without sufficient information on pathology to determine the histology group. Unclassified tumours cannot be determined as malignant or non-malignant.

The ASIR of primary CNS tumours did not change substantially between 2011 and 2017 in Canada (see Supplementary Figure S1 in Walker et al[75]). For simplicity, we assumed that the annual ASIR of primary CNS tumours would remain constant over the next 5 years. We then approximated the annual number of people with newly diagnosed primary CNS tumours by multiplying the average annual ASIR by the projected population size over the next 5 years.[75,76] We estimated that 20% of CNS tumours would be challenging diagnostic cases (Andrew Gao, MD, written communication, February 2025), resulting in an estimated 3,579 cases over the 5-year period (see Table 11). We further explored the budget impact of publicly funding first- and second-tier DNA methylation–based classifier tests for only malignant CNS tumours in the scenario analyses.[75]

Table 11: Projected Annual Incidence of Primary CNS Tumours in Ontario, 2025 to 2029 (Reference Case)

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Corresponding calendar year	2025	2026	2027	2028	2029	NA
Population projection in Ontario	16,411,616	16,570,493	16,667,124	16,747,707	16,916,618	NA
Annual age-standardized incidence rate (per 100,000 person-years)	21.48	21.48	21.48	21.48	21.48	NA
Newly diagnosed primary CNS tumours	3,525	3,559	3,580	3,597	3,634	17,895
Newly diagnosed primary CNS cancers (i.e., malignant tumours)	1,258	1,271	1,278	1,284	1,297	6,388
Challenging cases (%)	20	20	20	20	20	NA
Challenging cases (n)	**705**	**712**	**716**	**719**	**727**	**3,579**

Abbreviations: CNS, central nervous system; NA, not applicable.

We also conducted scenario analyses for the budget impact of publicly funding DNA methylation–based classifier tests for children and glioblastomas. For children aged 0 to 14 years, the average annual ASIR was 5.30 per 100,000 person-years (95% CI: 5.06–5.54).[75] We therefore estimated that there will be around 627 newly diagnosed primary CNS tumours in children over the next 5 years, of which 125 will be challenging diagnostic cases (see Table 12).

Table 12: Projected Annual Incidence of Primary CNS Tumours in Children (0 to 14 Years) in Ontario, 2025 to 2029 (Scenario 1)

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Corresponding calendar year	2025	2026	2027	2028	2029	NA
Population projection in Ontario	2,358,447	2,365,570	2,367,807	2,369,679	2,376,160	NA
Annual age-standardized incidence rate (per 100,000 person-years)	5.30	5.30	5.30	5.30	5.30	NA
Newly diagnosed primary CNS tumours	125	125	125	126	126	627
Challenging cases (%)	20	20	20	20	20	NA
Challenging cases (n)	25	25	25	25	25	125

Abbreviations: CNS, central nervous system; NA, not applicable.

We used the average annual ASIR of 4.01 per 100,000 person-years (95% CI: 3.93–4.09) to determine the size of challenging diagnostic cases of glioblastomas.[75] We estimated that Ontario will see around 3,340 people with newly diagnosed glioblastomas over the next 5 years, of which 669 will be challenging diagnostic cases (see Table 13).

Table 13: Projected Annual Incidence of Glioblastoma in Ontario, 2025 to 2029 (Scenario 2)

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Corresponding calendar year	2025	2026	2027	2028	2029	NA
Population projection in Ontario	16,411,616	16,570,493	16,667,124	16,747,707	16,916,618	NA
Annual age-standardized incidence rate (per 100,000 person-years)	4.01	4.01	4.01	4.01	4.01	NA
Newly diagnosed primary glioblastoma[a]	658	664	668	672	678	3,340
Challenging cases (%)	20	20	20	20	20	NA
Challenging cases (n)	132	133	134	134	136	669

Abbreviations: CNS, central nervous system; NA, not applicable.

[a]Primary glioblastoma is the most common and aggressive type of malignant CNS tumour.

Current Intervention Mix

Currently, DNA methylation–based classifier tests for CNS tumours are being used at 2 hospitals in Ontario; use is largely dependent on the global hospital budget or available research funding. Given that DNA methylation–based classifier tests are not currently publicly funded for the classification of CNS tumours, we assumed that there would be no cost to the Ministry of Health in the current scenario.

Uptake of the New Intervention and New Intervention Mix

If publicly funded, we expect that the uptake of DNA methylation–based classifier tests will be 100% for Years 1 to 5 (see Table 14). This assumption is based on the following considerations: 1) DNA methylation–based classifier tests are already being performed in Ontario, and 2) there is existing infrastructure and expertise for DNA methylation–based classifier tests. As such, we do not expect any major implementation barriers across the province for our populations of interest.

Table 14: Uptake and Volumes of New Intervention in Ontario, Reference Case

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Current scenario						
Volume of DNA methylation–based classifier tests	0	0	0	0	0	NA
New scenario						
Uptake rate	100%	100%	100%	100%	100%	NA
Volume of DNA methylation–based classifier tests[a]	705	712	716	719	727	3,579

Definition: NA, not applicable.

[a]The volume of interventions was calculated from the total number of interventions multiplied by the uptake rate of the new Intervention. For example, in the new scenario, the total volume in Year 1 is 705 and the uptake rate of DNA methylation–based classifier tests is 100%, so the volume of DNA methylation–based classifier tests in year 1 is 705 (705 × 100%).

Resources and Costs

On average, the cost of DNA methylation–based classifier testing was $1,500 per patient, and the cost of conventional testing (i.e., histology, IHC, FISH, and DNA sequencing) was $1,981.73 per patient. For additional details, please see the “Cost Parameters” section of the Primary Economic Evaluation, above. When DNA methylation–based classifier tests are used as a second-tier test, we did not account for the cost of conventional testing in our analysis since there is no change to the use of conventional testing for our population of interest. When DNA methylation–based classifier tests are used as a first-tier test (Scenario 3), the cost of this test remains at $1,500 per patient, but the cost of conventional testing is reduced to $1,632.69 per patient, accounting for the replacement of FISH tests. In this scenario, the incremental cost of DNA methylation–based classifier testing compared with conventional testing alone (at $1,981.73) decreases to $1,150.96 per patient. All costs are reported in 2024 CAD.

Internal Validation

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

Analysis

We conducted a reference case analysis and sensitivity analyses. Our reference case analysis represents the analysis with the most likely set of input parameters and model assumptions. Our sensitivity analyses explored how our results are affected by varying input parameters and model assumptions. For all scenarios except Scenario 7, which has a lower uptake rate, we assumed the same uptake rate (100%) as our reference case.

- **Scenario 1, subgroup analysis, children (0 to 14 years old):** the estimates for the size of this population can be found in Table 12
- **Scenario 2, subgroup analysis, glioblastoma:** (most common type of malignant CNS tumour)**:** the estimates for the size of this population can be found in Table 13
- **Scenario 3, DNA methylation–based classifier test as a first-tier test:** the estimates for the size of this population can be found in Table 11 ("Newly diagnosed primary CNS tumours")
- **Scenario 4, DNA methylation–based classifier test for people with CNS cancer:** the estimates for the size of this population can be found in Table 11 ("Newly diagnosed primary CNS cancers")
- **Scenario 5, higher and lower costs for the DNA methylation–based classifier test:** The costs of DNA methylation–based classifier tests may increase (e.g., due to licensing fees, the capital cost of molecular testing equipment, and costs of potential further testing for discordant or unclassifiable results) or decrease (e.g., due to more streamlined or efficient testing). In this scenario, we varied costs by ± 20%
- **Scenario 6, inflation-adjusted budget impact:** Adjusting the yearly budget impact for inflation may provide a more accurate financial prediction in the future.[90,91] We expected that the consumer price index (CPI) inflation rate (year-over-year percentage change) would be about 2% for 2025 (the first budget year in our analysis) over 2024 (when we conducted the analysis).[92] In this scenario, we assumed that the yearly CPI inflation rate would remain at 2% over the 5-year period
- **Scenario 7, a lower uptake rate:** Physicians may require an adjustment period for incorporating DNA methylation–based classifier test results into their practice, particularly for referral cases. We therefore considered a lower uptake in this scenario (40% in Year 1, increasing 10% each year to 80% in Year 5)
- **Scenario 8, increased need for DNA methylation–based classifier tests:** This scenario considers factors that may lead to more CNS tumours requiring DNA methylation–based classifier testing. For example, DNA methylation–based classifier tests may be used for patients with previously diagnosed CNS tumours, recurrences, or metastasis or there may be a greater number of newly primary diagnosed CNS tumours referred for DNA methylation–based classifier testing. In this scenario, we assumed that our population of interest will increase by 25% each year

Results

Reference Case

Results of the budget impact analysis for our reference case are presented in Table 15. The total cost in the current scenario was assumed to be $0, as DNA methylation–based classifier tests are currently not publicly funded for CNS tumours. Publicly funding second-tier DNA methylation–based classifier tests for challenging diagnostic cases of CNS tumours would result in an annual budget impact of an additional $1 million per year. The total 5-year budget impact of publicly funding DNA methylation–based classifier tests is an additional $5.37 million for testing approximately 3,600 patients with challenging diagnostic cases of CNS tumours.

Table 15: Budget Impact Analysis Results, Reference Case

Scenario	Budget impact, $ million[a]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total[b]
Current scenario	0	0	0	0	0	0
New scenario	1.06	1.07	1.07	1.08	1.09	5.37
Budget impact[b,c]	1.06	1.07	1.07	1.08	1.09	5.37

[a]All costs in 2024 CAD.

[b]Results may appear inexact due to rounding.

Sensitivity Analysis

Table 16 summarizes the results of the scenarios conducted for our budget impact analysis.

Overall, the budget impact of publicly funding DNA methylation–based classifier tests for children and glioblastomas were low. The 5-year budget impact of publicly funding DNA methylation–based classifier testing as a second-tier test was an additional $0.19 million and $1 million in children (Scenario 1) and in glioblastomas (Scenario 2), respectively.

If first-tier DNA methylation–based classifier tests are used for all newly diagnosed CNS tumours (Scenario 3), then the annual budget impact is estimated to be an additional approximately $4 million for testing 3,500 to 3,600 CNS tumours each year. The total 5-year budget impact of publicly funding first-tier DNA methylation–based classifier tests is an additional $20.60 million for testing a total of 17,895 CNS tumours.

If public funding of DNA methylation–based classifier tests is restricted to people with malignant CNS tumours (Scenario 4), the budget impact would be lower than the reference case. On the other hand, an annual inflation rate of 2% over the next 5 years (Scenario 6) would increase the total 5-year budget impact by $5.70 million. Lastly, a 25% annual increase in the size of our population of interest (Scenario 8) would increase the total 5-year budget impact by $6.71 million.

Although we did not explicitly define a scenario with a lower estimate of challenging CNS tumour cases for classification, the budget impact from the subgroup analyses in Scenario 2 (glioblastoma) and Scenario 4-1 (second-tier testing for CNS cancer) may be interpreted as representing cases where 4% and 7%, respectively, were considered challenging to classify.

Table 16: Budget Impact Analysis Results, Scenario Analyses

Scenario	Budget impact, $ million[a]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total[b]
Reference case						
Budget impact	1.06	1.07	1.07	1.08	1.09	5.37
Scenario 1, children (0–14 years) with CNS tumours						
Budget impact	0.04	0.04	0.04	0.04	0.04	0.19
Scenario 2, glioblastoma (most common type of malignant CNS tumour)						
Budget impact	0.20	0.20	0.20	0.20	0.20	1.00
Scenario 3, first-tier DNA methylation–based classifier tests for CNS tumours						
Current scenario	6.99	7.05	7.09	7.13	7.20	35.46
New scenario	11.04	11.15	11.22	11.27	11.38	56.06
Budget impact[b]	4.06	4.10	4.12	4.14	4.18	20.60
Scenario 4-1, second-tier DNA methylation–based classifier tests for CNS cancers						
Budget impact[b]	0.38	0.38	0.38	0.39	0.39	1.92
Scenario 4-2, first-tier DNA methylation–based classifier tests for CNS cancers						
Current scenario	2.57	2.60	2.61	2.62	2.65	13.05
New scenario	4.02	4.06	4.08	4.10	4.14	20.40
Budget impact[b]	1.45	1.46	1.47	1.48	1.49	7.35
Scenario 5-1: increased cost of DNA methylation–based classifier tests for CNS tumours						
Budget impact	1.27	1.28	1.29	1.29	1.31	6.44
Scenario 5-2: decreased cost of DNA methylation–based classifier tests for CNS tumours						
Budget impact	0.85	0.85	0.86	0.86	0.87	4.29
Scenario 6, inflation-adjusted budget impact for CNS tumours						
Budget impact	1.08	1.11	1.14	1.17	1.20	5.70
Scenario 7, a lower uptake rate						
Budget impact	0.42	0.53	0.65	0.75	0.87	3.23
Scenario 8, increased target population for DNA methylation–based classifier tests						
Budget impact	1.32	1.34	1.34	1.35	1.36	6.71

Definition: CNS, central nervous system.

[a]All costs in 2024 CAD.

[b]Results may appear inexact due to rounding.

Discussion

We estimated that the annual budget increase of adopting a second-tier DNA methylation–based classifier test will be around $1 million in Ontario. The overall 5-year budget impact is relatively low, at an additional $5.37 million. In 2021, CNS cancers cost Canada $498 million in direct costs to the health care system. Given that Ontario accounts for 39% of the population of Canada, we estimated that CNS cancers cost Ontario about $194 million in direct health care costs ($498 million × 39%).[93] Publicly funding second-tier DNA methylation–based classifier tests would therefore increase the current health

care funding for CNS cancers by around 0.5% ($1 million ÷ $194 million) when not accounting for the downstream impact of this test.

This budget increase would be even lower if public funding of DNA methylation–based classifier tests is restricted to only challenging diagnostic cases in 1) children with CNS tumours, 2) glioblastomas, or 3) malignant CNS tumours.

Lastly, conventional testing is sufficient for most CNS tumour classification (and sub-classification) cases. The additional benefit of first-tier DNA methylation–based classifier tests is therefore limited for most CNS tumours. As such, using DNA methylation–based classification as a second-tier test for challenging diagnostic cases of CNS tumours may be more resource-efficient than using it as a first-tier test for all CNS tumours.

Equity Considerations

We conducted scenario analyses for 2 subgroups of our population: challenging diagnostic cases in children with CNS tumours and in glioblastomas. Improved classification may have a larger impact for these 2 subgroups.

Strengths and Limitations

Our study had the following strengths:

- We consulted several stakeholders to understand the current funding status and context of using DNA methylation–based classifier tests in Ontario
- Our key parameters and main assumptions were verified by clinical experts in Ontario

The following limitations should be noted when interpreting the findings of this analysis:

- Challenging diagnostic cases are difficult to define and there is uncertainty in the population size estimate. Cases are dependent on clinical expertise and may vary
- Downstream treatment costs due to improved classification were not incorporated in our analysis because of the complexity of different types of CNS tumours and the lack of published data

Conclusions

We estimated that publicly funding second-tier DNA methylation–based classifier tests for the classification of primary CNS tumours would result in an annual budget increase of around $1 million each year, for a total 5-year budget impact of around $5.4 million to test 3,600 patients. If DNA methylation-based classifiers are used as first-tier tests for all patients with newly diagnosed primary CNS tumours, the annual budget impact increase would be around $4 million per year, with the total budget impact of around an additional $21 million over the initial 5-year period.

Patient Preferences and Values Evidence

Background

Exploring patient preferences and values provides a unique source of information about people's experiences of a health condition and the health technologies or interventions used to manage or treat the health condition. It includes the impact of the condition and its treatment on the person with the health condition, their family and other care partners, 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).[94-96] Additionally, lived experience can provide information and perspectives on the ethical and social values implications of health technologies or interventions.

DNA Methylation–Based Classification

For the current health technology assessment, we determined the scope and direction of patient and public engagement using a formal needs assessment. The purpose of this needs assessment was threefold:

- To determine if obtaining lived-experience information about DNA methylation–based classifier tests would be of value in understanding the impact of this technology
- If lived-experience information was of value, then to determine goals and objectives for patient engagement to obtain this information
- To scope out the optimal engagement activity

To complete the needs assessment, we completed background research on the topic in question, which included reviewing the clinical review plan and consulting clinical experts. As we refined the needs assessment, we consulted with lived-experience advisors on the Ontario Genetics Advisory Committee and the Ontario Health Technology Advisory Committee.

Through this consultation and the needs assessment, we determined that lived-experience information related to patient preferences and values for DNA methylation–based classifier tests would provide limited additional evidence to guide decision-making after considering the following factors:

- **Patient preferences and values in decision-making:** Patient engagement can often illuminate the context for patient preferences related to a technology and how patients make decisions surrounding its use. We concluded that it is unlikely that patient preferences and choices about DNA methylation–based classifier tests would affect whether it was used or not. The clinical experts we spoke with suggested that patients have no direct input or influence on decision-making when it comes to the use (or non-use) of this type of technology in their care. Further, patients are likely unable to distinguish between conventional testing and DNA methylation–based classifier tests

- **Direct effect on patients:** Health technology assessments typically involve devices or procedures that directly interact and affect a patient's physical state. For example, a device can be inserted or worn, or a procedure can be performed that can cause or relieve symptoms. Direct patient engagement to determine preferences and values for these treatments can illuminate among other things the outcomes most desired by patients and provide insights into their own decision-making framework for their health care. For DNA methylation–based classifier tests, the testing process itself does not directly affect the patient's physical state. It is a diagnostic tool used by a physician to classify tumours after a biopsy. Because of this, the types of patient insights and preferences informative for some health technologies such as how the technology feels, is used, or directly affects their quality of life are not relevant for DNA methylation–based classifier tests.
- **Patient outcomes:** A key component of health technology assessment is evaluating the impact of the technology on important patient outcomes. Direct patient engagement can often provide information about which outcomes are most important and relevant to patients. DNA methylation–based classifier test evidence reported in this HTA informed evaluation of outcomes including improved (more precise) results, downstream impact of testing, time to diagnosis or time to treatment, and test turnaround time. The findings of our needs assessment indicated these outcomes are relevant and important to patients. Because of this, we concluded that direct patient engagement to further elucidate relevant outcomes was not needed.

After careful consideration of these factors and through consultations, we concluded that direct patient engagement would provide limited additional evidence or impact to guide decision making.

Conclusions of the Health Technology Assessment

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

We did not identify any studies that evaluated the cost-effectiveness of DNA methylation–based classifier tests for CNS tumour classification. Our primary economic evaluation showed that the incremental cost per case with an improvement in primary CNS tumour classification was $5,521. 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.

We estimated that publicly funding second-tier DNA methylation–based classifier tests for challenging diagnostic primary CNS tumours would result in an annual budget increase of around $1 million each year, for a total 5-year budget impact of around $5.4 million to test 3,600 patients. If DNA methylation-based classifiers are used as first-tier tests for all patients with newly diagnosed primary CNS tumours, the annual budget increase would be around $4 million per year, with the total budget impact of around an additional $21 million over the initial 5-year period.

Direct patient engagement was not conducted because it was concluded that it would provide limited additional evidence or impact to guide decision-making.

Abbreviations

AI: artificial intelligence

ASIR: age-standardized incidence rate

CHEERS: Consolidated Health Economic Evaluation Reporting Standards

CI: confidence interval

CNS: central nervous system

CrI: credible interval

CT: conventional treatment

DKFZ: Deutsches Krebsforschungszentrum (German Cancer Research Center)

FISH: fluorescence in situ hybridization

GRADE: Grading of Recommendations Assessment, Development, and Evaluation

ICER: incremental cost-effectiveness ratio

IDH: isocitrate dehydrogenase

IHC: immunohistochemistry

MCSE: Monte Carlo standard error

MGMT: O^6-methylguanine-DNA methyltransferase

NICE: National Institute for Health and Care Excellence

NNT: number needed to test

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses

QALY: quality-adjusted life-year

RCT: randomized controlled trial

WHO: World Health Organization

WTP: willingness-to-pay

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., the affordability of the new intervention). It is based on predictions of how changes in the intervention mix will 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).

Cost–benefit analysis: A cost–benefit analysis is a type of economic evaluation that expresses the effects of a health care intervention in terms of a monetary value so that these effects can be compared with costs. Results can be reported either as a ratio of costs to benefits or as a simple sum that represents the net benefit (or net loss) of one intervention over another. The monetary valuation of the different intervention effects is based on either prices that are revealed by markets or an individual or societal willingness-to-pay value.

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 analysis. It illustrates the probability of health care interventions being cost-effective over a range of 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 is 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 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–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, 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.

Decision tree: A decision tree is a type of economic model used to assess the costs and benefits of two or more alternative health care interventions. Each intervention may be associated with different outcomes, which are represented by distinct branches in the tree. Each outcome may have a different probability of occurring and may lead to different costs and benefits.

Discounting: Discounting is 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 use an annual discount rate of 1.5% for both future costs and future benefits.

Dominant: A health care intervention is considered dominant when it is more effective and less costly than its comparator(s).

Equity: Unlike the notion of equality, equity is not about treating everyone the same way.[97] It denotes fairness and justice in process and in results. Equitable outcomes often require differential treatment and resource redistribution to achieve a level playing field among all individuals and communities. This requires recognizing and addressing barriers to opportunities for all to thrive in our society.

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.

Horizontal equity: Horizontal equity requires that people with like characteristics (of ethical relevance) be treated the same.

Incremental cost: The 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 health care consumer must pay to get an additional unit of benefit relative to an alternative intervention. It is obtained by dividing the incremental cost by the 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 costs and health benefits to include. Ontario Health 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).

Monte Carlo simulation: Monte Carlo simulation is an economic modelling method that derives parameter values from distributions rather than fixed values. The model is run several times, and in each iteration, parameter values are drawn from specified distributions. This method is used in microsimulation models and probabilistic analysis.

Probabilistic analysis: A probabilistic analysis (also known as a probabilistic sensitivity analysis) is used in economic models to explore uncertainty in several parameters simultaneously and 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.

Quality-adjusted life-year (QALY): The quality-adjusted life-year (QALY) 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.

Random forest algorithm: A supervised machine learning algorithm used for both classification, regression, and other tasks. It uses an ensemble method that combines the predictions of multiple decision trees to make more accurate predictions.

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 involve 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.

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.

Uptake rate: In instances where two technologies are being compared, the uptake rate is the rate at which a new technology is adopted. When a new technology is adopted, it may be used in addition to an existing technology, or it may replace an existing technology.

Utility: A utility is a value that represents a person's preference 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.

Vertical equity: Vertical equity allows for people with different characteristics (of ethical relevance) to be treated differently.

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: May 10, 2024

Databases searched: Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, NHS Economic Evaluation Database

Database segments: EBM Reviews - Cochrane Central Register of Controlled Trials <April 2024>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to May 8, 2024>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2024 Week 18>, Ovid MEDLINE(R) ALL <1946 to May 09, 2024>
Search Strategy:
---
1 exp Central Nervous System Neoplasms/ (637867)
2 ((brain* or central nervous system* or CNS or spinal cord*) adj3 (adenocarcinoma* or adenoma* or blastoma* or cancer* or carcinoma* or malignan* or metasta* or neoplasm* or oncolog* or tumo?r*)).ti,ab,kf. (274104)
3 exp Neoplasms, Neuroepithelial/ (155620)
4 (astroblastoma* or astrocytoma* or ependymoma* or ganglioglioma* or glioblastoma* or glioma* or medulloblastoma* or meningioma* or neuroblastoma* or neurocytoma* or neuroepithelioma* or neurofibroma* or neuro oncolog* or neurooncolog* or neuro patholog* or neuropatholog* or oligodendroglioma* or ((ependymal* or glial cell or intracrani* or meningeal* or neuroepithelial* or pineal* or (teratoid* adj2 rhabdoid*)) adj2 (adenoma* or blastoma* or neoplasm* or tumo?r*)) or AT?RT).ti,ab,kf. (611381)
5 or/1-4 (1026587)
6 DNA Methylation/ and (algorithm* or classifi* or pattern* or profil* or sequenc*).ti,ab,kf. (80722)
7 ((DNA meth* or DNAm or methyl*) adj3 (algorithm* or classifi* or pattern* or profil* or sequenc*)).ti,ab,kf. (55967)
8 DNA Methylation/ and Epigenomics/ (37201)
9 (methyl* adj3 (epigenet* or epigenom*)).ti,ab,kf. (11420)
10 (methyl* adj3 (based or tumo?r) adj3 (classifi* or profil*)).ti,ab,kf. (1483)
11 (methyl* adj5 ("450K" or "850K" or beadchip* or bead chip* or EPIC* or illumina* or infinium*)).ti,ab,kf. (8785)
12 ((MNP or "MNP2.0" or "MNP 2.0" or molecular neuropathol* or molecularneuropathol*) adj5 (classifi* or methyl* or profil*)).ti,ab,kf. (307)
13 ((Bethesda or c?IMPACT* or DKFZ or Deutsches Krebsforschungszentrum* or German Cancer Research Cent* or Heidelberg or NIH or National Institutes of Health or Northwestern Medicine or St Jude*) adj5 (classifi* or methyl* or profil*)).ti,ab,kf. (3543)
14 (human methylation* or humanmethylation* or methylation epic* or methylationepic*).ti,ab,kf. (6874)
15 ((beadchip* or bead chip* or EPIC* or infinium*) adj3 (array* or classifi* or microarray* or profil*)).ti,ab,kf. (5961)

16 (illumina* adj3 ("450K" or "850K" or array* or beadchip* or bead chip* or classifi* or EPIC* or microarray* or profil*)).ti,ab,kf. (15471)
17 or/6-16 (144559)
18 5 and 17 (8636)
19 exp Animals/ not Humans/ (16503966)
20 18 not 19 (7115)
21 Case Reports/ or Comment.pt. or Editorial.pt. or (Letter not (Letter and Randomized Controlled Trial)).pt. or Congress.pt. (6672608)
22 20 not 21 (6892)
23 limit 22 to english language [Limit not valid in CDSR; records were retained] (6816)
24 limit 23 to yr="2018 -Current" (4937)
25 24 use medall,coch,cctr,cleed (1269)
26 exp central nervous system tumor/ (637867)
27 ((brain* or central nervous system* or CNS or spinal cord*) adj3 (adenocarcinoma* or adenoma* or blastoma* or cancer* or carcinoma* or malignan* or metasta* or neoplasm* or oncolog* or tumo?r*)).tw,kw,kf. (278946)
28 exp neuroepithelioma/ (4374)
29 (astroblastoma* or astrocytoma* or ependymoma* or ganglioglioma* or glioblastoma* or glioma* or medulloblastoma* or meningioma* or neuroblastoma* or neurocytoma* or neuroepithelioma* or neurofibroma* or neuro oncolog* or neurooncolog* or neuro patholog* or neuropatholog* or oligodendroglioma* or ((ependymal* or glial cell or intracrani* or meningeal* or neuroepithelial* or pineal* or (teratoid* adj2 rhabdoid*)) adj2 (adenoma* or blastoma* or neoplasm* or tumo?r*)) or AT?RT).tw,kw,kf. (612298)
30 or/26-29 (1010717)
31 *DNA Methylation/ and (algorithm* or classifi* or pattern* or profil* or sequenc*).tw,kw,dv,kf. (38039)
32 ((DNA meth* or DNAm or methyl*) adj3 (algorithm* or classifi* or pattern* or profil* or sequenc*)).tw,kw,dv,kf. (56230)
33 *dna methylation/ and *epigenetics/ (3796)
34 dna methylation/ and classifier/ (553)
35 (methyl* adj3 (epigenet* or epigenom*)).tw,kw,dv,kf. (15919)
36 (methyl* adj3 (based or tumo?r) adj3 (classifi* or profil*)).tw,kw,dv,kf. (1485)
37 (methyl* adj5 ("450K" or "850K" or beadchip* or bead chip* or EPIC* or illumina* or infinium*)).tw,kw,dv,kf. (8964)
38 ((MNP or "MNP2.0" or "MNP 2.0" or molecular neuropathol* or molecularneuropathol*) adj5 (classifi* or methyl* or profil*)).tw,kw,dv,kf. (311)
39 ((Bethesda or c?IMPACT* or DKFZ or Deutsches Krebsforschungszentrum* or German Cancer Research Cent* or Heidelberg or NIH or National Institutes of Health or Northwestern Medicine or St Jude*) adj5 (classifi* or methyl* or profil*)).tw,kw,dv,kf. (3569)
40 (human methylation* or humanmethylation* or methylation epic* or methylationepic*).tw,kw,dv,kf. (7062)
41 ((beadchip* or bead chip* or EPIC* or infinium*) adj3 (array* or classifi* or microarray* or profil*)).tw,kw,dv,kf. (6064)
42 (illumina* adj3 ("450K" or "850K" or array* or beadchip* or bead chip* or classifi* or EPIC* or microarray* or profil*)).tw,kw,dv,kf. (15943)
43 or/31-42 (103526)
44 30 and 43 (5932)
45 (exp animal/ or nonhuman/) not exp human/ (12126081)

46 44 not 45 (5775)
47 Case Report/ or Comment/ or Editorial/ or (letter.pt. not (letter.pt. and randomized controlled trial/)) or conference abstract.pt. or conference review.pt. (11708733)
48 46 not 47 (3792)
49 limit 48 to english language [Limit not valid in CDSR; records were retained] (3733)
50 limit 49 to yr="2018 -Current" (2276)
51 50 use emez (1122)
52 25 or 51 (2391)
53 52 use medall (1227)
54 52 use coch (0)
55 52 use cctr (42)
56 52 use cleed (0)
57 52 use emez (1122)
58 remove duplicates from 52 (1516)

Economic Evidence Search

Search Date: May 14, 2024

Databases searched: Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, NHS Economic Evaluation Database

Database segments: EBM Reviews - Cochrane Central Register of Controlled Trials <April 2024>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to May 8, 2024>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2024 Week 19>, Ovid MEDLINE(R) ALL <1946 to May 10, 2024>

Search Strategy:
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1 exp Central Nervous System Neoplasms/ (638322)
2 ((brain* or central nervous system* or CNS or spinal cord*) adj3 (adenocarcinoma* or adenoma* or blastoma* or cancer* or carcinoma* or malignan* or metasta* or neoplasm* or oncolog* or tumo?r*)).ti,ab,kf. (274274)
3 exp Neoplasms, Neuroepithelial/ (155659)
4 (astroblastoma* or astrocytoma* or ependymoma* or ganglioglioma* or glioblastoma* or glioma* or medulloblastoma* or meningioma* or neuroblastoma* or neurocytoma* or neuroepithelioma* or neurofibroma* or neuro oncolog* or neurooncolog* or neuro patholog* or neuropatholog* or oligodendroglioma* or ((ependymal* or glial cell or intracrani* or meningeal* or neuroepithelial* or pineal* or (teratoid* adj2 rhabdoid*)) adj2 (adenoma* or blastoma* or neoplasm* or tumo?r*)) or AT?RT).ti,ab,kf. (611680)
5 or/1-4 (1027146)
6 DNA Methylation/ and (algorithm* or classifi* or pattern* or profil* or sequenc*).ti,ab,kf. (80788)
7 ((DNA meth* or DNAm or methyl*) adj3 (algorithm* or classifi* or pattern* or profil* or sequenc*)).ti,ab,kf. (56009)
8 DNA Methylation/ and Epigenomics/ (37237)
9 (methyl* adj3 (epigenet* or epigenom*)).ti,ab,kf. (11425)

10 (methyl* adj3 (based or tumo?r) adj3 (classifi* or profil*)).ti,ab,kf. (1483)
11 (methyl* adj5 ("450K" or "850K" or beadchip* or bead chip* or EPIC* or illumina* or infinium*)).ti,ab,kf. (8791)
12 ((MNP or "MNP2.0" or "MNP 2.0" or molecular neuropathol* or molecularneuropathol*) adj5 (classifi* or methyl* or profil*)).ti,ab,kf. (307)
13 ((Bethesda or c?IMPACT* or DKFZ or Deutsches Krebsforschungszentrum* or German Cancer Research Cent* or Heidelberg or NIH or National Institutes of Health or Northwestern Medicine or St Jude*) adj5 (classifi* or methyl* or profil*)).ti,ab,kf. (3550)
14 (human methylation* or humanmethylation* or methylation epic* or methylationepic*).ti,ab,kf. (6878)
15 ((beadchip* or bead chip* or EPIC* or infinium*) adj3 (array* or classifi* or microarray* or profil*)).ti,ab,kf. (5965)
16 (illumina* adj3 ("450K" or "850K" or array* or beadchip* or bead chip* or classifi* or EPIC* or microarray* or profil*)).ti,ab,kf. (15475)
17 or/6-16 (144679)
18 5 and 17 (8656)
19 exp Animals/ not Humans/ (16507108)
20 18 not 19 (7135)
21 Case Reports/ or Congress.pt. (2635819)
22 20 not 21 (7012)
23 limit 22 to english language [Limit not valid in CDSR; records were retained] (6936)
24 limit 23 to yr="2018 -Current" (5040)
25 24 use coch,cleed (0)
26 economics/ (265163)
27 economics, medical/ or economics, pharmaceutical/ or exp economics, hospital/ or economics, nursing/ or economics, dental/ (1096478)
28 economics.fs. (472868)
29 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).ti,ab,kf. (1357284)
30 exp "costs and cost analysis"/ (710777)
31 (cost or costs or costing or costly).ti. (346381)
32 cost effective*.ti,ab,kf. (481685)
33 (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* or increment*)).ab,kf. (326802)
34 models, economic/ (16469)
35 markov chains/ or monte carlo method/ (112258)
36 (decision adj1 (tree* or analy* or model*)).ti,ab,kf. (72960)
37 (markov or markow or monte carlo).ti,ab,kf. (188754)
38 quality-adjusted life years/ (59120)
39 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).ti,ab,kf. (119936)
40 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).ti,ab,kf. (212865)
41 or/26-40 (3553281)
42 24 and 41 (99)
43 42 use medall,cctr (23)
44 25 or 43 (23)
45 exp central nervous system tumor/ (638322)

46 ((brain* or central nervous system* or CNS or spinal cord*) adj3 (adenocarcinoma* or adenoma* or blastoma* or cancer* or carcinoma* or malignan* or metasta* or neoplasm* or oncolog* or tumo?r*)).tw,kw,kf. (279119)
47 exp neuroepithelioma/ (4376)
48 (astroblastoma* or astrocytoma* or ependymoma* or ganglioglioma* or glioblastoma* or glioma* or medulloblastoma* or meningioma* or neuroblastoma* or neurocytoma* or neuroepithelioma* or neurofibroma* or neuro oncolog* or neurooncolog* or neuro patholog* or neuropatholog* or oligodendroglioma* or ((ependymal* or glial cell or intracrani* or meningeal* or neuroepithelial* or pineal* or (teratoid* adj2 rhabdoid*)) adj2 (adenoma* or blastoma* or neoplasm* or tumo?r*)) or AT?RT).tw,kw,kf. (612598)
49 or/45-48 (1011278)
50 *DNA Methylation/ and (algorithm* or classifi* or pattern* or profil* or sequenc*).tw,kw,dv,kf. (38063)
51 ((DNA meth* or DNAm or methyl*) adj3 (algorithm* or classifi* or pattern* or profil* or sequenc*)).tw,kw,dv,kf. (56272)
52 *dna methylation/ and *epigenetics/ (3791)
53 dna methylation/ and classifier/ (551)
54 (methyl* adj3 (epigenet* or epigenom*)).tw,kw,dv,kf. (15928)
55 (methyl* adj3 (based or tumo?r) adj3 (classifi* or profil*)).tw,kw,dv,kf. (1485)
56 (methyl* adj5 ("450K" or "850K" or beadchip* or bead chip* or EPIC* or illumina* or infinium*)).tw,kw,dv,kf. (8970)
57 ((MNP or "MNP2.0" or "MNP 2.0" or molecular neuropathol* or molecularneuropathol*) adj5 (classifi* or methyl* or profil*)).tw,kw,dv,kf. (311)
58 ((Bethesda or c?IMPACT* or DKFZ or Deutsches Krebsforschungszentrum* or German Cancer Research Cent* or Heidelberg or NIH or National Institutes of Health or Northwestern Medicine or St Jude*) adj5 (classifi* or methyl* or profil*)).tw,kw,dv,kf. (3576)
59 (human methylation* or humanmethylation* or methylation epic* or methylationepic*).tw,kw,dv,kf. (7066)
60 ((beadchip* or bead chip* or EPIC* or infinium*) adj3 (array* or classifi* or microarray* or profil*)).tw,kw,dv,kf. (6069)
61 (illumina* adj3 ("450K" or "850K" or array* or beadchip* or bead chip* or classifi* or EPIC* or microarray* or profil*)).tw,kw,dv,kf. (15949)
62 or/50-61 (103597)
63 49 and 62 (5941)
64 (exp animal/ or nonhuman/) not exp human/ (12130580)
65 63 not 64 (5784)
66 Case Report/ or conference abstract.pt. or conference review.pt. (7674574)
67 65 not 66 (3848)
68 limit 67 to english language [Limit not valid in CDSR; records were retained] (3789)
69 limit 68 to yr="2018 -Current" (2320)
70 Economics/ (265163)
71 Health Economics/ or Pharmacoeconomics/ or Drug Cost/ or Drug Formulary/ (153364)
72 Economic Aspect/ or exp Economic Evaluation/ (573350)
73 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw,kw,kf. (1377853)
74 exp "Cost"/ (710777)
75 (cost or costs or costing or costly).ti. (346381)
76 cost effective*.tw,kw,kf. (490637)

77 (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* or increment*)).ab,kw,kf. (337075)
78 Monte Carlo Method/ (86962)
79 (decision adj1 (tree* or analy* or model*)).tw,kw,kf. (76401)
80 (markov or markow or monte carlo).tw,kw,kf. (192246)
81 Quality-Adjusted Life Years/ (59120)
82 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw,kw,kf. (123304)
83 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw,kw,kf. (233919)
84 or/70-83 (3058403)
85 69 and 84 (49)
86 85 use emez (27)
87 44 or 86 (50)
88 87 use medall (22)
89 87 use emez (27)
90 87 use coch (0)
91 87 use cctr (1)
92 87 use cleed (0)
93 remove duplicates from 87 (31)

Grey Literature Search

Performed on: May 22-30, 2024
Websites searched:
Alberta Health Evidence 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), University Of Calgary Health Technology Assessment Unit, Ontario Health Technology Assessment Committee (OHTAC), McGill University Health Centre Health Technology Assessment Unit, Centre Hospitalier de l'Universite de Quebec-Universite Laval, Contextualized Health Research Synthesis Program of Newfoundland (CHRSP), Health Canada Medical Device Database, International HTA Database (INAHTA), Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers, Centers for Medicare & Medicaid Services Technology Assessments, Veterans Affairs Health Services Research and Development, Institute for Clinical and Economic Review, Oregon Health Authority Health Evidence Review Commission, Washington State Health Care Authority Health Technology Reviews, National Institute for Health and Care Excellence (NICE), National Health Service England (NHS), Healthcare Improvement Scotland, Health Technology Wales, Ireland Health Information and Quality Authority Health Technology Assessments, Adelaide Health Technology Assessment, Australian Government Medical Services Advisory Committee, Monash Health Centre for Clinical Effectiveness, The Sax Institute, Australian Government Department of Health and Aged Care, Australian Safety and Efficacy Register of New Interventional Procedures - Surgical (ASERNIP-S), Pharmac, Italian National Agency for Regional Health Services (Aegnas), Belgian Health Care Knowledge Centre, Ludwig Boltzmann Institute for Health Technology Assessment (Austria), The Regional Health Technology Assessment Centre (HTA-centrum), Swedish Agency for Health Technology Assessment and Assessment of Social Services, Norwegian Institute of Public Health - Health Technology Assessments, The Danish Health Technology Council, Ministry of Health Malaysia - Health Technology Assessment Section, Tuft's Cost-Effectiveness Analysis Registry, Sick Kids PEDE Database, PROSPERO, EUnetHTA, clinicaltrials.gov, Cancer Care Ontario Guidelines and Advice, Canadian Task Force on Preventive Health Care, U.S. Preventive Services Task Force
Keywords used:

dna methylation, methylation, profiling, profiler, classifier, classification, epigenomic, epigenetic, epic, illumina, infinium, bead chip, beadchip, 450, 850, dkfz, central nervous system tumour or tumor, CNS tumour or tumor, brain tumour or tumor, brain cancer, glioma, glioblastoma, medulloblastoma, meningioma, ependymoma, meningeal

Clinical results (included in PRISMA): 0
Economic results (included in PRISMA): 0
Ongoing HTAs (PROSPERO/EUnetHTA/NICE/MSAC): 3
Ongoing clinical trials: 83

Appendix 2: Characteristics of Included Studies on DNA Methylation–Based Classification of Central Nervous System Tumours

Table A1: Characteristics of Studies Included in the Clinical Literature Review

Author, year Country	Study design	Type of classifier test, Score thresholds	Participants, n	Eligibility criteria	Age	Tumour type
Abe et al, 2024[37] Japan	Retrospective	DKFZ, version NR ≥ 0.9, 0.3–0.9, < 0.3	15	Spinal tumours resected and diagnosed as ependymoma at the Spine and Spinal Center of Juntendo University Hospital from 2010 to 2020 Posterior fossa tumours resected and diagnosed as PF ependymoma at the Neurosurgery Center, 2013–2020	Median: 33 y (range 3–70 y)	Ependymomas
Bode et al, 2023[39] Germany	Retrospective	DKFZ, v12.5 Threshold NR	79	Histologically diagnosed as pilocytic astrocytoma, ≥ 18 y	Mean: 33 y (range 18–75 y)	Pilocytic astrocytoma
Capper et al, 2018[23] Germany, United States	Prospective	DKFZ ≥ 0.9, 0.3–0.9, < 0.3	1,104 Adult: 17% Pediatric: 29%	CNS tumours	NR	82 CNS tumour classes
Diaz de Stahl et al, 2023 Sweden[41]	Prospective	DKFZ, v11b2 Threshold: NR	73	Pediatric patients diagnosed with CNS and other solid tumours	Median: 5.8 y (range 1 mo to 18 y)	Not specified
Drexler et al, 2024[35] Germany	Unclear	DKFZ, v11.4 and v12.8 ≥ 0.84, 0.3–0.84, < 0.3	1,481	People who underwent surgery for CNS tumour, whose tumours were evaluated by DNA methylation profiling as part of routine clinical workup from January 1, 2018, to December 31, 2021	NR	Not specified
Djirackor et al, 2021[42] Norway	Prospective	DKFZ Version and score threshold: NR	Adult: 55 Pediatric: 50	Tissue biopsy and corresponding clinical data from	Overall: median 26 y (range: 0–84 y) Adults: > 20 y Pediatric: ≤ 20 y	Tumour location: frontal, midline, parietal, temporal, posterior fossa, ventricular, extra-axial, occipital, spinal, or sella
Fukuoka et al, 2020[44] Japan	Retrospective	DKFZ, version NR	152 pediatric	Pediatric low-grade glioma from Hospital for Sick Children and St. Jude Children's Research Hospital	NR	Low-grade gliomas
Galbraith et al, 2023[45] United States	Prospective	DKFZ, version NR ≥ 0.9, 0.3-0.9, < 0.3	1,921	Primary CNS tumours diagnosed at NYU Langone Health between 2014 and 2022	1,303 (68%) adults 545 (28%) pediatric	Not specified

Author, year Country	Study design	Type of classifier test, Score thresholds	Participants, n	Eligibility criteria	Age	Tumour type
Hasselblatt et al, 2018[46] Germany	Retrospective	DKFZ, 11b2 Threshold: NR	25	Tumour samples of 212 consecutive open biopsies or resections of diffuse astrocytomas operated at 3 neurosurgical departments, 2011–2016	From larger cohort with 212 tumours: Median: 44 y (IQR: 35–52 y; range: 18–81 y)	Diffuse astrocytomas
Jaunmuktane et al, 2019[47] United Kingdom	Retrospective		325	Tumour cases that originated from the Division of Neuropathology, the National Hospital for Neurology or were referred for a second opinion or conventional and advanced molecular profiling	NR	Not specified
Kalawi et al, 2022[48] United States	Retrospective	DKFZ, v11b and v12 ≥ 0.84, 0.3–0.84, < 0.3	4 pediatric	Children histologically diagnosed with neurocytoma at Rady Children's Hospital in San Diego, 2012–2018	Age at diagnosis: 9–13	Neurocytoma
Karimi et al, 2019[22] Canada	Prospective	DKFZ, 11b2 or 11b4 ≥ 0.9, 0.3-0.9, < 0.3	55	All brain tumour cases reviewed at hospital multidisciplinary CNS tumour board meetings selected for methylation analysis between November 1, 2015, and September 30, 2018 Reasons for selection: challenging diagnoses, diffuse gliomas requiring final IDH status determination, ependymomas or medulloblastomas requiring molecular subtyping, diffuse gliomas requiring 1p/19q co-deletion determination, discrepancies between clinical or imaging features, and histopathological diagnoses	Mean: 41.0 y Range: 18–71 y	Tumour location: supratentorial, infratentorial, intracranial, spinal, intradural
Pages et al, 2019[51] France	Retrospective	DKFZ, version NR	40 pediatric	Patients with tumours initially diagnosed as supratentorial ependymomas by histopathological assessment between 1993 and 2014, from Sainte-Anne and Necker-Enfants-Malades Hospitals in Paris Exclusion: cases diagnosed as sub-ependymoma (WHO grade I)	Median age at surgery: 6.5 y (range: 1–17 y)	Pediatric supratentorial ependymomas
Pages et al, 2021[52] France	Prospective	DKFZ, 11b4 ≥ 0.84, 0.3–0.84, < 0.3	62	Pediatric tumours that: lacked diagnosis consensus, had conflicting morphological and/or molecular findings, noninformative molecular testing, or other confusing diagnosis aspects, between October 2018 and August 2020	Pediatric (NR)	Gliomas or glioneural tumours, ependymal tumours, embryonal tumours, plexus choroid, unclassified
Price et al, 2024[53] South Africa	Retrospective	DKFZ, 11b4 ≥ 0.9, 0.3–0.9, < 0.3	8	People over 18 y, primary gliomas including diffuse astrocytoma, oligodendroglioma, and glioblastoma Exclusion: pediatric cases, samples with limited tumour (tumour < 30% total surface area), samples with significant necrosis and those for which IHC and/or FISH	NR	Astrocytic and oligodendroglial tumours

Author, year Country	Study design	Type of classifier test, Score thresholds	Participants, n	Eligibility criteria	Age	Tumour type
				results were not available, benign CNS tumours, non-glial tumours, metastatic tumours		
Priesterback-Ackley et al, 2020[54] Netherlands	Prospective	DKFZ, v11b2 and v11b4 ≥ 0.9, 0.3–0.9, < 0.3	502 Adult: 279 Pediatric: 223	CNS tumours analyzed between October 2016 and April 2018 Exclusion: diagnosis other than primary CNS tumour, no suggested histological diagnosis before DNA methylation profiling, missing clinical information, cases analyzed in research setting, duplicate cases	Adult: 50.9 y Pediatric: mean 8.7 y	NR
Rajagopal et al, 2023[56] Malaysia	Retrospective	DKFZ, version NR	50	Children ≤ 18 y diagnosed with medulloblastoma at University Malaya Medical Center, Penang General Hospital, Sarawak General Hospital, and Sabah Women and Children's Hospital, Malaysia between January 2003 and June 2017	Median at diagnosis: 6 y (range 0.25–16 y)	Medulloblastoma
Reinhardt et al, 2022[36] Austria	Retrospective	DKFZ, v11b4, v12.3, and v12.5	54 people 56 samples	People histologically diagnosed with anaplastic ganglioglioma between 2000 and 2018	Median: 25 y (range 1–81 y)	Anaplastic ganglioglioma
Rohrich et al, 2018[57] Germany	Retrospective	DKFZ, version NR	44	Adults with newly diagnosed WHO grade II to IV glioma (according to the 2007 WHO classification) from the university hospitals of Heidelberg and Munich, from August 2011 to March 2017	Mean: 53 ± 16 y (range 20–85 y)	Gliomas
Schepke et al, 2023[59] Sweden	Retrospective	DKFZ, v12.5 ≥ 0.9, 0.3–0.9, < 0.3	71	Pediatric people (< 18 y) diagnosed with supratentorial CNS-PNET and registered in the Swedish Childhood Cancer Registry between January 1, 1984, and December 31, 2015	Age at diagnosis: median 6.2 y (range: 0.2–17.4), mean: 7.1 y	Supratentorial CNS-PNET
Shen et al, 2023[55] United States	Retrospective	DKFZ, v12.5 and 12.6	17	Meningioma tumour samples from the Department of Neurosurgery, University of Connecticut Health Cetner	Age at diagnosis: 50 y (range 30–72 y)	Meningioma
Singh et al, 2023[58] India	Unclear	DKFZ, v11b4, meningioma classifier v2.4 ≥ 0.9, 0.3–0.9, < 0.3	35 Pediatric: 3	Histopathologically-proven meningiomas operated at the Department of Neurosurgery, All India Institute of Medical Sciences	Mean: 36.8 y (range: 8–77 y)	Meningiomas
Tam et al, 2023[60] Hong Kong	Retrospective	DKFZ, v11b4 ≥ 0.9, 0.3–0.9, < 0.3	97	People with CNS embryonal tumours and associated diagnostic entities diagnosed between 1999 and 2017, with available FFPE tumour tissue	Median age at diagnosis: 5.7 y (range 0.6–22.2 y)	Medulloblastoma, CNS-PNET, pineal parenchymal tumours, embryonal tumour with multilayered rosettes and its variants, embryonal tumour not otherwise specified; high-

Author, year Country	Study design	Type of classifier test, Score thresholds	Participants, n	Eligibility criteria	Age	Tumour type
						grade neuroepithelial tumour
Tauziede-Espariat et al, 2022[61] France	Retrospective	DKFZ, v11b4 and 12.2	10 4 pediatric	Tumour samples and clinical data were from the consultation archive database (1982–2020) of Sainte-Anne Hospital pathology department and by French expert centres	Median age at presentation: 23 y (range: 8–73)	Primary intracranial mesenchymal tumours
Wenger et al, 2022[63] Sweden	Prospective	DKFZ, v12.5 ≥ 0.9, 0.3–0.9, < 0.3	49 spatial samples from 11 patients 72 temporal samples from 35 patients	Pediatric patients undergoing brain tumour resection from 2018 to 2021 at Sahlgrenska University Hospital in Sweden	NR	Not specified
White et al, 2023[64] Australia, New Zealand	Prospective	DKFZ, 11b4 and 12.5 ≥ 0.9, 0.3–0.9, < 0.3	269	Suspected or confirmed primary CNS tumour (diagnosis or relapse), had adequate sample, aged ≤ 21 y	Mean age: 8.53 y (SD: 5.45 y), range 15 days to 20.75 y	Diffuse astrocytic and oligodendroglial, neuronal and mixed neuronal, choroid plexus, embryonal, cranial and paraspinal nerve, meningioma, germ cell, mesenchymal nonmeningiothelial, tumours of sellar and pineal region, other glioma
Witt et al, 2018[65] Germany	Retrospective	DKFZ	122	Adult patients with gliomas from 9 clinical centres in Germany, 2004–2012 Newly diagnosed tumours histologically diagnosed as subependymoma, myxopapillary ependymoma, ependymoma, or anaplastic ependymoma	Median: 46 y (range: 18–80 y)	Subependymoma, myxopapillary ependymoma, ependymoma, or anaplastic ependymoma
Wood et al, 2023[66] United States	Retrospective	DKFZ, v12.5	72	Patients ≤ 18 y with a tissue diagnosis of a high-grade primary CNS tumour between 2020 and 2022 at Oregon Health & Science University	Median age at initial diagnosis: 12 y (range: 6–17 y)	Astrocytomas
Wu et al, 2021[67] United States	Prospective	DKFZ, version NR ≥ 0.84, 0.3–0.84, < 0.3	1,258 (1,045 from outside institutions)	Consecutive series of surgical neuropathology cases in a predominantly consultative practice between 2018 and 2020	NR	Not specified
Zschernack et al, 2021[69] Germany	Retrospective	DKFZ v11b4 ≥ 0.9, 0.3–0.9, < 0.3	18	Pediatric NRNY ependymomas with supratentorial location reviewed at the Brain Tumour Reference Center of the German Society of Neuropathology and Neuroanatomy at the Institute of Neuropathology, University of Bonn Medical Center, 2003–2017	Median age at diagnosis: 8.3 y (0.5–17.8 y)	Supratentorial ependymoma

Note: score thresholds are listed from high certainty to low certainty.

Abbreviations: CNS, central nervous system; DKFZ, Deutsches Krebsforschungszentrum (German Cancer Research Center); FISH, fluorescence in situ hybridization; FFPE, formalin-fixed paraffin-embedded; IDH, isocitrate dehydrogenase; IHC, immunohistochemistry; NR, not reported; NRNY, non-RELA (v-rel avian reticuloendotheliosis viral oncogene homolog A)-non-YAP (Yes-associated protein); SD, standard deviation; WHO, World Health Organization.

Appendix 3: Critical Appraisal of Clinical Evidence

Table A2: Risk of Bias[a] Among Observational Studies (RoBANS)

Author, year	Selection of participants	Confounding variables	Measurement of the intervention	Blinding of the outcome assessment	Incomplete outcome data	Selective outcome reporting
Abe et al, 2024[37]	Unclear[b]	Low	Low[c]	Low[d]	Low[e]	High
Alharbi et al, 2020[38]	Low	Low	Low[c]	Low[d]	Low[e]	High
Bode et al, 2023[39]	Low	Low	Low[c]	Low[d]	Low[e]	Low
Capper et al, 2018[23]	Low	Low	Low[c]	Low[d]	Low[e]	Low
Chiang et al, 2024[40]	Unclear[b]	Low	Low[c]	Low[d]	Low[e]	Low
Diaz de Stahl et al, 2023[41]	Unclear[b]	Low	Low[c]	Low[d]	Low[e]	Low
Drexler et al, 2024[35]	Low	Low	Low[c]	Low[d]	Low[e]	High
Djirackor et al, 2021[42]	Unclear[b]	Low	Low[c]	Low[d]	Low[e]	Low
Ebrahimi et al, 2022[43]	Unclear[b]	Low	Low[c]	Low[d]	Low[e]	Low
Fukuoka et al, 2020[44]	Low	Low	Low[c]	Low[d]	Low[e]	Low
Galbraith et al, 2023[45]	Unclear[b]	Low	Low[c]	Low[d]	Low[e]	Low
Hasselblatt et al, 2018[46]	Unclear[b]	Low	Low[c]	Low[d]	Low[e]	Low
Jaunmuktane et al, 2019[47]	Low	Low	Low[c]	Low[d]	Low[e]	Low
Karimi et al, 2019[22]	Unclear[b]	Low	Low[c]	Low[d]	Low[e]	Low
Kalawi et al, 2022[48]	Unclear[b]	Low	Low[c]	Low[d]	Low[e]	High[f]
Lebrun et al, 2021[49]	Low	Low	Low[c]	Low[d]	Low[e]	Low
Mortensen et al, 2022[50]	Unclear[b]	Low	Low[c]	Low[d]	Low[e]	Low
Pages et al, 2019[51]	Low	Low	Low[c]	Low[d]	Low[e]	High[f]
Pages et al, 2021[52]	Unclear[b]	Low	Low[c]	Low[d]	Low[e]	High[f]
Price et al, 2024[53]	Unclear[b]	Low	Low[c]	Low[d]	Low[e]	Low
Priesterbach-Ackley et al, 2020[54]	Unclear[b]	Low	Low[c]	Low[d]	Low[e]	High[f]
Shen et al, 2023[55]	Unclear[b]	Low	Low[c]	Low[d]	Low[e]	Low
Rajagopal et al, 2023[56]	Unclear[b]	Low	Low[c]	Low[d]	Low[e]	High[f]
Reinhardt et al, 2022[36]	Unclear[b]	Low	Low[c]	Low[d]	Low[e]	Low

Author, year	Selection of participants	Confounding variables	Measurement of the intervention	Blinding of the outcome assessment	Incomplete outcome data	Selective outcome reporting
Rohrich et al, 2018[57]	Unclear[b]	Low	Low[c]	Low[d]	Low[e]	Low
Singh et al, 2023[58]	Unclear[b]	Low	Low[c]	Low[d]	Low[e]	High[f]
Schepke et al, 2023[59]	Low	Low	Low[c]	Low[d]	Low[e]	High[f]
Tam et al, 2023[60]	Unclear[b]	Low	Low[c]	Low[d]	Low[e]	Low
Tauziede-Espariat et al, 2022[61]	Unclear[b]	Low	Low[c]	Low[d]	Low[e]	Low
Trager et al, 2023[62]	Unclear[b]	Low	Low[c]	Low[d]	Low[e]	Low
Wenger et al, 2022[63]	Low	Low	Low[c]	Low[d]	Low[e]	High[f]
White et al, 2023[64]	Low	Low	Low[c]	Low[d]	Low[e]	Low
Witt et al, 2018[65]	Unclear[b]	Low	Low[c]	Low[d]	Low[e]	High[f]
Wood et al, 2023[66]	Low	Low	Low[c]	Low[d]	Low[e]	High[f]
Wu et al, 2021[67]	Unclear[b]	Low	Low[c]	Low[d]	Low[e]	Low
Vega et al, 2021[68]	Unclear[b]	Low	Low[c]	Low[d]	Low[e]	High[f]
Zschernack et al, 2021[69]	Low	Low	Low[c]	Low[d]	Low[e]	High[f]

[a]Risk of bias assessed using RoBANS, Risk of Bias Assessment Tool for Nonrandomized Studies.[32] Possible risk of bias levels: low, high, unclear.

[b]Limited details about patient characteristics or patient selection and eligibility process. Unclear how patient selection impacts results.

[c]Widely-used and validated DNA methylation–based classifier test.

[d]Blinding is not possible.

[e]Categories and calibration scores are established for DNA methylation–based classifier tests.

[f]Selective/incomplete reporting of outcomes. Missing detailed information about classification results (e.g., improved or refined classification, or misleading, discarded, or unclassifiable result).

Table A3: GRADE Evidence Profile for the Comparison of DNA Methylation–Based Classifier Tests and Conventional Testing

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
Classification results							
38 (observational)	No serious limitations	Serious limitations (−1)[a]	No serious limitations	No serious limitations	Undetected	Large magnitude of effect (+2)[b]	⨁⨁ Low
Downstream impact of testing							
3 (observational)	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[c]	Undetected	None	⨁ Very Low
Time to treatment							
1 (observational)	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[c]	Undetected	None	⨁ Very Low

Abbreviations: CNS, central nervous system; GRADE, Grading of Recommendations Assessment, Development, and Evaluation.

[a]CNS tumour classification is dependent on clinical expertise and may be subjective. Different score thresholds for DNA methylation–based classifier tests were also used between studies and exceptions to score thresholds may be made for specific CNS tumours cases.

[b]DNA methylation–based classifier tests provide classification results in additional to conventional tests. DNA methylation profiling results are used as test input.

[c]Limited information on outcome assessment.

Appendix 4: Application of CHEERS-AI Reporting Guideline Extension

Table A4: Application of CHEERS-AI Reporting Guideline Extension[74]

Section/topic[a]	No.	Guidance for reporting for AI components	Reported in section
AI elaborations on CHEERS 2022			
Title	1	Indicate that the intervention involves an AI component that is under evaluation	No[b]
Abstract	2	Specify the purpose of the intervention with an AI component and the AI technique used	Abstract
Methods			
Comparators	7	Describe key details of the AI component of the intervention (and comparators, if appropriate), including: a) the classification by intended purpose and risk tier (for digital health technologies) b) the AI technique used c) whether it is "locked" (static) or adaptive d) the version under evaluation e) the purpose of the intervention, including its potential impact on care f) the intended user(s), and how users interact with it g) additional requirements to use it h) how it is expected to provide benefit over the standard of care	CER background: health technology under review
Selection of outcomes	11	Describe whether the measure(s) chosen to indicate the benefits and harms of the AI intervention (and comparators) relates to health outcomes, diagnostic outcomes, process outcomes, or other/multiple outcomes	PEE methods: clinical outcomes and Table 4
Measurement of outcomes	12	For model-based analysis, describe any assumptions used to inform the potential benefit(s) and harm(s) of the AI intervention in the model (and comparators, if appropriate). Describe the plausibility of analyst assumptions, citing any supportive evidence	PEE methods: main assumptions
Measurement and valuation of resources and costs	14	Describe the purchase cost of the AI intervention (and comparators, if appropriate) and what it is composed of. Describe any additional implementation and maintenance costs	PEE methods: cost parameters and Table 5
Rationale and description of model	16	Describe if the AI component of the intervention has influenced the choice of health economic model and explain why	PEE methods: model structure
Discussion			
Study findings, limitations, generalizability, and current knowledge	26	Comment on potential biases associated with the AI intervention (e.g., algorithmic bias) and implications for the generalizability and interpretation of results (e.g., reinforcing existing health inequalities)	PEE discussion
AI extensions to CHEERS 2022			
Methods			
User autonomy	AI 1	Indicate whether the AI intervention (and comparators, if appropriate) is directive, or whether the user(s) retains autonomy to make the care decision	PEE methods: interventions and comparators
Measurement of AI effect	AI 2	Describe the data sources (assessment studies) for the AI intervention's impact on outcomes	CER results

Measurement of AI learning over time	AI 3	If the AI intervention (and comparators, if appropriate) learns over time, explain how this affects its performance at the individual level and how this was measured	PEE methods: analysis (Scenario 4)
Development of AI component	AI 4	Describe how the AI component of the intervention (and comparators, if appropriate) was developed, including the training data used and how errors and biases were identified, or cite a source that provides this information	CER background: health technology under review
Validation of AI component	AI 5	Describe how the AI component of the intervention (and comparators, as appropriate) and its performance estimates were validated, or cite a source that provides this information	CER background: health technology under review
Health benefit	AI 6	Describe how the AI intervention (and comparators, if appropriate) could directly or indirectly provide a health benefit	CER results
Population differences	AI 7	Describe important differences between the data sources (assessment studies) for the AI intervention's impact on outcomes and the data set that was used to develop the AI intervention (training data set)	CER background: health technology Under review
Modeling of AI learning over time	AI 8	If the AI intervention (and comparators, if appropriate) learns over time at the individual level, describe any assumptions used to model how this learning affects its performance over time	PEE methods
Results			
Impact of AI uncertainty	AI 9	Indicate the extent to which features of the AI intervention may contribute to increased uncertainty about its cost-effectiveness	PEE results
Discussion			
Implementation of AI	AI 10	Comment on any requirements needed to integrate the AI intervention (and comparators, as appropriate) into practice, and other implementation considerations relating to the AI component of the intervention, including implications for the interpretation of cost-effectiveness results	PEE discussion

Abbreviations: AI, artificial intelligence; CER, clinical evidence review; CHEERS, Consolidated Health Economic Evaluation Reporting Standards; HTA, health technology assessment; PEE, primary economic evaluation.

[a]We included AI-related components (CHEERS-AI) in this Table.[74]

[b]Machine learning algorithms were used to develop the DNA methylation-classifier test.

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About Us

We are an agency created by the Government of Ontario to connect, coordinate, and modernize our province's health care system. We work with partners, providers, and patients to make the health system more efficient so everyone in Ontario has an opportunity for better health and well-being.

Equity, Inclusion, Diversity and Anti-Racism

Ontario Health is committed to advancing equity, inclusion and diversity and addressing racism in the health care system. As part of this work, Ontario Health has developed an Equity, Inclusion, Diversity and Anti-Racism Framework, which builds on existing legislated commitments and relationships and recognizes the need for an intersectional approach.

Unlike the notion of equality, equity is not about sameness of treatment. It denotes fairness and justice in process and in results. Equitable outcomes often require differential treatment and resource redistribution to achieve a level playing field among all individuals and communities. This requires recognizing and addressing barriers to opportunities for all to thrive in our society.

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