



**Australian Government**

**Medical Services Advisory Committee**

## **Public Summary Document**

### ***Application No. 1709 Somatic gene testing for the diagnosis of glioma, including glioblastoma***

**Applicant:** Royal College of Pathologists of Australasia

**Date of MSAC consideration:** MSAC 84th Meeting, 31 March - 1 April 2022

#### **1. Purpose of application**

An application requesting Medicare Benefits Schedule (MBS) listing of a somatic gene panel test for the diagnosis of glioma, including glioblastoma, was received from the Royal College of Pathologists of Australasia (RCPA) by the Department of Health.

#### **2. MSAC's advice to the Minister**

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC supported the creation of a new Medicare Benefits Schedule (MBS) item for a somatic gene panel test for characterisation of variants including single nucleotide variants, structural variants, fusions and copy number alterations in the initial diagnosis, and at relapse, of patients presenting with morphological features of glioma, glioneuronal tumours or glioblastoma. MSAC advised the proposed gene panel is safe, allows diagnosis that integrates molecular profiling and morphological assessment, is likely cost-effective, and would have small budget implications with a low risk of utilisation outside the proposed clinical indication as the patient population is well defined.

MSAC advised that MBS items 73371 and 73372, which are single gene items used in the diagnostic work-up of gliomas, should be phased out no more than 12 months after introduction of the newly supported item. MSAC advised the Department should consult further with the Royal College of Pathologists of Australasia (RCPA) and pathology providers before recommending the removal of 73371 and 73372 to the Minister.

MSAC advised that the use of a diagnostic genetic panel for gliomas for the additional purposes of prognostication and/or determining predictive targets may require a larger panel that would require further consideration through the MSAC process.

#### **Consumer summary**

This application from the Royal College of Pathologists of Australasia was for the Medicare Benefits Schedule (MBS) listing of a gene panel test for the diagnosis of brain cancers called gliomas, which include glioblastomas and glioneuronal tumours. The brain and rest of the central nervous system are made up of different types of cells: neurons, which transmit information,

## **Consumer summary**

and glial cells that surround and support the neurons. Cancer of the glial cells is called glioma. Astrocytes are one type of glial cell: cancer in astrocytes is called glioblastoma, an aggressive type of cancer and the most common type of glioma. Other types of glial cells that can become cancerous are oligodendrocytes (causing oligodendrogliomas) and ependymal cells (causing ependymomas). Glioneuronal tumours are a rare type of cancer where a mixture of neurons and glial cells become cancerous.

In 2021, the World Health Organization recommended adding genetic testing for specific genes to aid in the diagnosis and severity grading of brain cancers and other central nervous system cancers. Finding changes in these particular genes will help patients and their clinicians better understand the patient's specific type of cancer and how their disease is likely to progress (also called prognosis), and to achieve the best possible outcomes, including potentially identifying an appropriate treatment.

A gene panel test is where the laboratory looks for genetic changes in multiple genes at once, rather than looking at genes one at a time, as is currently funded on the MBS. Using a gene panel test would be faster and more efficient than testing each gene in turn, and will also use up less of the brain cancer sample.

Genetic changes found in a patient's cancer are generally somatic (occurring after conception), rather than heritable. This means family members do not require testing if a patient's cancer is found to have a genetic change.

MSAC considered glioma gene panel testing to be effective in helping patients receive the best information on their diagnosis more efficiently, to achieve the best possible outcomes. Glioma gene panel testing is also safe and represents good value for money.

### **MSAC's advice to the Commonwealth Minister for Health**

MSAC recommended that a gene panel test for the diagnosis of glioma, including glioblastoma, be listed on the MBS. MSAC considered the testing to be effective, safe and good value for money.

## **3. Summary of consideration and rationale for MSAC's advice**

MSAC noted that this application from the Royal College of Pathologists of Australasia (RCPA) was for the Medicare Benefits Schedule (MBS) listing of a somatic gene panel test for the diagnosis of glioma, including glioblastoma. MSAC recalled that in 2019 it had supported Application 1527 for somatic gene testing of central nervous system tumours and sarcomas, including three single gene tests for the diagnosis of glioma that have since been listed on the MBS.

MSAC noted that the World Health Organization (WHO)'s most recent update in 2021 to its central nervous system (CNS) tumour classification, CNS5, describes the need for molecular genetic testing for the diagnosis and grading of CNS tumours, independent of histology and morphology. CNS5 includes the description of 14 new tumour types, and now recommends using multiple test methodologies as an integrated approach to CNS tumour diagnosis. MSAC noted the pre-MSAC response stated that the WHO classification of brain tumours highlights the role of molecular testing in achieving the best possible outcomes for patients with glioma, glioneuronal tumours or glioblastomas, and that these tests are not currently reimbursed on the MBS, requiring patients/families to bear the cost of genetic testing.

MSAC noted that this application builds on the existing MBS items for single genetic tests (arising from application 1527), by creating a new MBS item for a multigene next-generation sequencing (NGS) panel with broader coverage:

- MBS item 73371: detection of co-deletion of 1p/19q chromosome regions (fee \$340)
- MBS item 73372: gene testing to determine *IDH1/2* variant status (fee \$340)
- MBS item 73373: characterisation of *MGMT* promoter methylation (fee \$400).

MSAC noted the proposed population was patients who have been identified as likely to have a glioma. While the initial application excluded those with an IDH-wildtype glioblastoma where a diagnosis can be made based on IDH1 immunohistochemistry (IHC) testing, MSAC considered that the test should be made for all patients with suspected glioma at diagnosis or relapse of disease, as referred to by “one test per diagnostic episode” in the item descriptor.

MSAC noted concerns regarding the amount of tissue that is required for the panel test, and considered that while continuing the current items would be useful for biopsies with insufficient DNA for panel testing, there is little value in retaining MBS items for single gene testing and doing so risks patients receiving inferior tests. MSAC therefore advised that the proposed gene panel should replace MBS items 73371 and 73372, because gene panel testing is faster, more efficient and more reliable than the existing sequential single gene tests. MSAC recommended that MBS items 73371 and 73372 be phased out within no more than 12 months of listing the new MBS item for glioma gene panel testing. MSAC recommended that the Department liaise with the RCPA to assist with this sunseting. MSAC recommended that MBS item 73373 be retained as a standalone item as the methodology required to characterise *MGMT* methylation is likely to differ from the methodology for the proposed service. MSAC also advised that the proposed service should be made pathologist-determinable because glioma panel testing would not replace this standalone test.

MSAC noted the applicant’s pre-MSAC response confirmed that the 85% MBS fee was proposed to be \$800. Considering that the Greatest Permissible Gap is \$87.90 the proposed 85% MBS fee of \$800 equates to a full MBS fee of \$887.90. MSAC considered that this fee would permit testing of more than the minimum set of nine genes listed in the item descriptor, with up to 25 genes commonly tested in this clinical setting.

MSAC noted that the application was for diagnostic purposes specifically, and advised that the use of glioma genetic panels for the purposes of prognostication or determining predictive targets (i.e. those with targeted therapies) would require a larger panel and fee, and that such a proposal would require further consideration through the MSAC process. MSAC noted the Department-Contracted Assessment Report (DCAR) considered up to 48 genes could be relevant to testing, including genes from the CNS5 and also genes included in other guidelines. MSAC considered that in particular, identification of genetic changes in the *IDH1*, *IDH2*, *H3F3A*, *TERT*, *EGFR*, *CDKN2A*, *CDKN2B*, and *BRAF* genes, as well as 1p/19q chromosomal abnormalities, impacts diagnosis and prognosis. MSAC also noted that, to provide the best patient outcomes, there needed to be a balance between limiting the size of the gene panel to facilitate short turn-around times, against performing more comprehensive testing (up to 48 genes) to identify all potential predictive targets, which has longer turn-around times.

MSAC noted that the evidence base relied on the incremental cost-effectiveness ratios (ICERs) included the nine “core” genes proposed by the applicant in line with the current WHO CNS5, plus others reported in guidelines and the literature. MSAC considered there is some uncertainty around the optimum gene panel composition, given the lack of a widely adopted gene list, and around the applicability of the findings from Cheung et al 2021<sup>1</sup> (which used a 26-gene glioma panel) to the

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<sup>1</sup> Cheung VKY, Buckland ME, et al (2021). Next generation sequencing impacts the classification and management of primary brain tumours. *Pathology*, 53(6): 780-782.

proposal for a 9–25 gene panel. MSAC considered that while the inclusion of other genes such as *HIST1H3B* and *HIST1H3C* on the panel may be desirable, they do not need to be specified in the minimum gene list. MSAC noted the rejoinder’s proposal to add *ATRX* to the minimum gene list specified in the item descriptor, on the basis that it is included in NHS England panels and was also included in the panel used by Cheung et al. MSAC also noted the applicant’s post-MSAC request to remove the *ATRX* gene from the mandatory genes listed in the item descriptor, on the basis that IHC testing is not inferior to NGS in detecting *ATRX* loss-of-function variants<sup>2</sup>. MSAC noted that *ATRX* is a desirable but not essential disease-defining gene, and recognised that the gene panel will not completely replace IHC testing, as at least a small IHC panel will still be required to establish eligibility for the gene panel. MSAC noted that no recent evidence had been provided that IHC is superior to NGS, but accepted that this was the basis for removing *ATRX* from the mandatory gene list, together with the size and complexity of *ATRX*, which may increase the cost of testing. MSAC advised that the minimum gene set listed in the item descriptor did not need to be further expanded. MSAC considered that as the WHO gene lists are updated regularly, a review of this item after 1 year was appropriate. MSAC considered that referring to “the current WHO criteria” rather than naming CNS5 specifically would remove the need for regular item descriptor updates with WHO revisions, unless there is a large number of additional genes added to the WHO CNS panel in future. MSAC considered that including any reference to the WHO CNS5 in a practice or explanatory note rather than within the item descriptor itself would better futureproof the item descriptor, but that this note needed to not restrict testing to only genes within the CNS5, as other relevant genes may be identified in the future. MSAC noted the WHO CNS5 recommends testing a different selection of genes for tumours in children, and considered that the Zero Childhood Cancer program already funds genetic testing for paediatric gliomas. MSAC therefore considered that it was likely appropriate to focus the glioma panel testing under this application on the adult population whose needs are not yet addressed. MSAC considered that specifying genes that are more relevant to adult glioma in the MBS item should not create inequitable access for paediatric glioma patients, though requested the Department contact the Zero Childhood Cancer program to confirm this.

MSAC considered it appropriate that the MBS item descriptor specify the minimum set of genes to be included on the gene panel, and that the maximum number of genes examined would not be specified but would be essentially constrained by the fee. MSAC noted the pre-MSAC response’s proposal to restrict *IDH1/2* testing to two specific variants, but considered that current MBS item 73372 uses sequencing to interrogate all *IDH1/2* variants, and that Cheung et al found 20% of cases had other *IDH1* variants. MSAC therefore advised *IDH1/2* testing should not be restricted to two variants. MSAC considered it desirable that the laboratory test the whole of each gene, rather than only specific variants in each gene, in order to provide a comprehensive diagnosis. MSAC considered that requiring testing to include the whole of each gene would be most appropriately addressed through the item descriptor rather than a practice note, and considered that requiring the test to interrogate a range of types of variant would effectively require each gene to be sequenced. MSAC considered that requiring this scope of testing would also have the advantage of limiting testing to laboratories with the appropriate expertise and equipment. MSAC therefore advised that the item descriptor should require the gene panel test to characterise single nucleotide variants, structural variants, fusions and copy number alterations.

MSAC’s supported item descriptor is provided below (Table 1).

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<sup>2</sup> Zacher A, et al. (2017), Molecular Diagnostics of Gliomas Using Next Generation Sequencing of a Glioma-Tailored Gene Panel. *Brain Pathology*, **27**: 146-159.

**Table 1 MSAC's supported item descriptor**

MBS item xxxxx	Category 6 – Genetics P7
<p>Characterisation of variants including single nucleotide variants, structural variants, fusions and copy number alterations in a single gene panel in the diagnostic work-up by the pathologist, specialist or consultant physician, of a patient with clinical or laboratory evidence of a glioma, glioneuronal tumour or glioblastoma to aid diagnosis and classification in line with the current WHO criteria and management, including but not limited to:</p> <ul style="list-style-type: none"> <li>a) <i>IDH1, IDH2</i> variant testing</li> <li>b) 1p/19q co-deletion assessment</li> <li>c) <i>H3F3A</i> variant status</li> <li>d) <i>TERT</i> promoter variant status</li> <li>e) <i>EGFR</i> amplification</li> <li>f) <i>CDKN2A/B</i> deletion</li> <li>g) <i>BRAF</i> variants.</li> </ul> <p>Maximum one test per diagnostic episode.            Fee: \$887.90, Benefit 75%=\$665.95, 85%=\$800.00</p>	

Practice Note: Testing should include, but not be restricted to, genes described in the 2021 World Health Organization Classification of Tumours, 5<sup>th</sup> Edition, Volume 6 (Central Nervous System Tumours).

Source: MSAC.

MSAC considered it appropriate that the gene panel test be available on diagnosis and on relapse of disease, in keeping with its advice in MSAC Application 1527. However, MSAC considered loosening the frequency restriction on existing MBS items 73371, 73372, and 73373 would be inappropriate, and retaining the existing frequency restriction would encourage use of the superior panel test.

MSAC noted the location of the proposed glioma gene panel in the clinical management algorithm and considered it possible that in the future glioma panel testing could be conducted before any immunohistochemical testing. MSAC noted IDH IHC may become irrelevant in the future, so considered tissue pathology testing to be a more appropriate trigger to reflex to panel testing.

MSAC noted that glioma gene panel testing can change tumour classification/grading and exclude, confirm or refine the initial diagnosis. MSAC noted that the yields for various measures of effectiveness ranged from 21% to 80% of patients. MSAC considered that supporting this testing may also assist in the Pharmaceutical Benefits Advisory Committee (PBAC)'s consideration of future codependent applications for PBS listing of glioma medicines, if the associated test to establish eligibility were already funded on the MBS on this panel. MSAC considered that establishing eligibility for entry into clinical trials is not an appropriate primary purpose of MBS-funded testing, and advised testing for the primary purpose of clinical trial entry would be more appropriately funded through other mechanisms.

MSAC considered the proposed glioma panel to have superior effectiveness and non-inferior safety, as it is faster, uses less tumour tissue, and usually provides a more precise diagnosis and may identify more predictive targets than sequential single gene assays.

MSAC noted that cost-effectiveness analyses were presented with effectiveness expressed in terms of incremental cost per patient who received a result that:

- Altered diagnosis (added by MSAC)
- Altered diagnosis or prognosis
- Altered or refined diagnosis, or altered prognosis
- Altered or refined diagnosis, altered prognosis, or identified a potential predictive target

- Altered diagnosis or prognosis, refined or confirmed diagnosis per WHO CNS5, or identified a potential predictive target

MSAC noted the resulting ICERs ranged from \$2,609 per patient with altered diagnosis, to \$687 per patient with altered diagnosis or prognosis, refined or confirmed diagnosis per WHO CNS5, or identified a potential predictive target. MSAC considered the ICERs may overestimate clinical utility, as refining or confirming a diagnosis will not always result in a change in management, and the benefit of identifying potential predictive targets may not be realised if there are no treatments available. MSAC also considered that the cost of the comparator may have been underestimated as it did not take into account some patients receiving both 1p/19q and *IDH1/2* testing at present. Nonetheless, MSAC considered that these ICERs are within the range of cost-effectiveness in terms of cost per proband identified that it had previously accepted for germline gene panel testing applications, and advised that the proposed testing likely represented acceptable cost-effectiveness.

MSAC also noted that the DCAR had omitted an assessment of the risk of bias of the included studies, and that a key study used in the evidence base, Cheung et al, was published as a letter, which MSAC does not typically accept.

MSAC noted the DCAR had used an epidemiological approach to estimate 1,070 services in the first year, and that the applicant's expert had advised the NSW and WA Centres of Excellence provided 659 glioma panel services in 2021. MSAC agreed with the applicant that 659 may be an underestimate as the Centres of Excellence also provide services to Victoria, Queensland, South Australia and New Zealand, and that the true utilisation is likely to fall in between these two estimates. MSAC noted that the "people" considered in the utilisation estimates appears to include adults, adolescents and children, though the DCAR did not explicitly state this. MSAC considered that utilisation outside the intended clinical indication was unlikely given the well-defined patient population.

MSAC noted the rejoinder had provided revised financial analyses based on the pre-MSAC response confirmation that the 85% fee was proposed to be \$800. MSAC noted the estimated budget impact to the MBS of \$768,123 in year 1 after listing to \$807,305 in year 6. MSAC considered that this did not include repeat testing or all its supported changes in use of the single gene tests, but considered inclusion of these costs would have a negligible impact on the estimates of overall financial impact, given practical difficulties in obtaining additional tissue samples for repeat testing and the low service utilisation of existing single gene tests.

MSAC supported listing somatic gene panel testing on the MBS for single nucleotide variants, structural variants, fusions and copy number alterations in the initial diagnosis, and at relapse, of patients presenting with morphological features of glioma, glioneuronal tumours or glioblastoma. MSAC advised the proposed gene panel is safe, allows diagnosis that integrates molecular profiling and morphology, is likely cost-effective, and would have small budget implications with a low risk of leakage as the patient population is well defined.

## 4. Background

Primary brain malignancies account for approximately 30% of all primary brain tumours, and are a rare cancer, with a lifetime risk up to the age of 85 of 0.62%. Despite being the 18<sup>th</sup> most common cancer diagnosed in Australia, it is the leading cause of cancer-related deaths in Australians under the age of 40 and the 9<sup>th</sup> leading cause of death from cancer in adults overall in 2021<sup>3</sup>. The average 5-year survival rate of patients with brain cancer is 22.3%<sup>4</sup>.

<sup>3</sup><https://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/3303.0~2016~Main%20Features~Cancer%20deaths%20in%20younger%20Australians%20-%20changes%20over%2020%20years~10000> accessed 12 February 2022.

Malignant primary brain tumours are captured within Australian Institute of Health and Welfare (AIHW) data under the ICD-10 code C71: brain cancer<sup>4</sup>. Approximately 81% of brain cancers are gliomas<sup>5</sup>, and arise from three types of glial cells: astrocytes (giving rise to astrocytomas or glioblastomas), oligodendrocytes (giving rise to oligodendrogliomas) and ependymal cells (giving rise to ependymomas).

Glioblastomas are the most common and most aggressive type of glioma, representing 48-54% of all gliomas.<sup>5,6</sup> Annual figures for the incidence of glioblastoma could not be located but in 2013, AIHW data indicate there were 982 individuals with this diagnosis from a total of 1592 brain cancers of neuroepithelial tissue<sup>7</sup>. In another Australian study published from a review of data from 2000-2008, the rates of glioblastoma were noted to be increasing and estimated at 3.4/100 000 person years<sup>8</sup>.

## WHO Classification of Tumours of the Central Nervous System

In 2021, the fifth edition of the WHO Classification of Tumours of the Central Nervous System (CNS5)<sup>9</sup> was published<sup>10</sup>. This seeks to integrate molecular diagnostics with the established technologies of immunohistochemistry and histology and present an integrated approach to diagnosing brain and spinal cord tumours. Molecular characterisation facilitates making a diagnosis (including subtyping) and in some instances is essential to establish a diagnosis, for prognostication and provides predictive information in some instances.<sup>11</sup> As such, it has become the key guideline for diagnosing CNS tumours.

Key changes with the WHO CNS5 are:

- molecular profiling contributes now to grading in some CNS tumours, independent of histology and morphology
- 14 newly recognised glioma, glioneuronal and neuronal tumour types have been added
- a layered reporting approach is now recommended, incorporating an integrated diagnosis (histological and molecular diagnosis) with histopathological classification, CNS WHO grade and any defining molecular information.

## Molecular profiling, predictive biomarkers and treatment options

While surgery, chemotherapy and radiation therapy form the basis of treatment, recently approved targeted therapies include the tumour-agnostic approvals of NTRK inhibitors, which are reported to have an overall response rate in 5/24 (21%) patients including 2/24 (8%) with complete responses<sup>12</sup>, while BRAF inhibitors have been reported to have encouraging results, particularly in paediatric or young adult glioblastomas.<sup>11</sup> NGS panels for identification of predictive targets in solid tumours<sup>13</sup> or designed specifically for brain tumours<sup>14</sup> have been used to identify predictive biomarkers to determine eligibility for clinical trials or for off-label usage with detection rates of 31-

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<sup>4</sup> <https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/cancer-summary-data-visualisation> accessed 11 February 2022.

<sup>5</sup> Ostrom QT, Cioffi G, Gittleman H, et al. (2019). CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2012-2016. *Neuro Oncol*, **21**(Suppl 5):v1-v100.

<sup>6</sup> Park SH, Won J, Kim SI, et al. (2017). Molecular Testing of Brain Tumor. *J Pathol Transl Med*, **51**(3):205-223.

<sup>7</sup> <https://www.aihw.gov.au/getmedia/d2914a17-052e-45bb-bbd3-17047c7d5da1/20566.pdf.aspx?inline=true#:~:text=In%202009%E2%80%932013%2C%20Australians%20diagnosed,over%20the%20last%2030%20years>. accessed 17 February 2022.

<sup>8</sup> Dobes M, Khurana VG, Shadbolt B, et al. (2011). Increasing incidence of glioblastoma multiforme and meningioma, and decreasing incidence of Schwannoma (2000-2008): Findings of a multicenter Australian study. *Surg Neurol Int*, **2**:176.

<sup>9</sup> WHO Classification of Tumours Editorial Board. *World Health Organization Classification of Tumours of the Central Nervous System*. 5th ed. Lyon: International Agency for Research on Cancer; 2021.

<sup>10</sup> Louis DN, Perry A, Wesseling P, et al. (2021). The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. *Neuro-Oncology*, **23**(8): 1231–1251.

<sup>11</sup> Behling F, Schittenhelm J (2019). Oncogenic *BRAF* Alterations and Their Role in Brain Tumors. *Cancers (Basel)*, **11**(6):794.

<sup>12</sup> <https://www.tga.gov.au/sites/default/files/auspar-larotrectinib-201216-pi.pdf> accessed 11 February 2022.

40%<sup>13,14</sup>, and either complete or partial responses per Response Assessment in Neuro-Oncology criteria to matched targeted therapies of 43%<sup>13</sup>.

This application proposes public funding for multigene testing of up to 25 genes within a panel, primarily to align with the WHO CNS5 diagnostic criteria for patients with glial tumours including glioblastomas. This builds on Application 1527, which was previously supported by MSAC and led to inclusion in the MBS of three single genetic tests in gliomas and glioblastomas from 1 May 2020 (MBS items 73371, 73372 or 73373).

## 5. Prerequisites to implementation of any funding advice

The proposed technology does not include a therapeutic good that requires Therapeutic Goods Administration (TGA) approval.

The Applicant states that the National Association of Testing Authorities (NATA) and the Royal College of Pathologists of Australasia (RCPA) oversee the regulation of pathology testing for clinical purposes. Laboratories require accreditation by a joint NATA/RCPA process to ISO 15189, and are specifically accredited to provide genetic testing. This accreditation process covers the technical aspects of the sample reception and processing, laboratory sequencing, analysis pipelines, curation (or interpretation) of results and production of the report to a clinical standard. There are no requirements for use of specific manufacturer's reagents, equipment or analysis pipelines.

Molecular profiling is a complex investigation and quality issues pose a risk primarily and directly to the patient, and secondarily to the MBS if repeat testing is deemed necessary to address concerns about the adequacy or limitations of initial testing (e.g. through the use of a panel that is not sufficiently comprehensive). The recently published WHO CNS5 provides a list of genes, and variants that define or characterise an entity by their presence or absence.

### Scope of testing

The scope of gene panel testing may be problematic if it does not include candidate genes and known variants regarded as the standard of care at the time of the test being performed. NGS gene panels offer the opportunity to test a broad range of genes for a range of purposes (diagnostic, prognostic, predictive, potential familial predisposition), for which there is established evidence or emerging evidence, that may offer clinical management options and improved outcomes. With a range of providers, the scope of testing and therefore, suitability for different test purposes, may differ unless there is some agreed scope, and clear communication of the scope.

Consideration could be given to:

1. Stipulating in the item descriptor a minimum core number of genes to be analysed as part of the service that:
  - a. align with the diagnostic WHO CNS5, especially where these are defining
  - b. incorporate wider test purposes e.g., to identify potential treatment options.
2. Establishing and maintaining a directory, updated at intervals by Australian experts, with agreed genes within a panel test as is done in the NHSE Genomic Test Directory, or similar to PanelApp Australia<sup>15</sup>. This would support equitable access to appropriate testing.

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<sup>13</sup> Zeitouni D, Catalino M.P, Wise J, et al. (2021). Clinical Application of Next-Generation Sequencing in Recurrent Glioblastoma. *Onco*, **1**: 38–48.

<sup>14</sup> Siegel C, Aboud O, Brown M, et al. (2018). Utilizing next generation sequencing reports in clinical decision making: Report from the National Institutes of Health (NIH) Neuro-oncology Branch (NOB) natural history study (NHS) Primary brain tumor panel (PBTP). *Neuro-Oncology*, **20**: vi170.

<sup>15</sup> <https://panelapp.gha.umccr.org> accessed 12 February 2022.

Stipulating a list of specific genes within the item descriptor as the minimum expected gene set for analysis will inevitably become outdated as new genes or variants are identified and may be difficult to update without a streamlined process.

3. Requiring providers to list/have available the genes and targeted gene regions offered, to provide requesters with an understanding of the genes tested and to identify the differences between tests provided. This would be important for requesters where a patient is seeking to pursue all treatment avenues (including self-funded or investigational), if only some providers may offer gene panels that include predictive targets alongside diagnostic genes. The Mayo Clinic provides such a list for each of its tests including the targeted DNA gene regions interrogated within their comprehensive adult and paediatric 118-gene Neuro-oncology panel<sup>16</sup>.

## 6. Proposal for public funding

The proposed technology (or technologies) is an existing technology, though not publicly funded.

The proposal intends to build on existing MBS items 73371, 73372 and 73373, which are single genetic tests, by creating a new MBS item for a multi-gene NGS panel with broader coverage than currently provided.

Limitations of this proposal are:

1. With the application limited to the somatic testing of glial neoplasms (including glioblastoma), which constitute 81% of brain cancers, 19% of brain cancers would remain without publicly funded genetic testing.
2. The nominated essential genes within the proposed panel are focused mostly towards diagnosing tumours found in the adult population. The Applicant's expert clarified in a meeting on 17 February 2022, that it is envisaged the proposed panel would be used predominantly in the young adult population (who potentially have gene alterations found more commonly in paediatric gliomas) and adults. It was noted that the paediatric population are likely to be able to access broad genetic testing within programs offered in specialist hospital services. Utilisation data for the existing single genetic tests (Items 73371 and 73372) indicate low usage in 2021 in the paediatric age group.
3. The application lacks detail about the specific genes and the types of variants that are required to be tested to be fit for purpose.
  - a. Currently, nine genes or copy number variants are nominated as essential in the Applicant's proposed panel with the intended scope and costing to allow for up to 25 genes in total. However, the Applicant's experts proposed gene list was compared with the WHO CNS5 list of 44 genes with diagnostic, prognostic and predictive utility. MSAC noted it is difficult to convey within the confines of an item descriptor the expected panel size necessary to be fit-for-purpose when only a subset of the WHO CNS5 genes are provided for. Testing limited to just the Applicant's essential genes would meet the requirements for the claiming the fee but may not adequately characterise all glial tumours.
  - b. The types of variants are not specified in the applicant's proposed item descriptor, noting that *BRAF* aberrations may be simple genetic variants (e.g., *BRAF* V600 point substitutions) or structural variants (e.g. *BRAF-KIAA1579* gene fusions). Both DNA and RNA analysis within the NGS panels may be required to cover the

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<sup>16</sup> [https://www.mayocliniclabs.com/~/media/it-mmfiles/special-instructions/Targeted\\_DNA\\_Gene\\_Regions\\_Interrogated\\_by\\_Neuro-Oncology\\_Panel.pdf](https://www.mayocliniclabs.com/~/media/it-mmfiles/special-instructions/Targeted_DNA_Gene_Regions_Interrogated_by_Neuro-Oncology_Panel.pdf) accessed 12 February 2022.

expected range of single or multiple nucleotide level variants and structural or copy number variants; any costing would need to reflect these complexities.

- c. The application does not define the diagnostic pathway or funding source for further investigations for patients who remain without a diagnosis after being tested with the proposed panel, which may require other additional testing and also lead to potential equity issues.

The following new MBS item descriptor was proposed by the applicant:

**Table 2 Applicant’s proposed MBS item descriptor**

<b>Category 6 –Genetics P7</b>
<p>Analysis of tumour tissue from a patient with clinical or laboratory evidence, including morphological features, of glioma, glioneuronal tumour or glioblastoma that cannot be definitively classified by the current WHO criteria using morphology, immunohistochemistry and/or single gene testing. As requested by a pathologist, specialist or consultant physician, for the detection of at least, but not limited to, the following variants on a single panel:</p> <ul style="list-style-type: none"> <li>• <i>IDH1</i>, <i>IDH2</i> variant testing</li> <li>• 1p/19q co-deletion assessment</li> <li>• <i>H3F3A</i> K27 and <i>H3F3A</i> G34 mutation status</li> <li>• <i>TERT</i> promoter mutation status</li> <li>• <i>EGFR</i> amplification</li> <li>• <i>CDKN2A/B</i> deletion</li> <li>• <i>BRAF</i> mutation status.</li> </ul> <p>Maximum one test per episode of disease            Fee: \$800 (85%)</p>

Source: Application form.

In the letter from the RCPA dated 20 September 2021, the proposed fee was \$800. As currently proposed in the application form lodged subsequently, it is unclear whether the fee is nominated here or the 85% benefit and this requires clarification. The fee would need to be \$887.90 for the 85% benefit to \$800, taking in to account the Greatest Permissible Gap (currently \$87.90) to ensure patients are minimally out of pocket for specialist services. The Applicant is requested to clarify this issue as it affects the item descriptor, cost-effectiveness assessments and calculations of the financial impact on the MBS. The \$800 fee proposed in the letter of 20 September 2021 has been used in the calculations, with an 85% benefit of \$712.10, taking into account the Greatest Permissible Gap.

To date, no gene panels listed in the MBS proposing ‘up to 25 genes’ (although this is not included in the item descriptor) have been costed at a fee of \$887.90. A gene panel for somatic testing with ‘at least’ 20 genes at a fee of \$700 (Application 1532) was supported by MSAC. Cost considerations include the complexity of the gene analysis, the need to identify copy number variants and gene fusions and the likely number of additional genes to provide a workable multigene panel that is cost-effective. In addition, consideration of the likely requirement for complementary approaches utilising both DNA and RNA strategies for the identification of the required range of variants will be necessary. There are a further 36 genes in addition to the 9 genes/chromosomes nominated with clinical utility in classifying gliomas in the WHO CNS5. The application form did not include a list of these genes, so to identify the potential candidate genes that might make up the proposed 25 genes (and by corollary, which would be excluded), the Applicant’s nominated expert was asked to provide a list prioritised according to maximum clinical utility (‘essential’, ‘highly desirable’ and ‘desirable’) and the WHO CNS5 and NHSE Genomic Test Directory were examined to identify any overlap with this list.

Thus a total of 48 targets for variant characterisation are presented, reduced to a working list of 26 genes or chromosomes are presented in Table 3, incorporating the intersection of those from the Applicant's essential list, any additional genes from WHO CNS5 (all of which were included in the NHSE Test Directory list) plus those from the NHSE Test Directory that have been demonstrated to have clinical utility per their assessment process, but not considering paediatric gliomas or glioblastomas. Key differences are the inclusion of potentially predictive targets in the NHSE Genomic Test Directory, indicated if "(the) Patient's clinical status means they are eligible for an *NTRK* inhibitor in the event an *NTRK* rearrangement is detected." It would be valuable to have a genomic test directory, led by Australian clinical experts including treating doctors to guide regarding the scope, purpose and costing of testing, especially if funding is restricted to analysing variants in 25 rather than the potential 48 target gene variants or copy number variants.

**Table 3 Genes, chromosomes and/or variants in the Applicant's lists of 'essential', 'highly desirable' and 'desirable' genes, in comparison with NHS England's Test Directory and WHO CNS5 genes.**

Essential (8, excluding <i>MGMT</i> )	Highly desirable (4)	Desirable (31)	NHSE Directory/WHO CNS5 (5)
<b>IDH1</b>	<b>CDKN2A*</b>	<i>ACVR1</i>	<b>ATRX</b>
<b>IDH2</b>	<b>CDKN2B*</b>	<b>ALK</b>	<b>BRAF-KIAA1549 fusion</b>
<b>TERT</b>	<b>HIST1H3B</b>	<i>BCOR</i>	<b>H3F3B</b>
<b>BRAF</b>	<b>HIST1H3C</b>	<i>CIC</i>	<b>TP53</b>
<b>H3F3A K27, G34</b>		<i>FGFR1#</i>	<b>VHL</b>
<b>EGFR</b>		<i>FGFR3</i>	
<b>MGMT methylation (Item 73373)</b>		<i>FOXR2</i>	
<b>1p</b>		<i>FUBP1</i>	
<b>19q</b>		<b>HIST2H3C*</b>	
		<i>MN1</i>	
		<i>MYB</i>	
		<i>MYBL1</i>	
		<b>MYC</b>	
		<i>MYCN</i>	
		<b>NF1</b>	
		<i>NF2</i>	
		<b>NTRK1</b>	
		<b>NTRK2</b>	
		<b>NTRK3</b>	
		<b>PDGFRA</b>	
		<i>PIK3CA</i>	
		<i>PIK3R1</i>	
		<i>PRKCA</i>	
		<b>PTEN</b>	
		<i>RB1</i>	
		<b>ROS1</b>	
		<b>TACC1</b>	
		<i>TSC1</i>	
		<i>TSC2</i>	
		<b>YAP1</b>	

		<b>ZFTA</b>	
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Genes with clinical utility per NHSE Genomics assessment are highlighted in green, and bold type indicates structural variants. The number of genes in each category is indicated in brackets.

\* nominated in proposed item descriptor

#also harbours mutations (SNVs) pertinent to dx of low grade neuroepithelial tumours

\*found to occur in 1 case of diffuse midline glioma, H3 K27-altered

In the meeting with the Applicant's nominated expert, no defined approach to determining the ideal number of genes was reached (or indeed, those that might reasonably be excluded); however, it is presumed that if costed at, and restricted to the nominated genes with flexibility to include up to 25 genes, then additional testing would be required if initial testing was non-diagnostic or if it did not include predictive tests. Updated costing was not provided and would be needed to understand the cost implications of expanding the panel size and increasing the complexity. MSAC may wish to guide as to whether a more comprehensive testing approach is supported, and whether additional costing is required.

The HTA Group acknowledges MSAC's previous advice about wording<sup>17</sup> and proposes the following modified Item descriptor.

**Table 4 HTA group's proposed MBS item descriptor**

<b>Category 6 – Genetics P7</b>
<p>Characterisation of variants including simple gene variants, structural variants and copy number alterations in a single gene panel in the diagnostic work-up by the pathologist, specialist or consultant physician, of a patient with clinical or laboratory evidence of a glioma, glioneuronal tumour or glioblastoma to aid diagnosis (classification by the current WHO criteria) and management, including but not limited to:</p> <ul style="list-style-type: none"> <li>(a) <i>IDH1, IDH2</i> variant testing</li> <li>(b) 1p/19q co-deletion assessment</li> <li>(c) <i>H3F3A K27</i> and <i>H3F3A G34</i> variant status</li> <li>(d) <i>TERT</i> promoter mutation status</li> <li>(e) <i>EGFR</i> amplification</li> <li>(f) <i>CDKN2A/B</i> deletion</li> <li>(g) <i>BRAF</i> variant status.</li> </ul> <p>Maximum one test per diagnostic episode            Fee: \$800; Benefit: 75%= \$525, 85%= \$712.10</p>

Source: DCAR Table 3.

This test has diagnostic, prognostic and predictive clinical utility – as such, the HTA group proposes it should be pathologist-determinable because it is embedded within a diagnostic testing algorithm, with the preceding tests determining whether it is required and what diagnostic uncertainty is resolved. This would be consistent with the NHSE National Genomic Test Directory approach for CNS tumours. There will also be requests from clinicians, seeking a review of existing cases or those investigated where these tests were not available.

The test will need to be provided within laboratories with NATA accreditation, and specialist neuro-oncology expertise<sup>18</sup>.

<sup>17</sup>[http://www.msac.gov.au/internet/msac/publishing.nsf/Content/C676085C1BBC91D9CA258227001DA027/\\$File/1527%20-%20Final%20%20PSD.pdf](http://www.msac.gov.au/internet/msac/publishing.nsf/Content/C676085C1BBC91D9CA258227001DA027/$File/1527%20-%20Final%20%20PSD.pdf) accessed 31 January 2022.

<sup>18</sup> White A, Fabian V, McDonald K, Nowak AK (2016). Compliance with reporting guidelines by Australian pathologists: an audit of the quality of histopathology reporting in high-grade glioma. *Neurooncol Pract*, 3(2):97-104.

Currently available testing with glioma panels in Australia besides the Royal Prince Alfred Hospital gene panel:

- Sonic Genetics Glioma panel<sup>19</sup>: *BRAF*, *IDH1*, *IDH2*, *TP53* with additional 1p/19q co-deletion status able to be determined by FISH in a putative oligodendroglioma - \$350
- Genomics for Life Pty Ltd (Qld) Comprehensive *Plus* Solid Tumour Analysis<sup>20</sup>: 500 genes – unable to locate list of genes or a cost on the website

## 7. Population

This application was not considered by PASC.

The target population(s) likely to receive testing with the Glioma Panel if it is publicly funded via the MBS, are patients who have been initially identified as likely to have a glioma, excluding those with an IDH-wildtype glioblastoma where a diagnosis can be made based on IDH1 IHC testing, morphological and histological analysis and clinical factors such as age, tumour location.

The HTA group agrees with the Applicant's use of the 2021 AIHW estimates of total number of patients with brain cancer, and the projected 1% population increase per year. However, a review of the literature identified that approximately 81% of brain cancers were glial tumours rather than the 40% figure used by the Applicant in estimating the population likely to be eligible for the test. Thus, the proportion of patients with gliomas is likely to be much larger than estimated by the Applicant. The Applicant estimated the number of individuals diagnosed with glioblastomas at 347 and an independent review of the literature revealed these are likely to be between 48-54%<sup>21,22</sup> of gliomas. In 2013, the AIHW specifically reported the incidence of glioblastomas (982 cases of glioblastoma, representing 62% of neuroepithelial tumours diagnosed that year). There is no reason to consider the number of cases would have decreased over time, but no updated data could be located. Applying the figure of 62% to derive the proportion of gliomas, still only yields a total of 952 cases of glioblastoma<sup>8</sup>, potentially still an underestimate but more concordant with the reported 2013 AIHW figure.

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<sup>19</sup> <https://www.sonicgenetics.com.au/our-tests/all-tests/glioma-focused-gene-panel/> accessed 11 February 2022

<sup>20</sup> <https://www.genomicsforlife.com.au/cancer-oncology-testing/comprehensive-tumour-analysis/> accessed 11 February 2022.

<sup>21</sup> Perry A.& Wesseling P (2016). 'Histologic classification of gliomas'. *Handb Clin Neurol*, **134**: 71-95.

<sup>22</sup> Ostrom QT, Cioffi G, Gittleman H, et al. (2019). CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2012-2016. *Neuro Oncol*, **21**(Suppl 5):v1-v100.

**Table 5 Estimated population eligible for testing with a Glioma Panel**

	2021	2022	2023	2024	2025	2026	2027	2028
A. Brain cancer	1,896*	1,915	1,934	1,953	1,973	1,993	2,013	2,033
B. Glioma (40% 81%† of A)	<del>758</del> 1,536†	1,551	1,567	1,582	1,598	1,614	1,630	1,647
C. Glioblastoma total (62% of B)	952	962	971	981	991	1,001	1,011	1,021
D. Glioblastomas not requiring additional testing (WHO grade 4, age, histology morphology) (C x 50%**)	476	481	486	491	495	500	505	510
E. Total number eligible (B-D)	1,060	1,070	1,081	1,092	1,103	1,114	1,125	1,136

Source: DCAR Table 4, with updates to correct rounding.

\* AIHW estimate of brain cancer incidence in 2021

† using percentage of brain cancers that are glial tumours identified by literature review

\*\* using Applicant's expert's estimated 50% of patients with glioblastoma not requiring further genetic testing for a diagnosis

The proposed Glioma Panel already appears to have largely replaced the use of stand-alone *IDH1/2* testing (Item 73372) as panel usage in the period 1 January to 31 December 2021 was reported to be 659 tests conducted in New South Wales and Western Australia (with an unknown number tested at other potential sites e.g., in Victoria). MBS utilisation data were examined to determine the current usage of Items 73371, 73372 and 73373. A calendar year was used rather than financial year as these items were listed in May 2020 and a financial year approach may not reflect usage as accurately due to delays in commencing billing.

From January 1-December 31, 2021, the MBS item usage was:

Item 73371	139
Item 73372	203
Item 73373	265
Glioma Panel	659

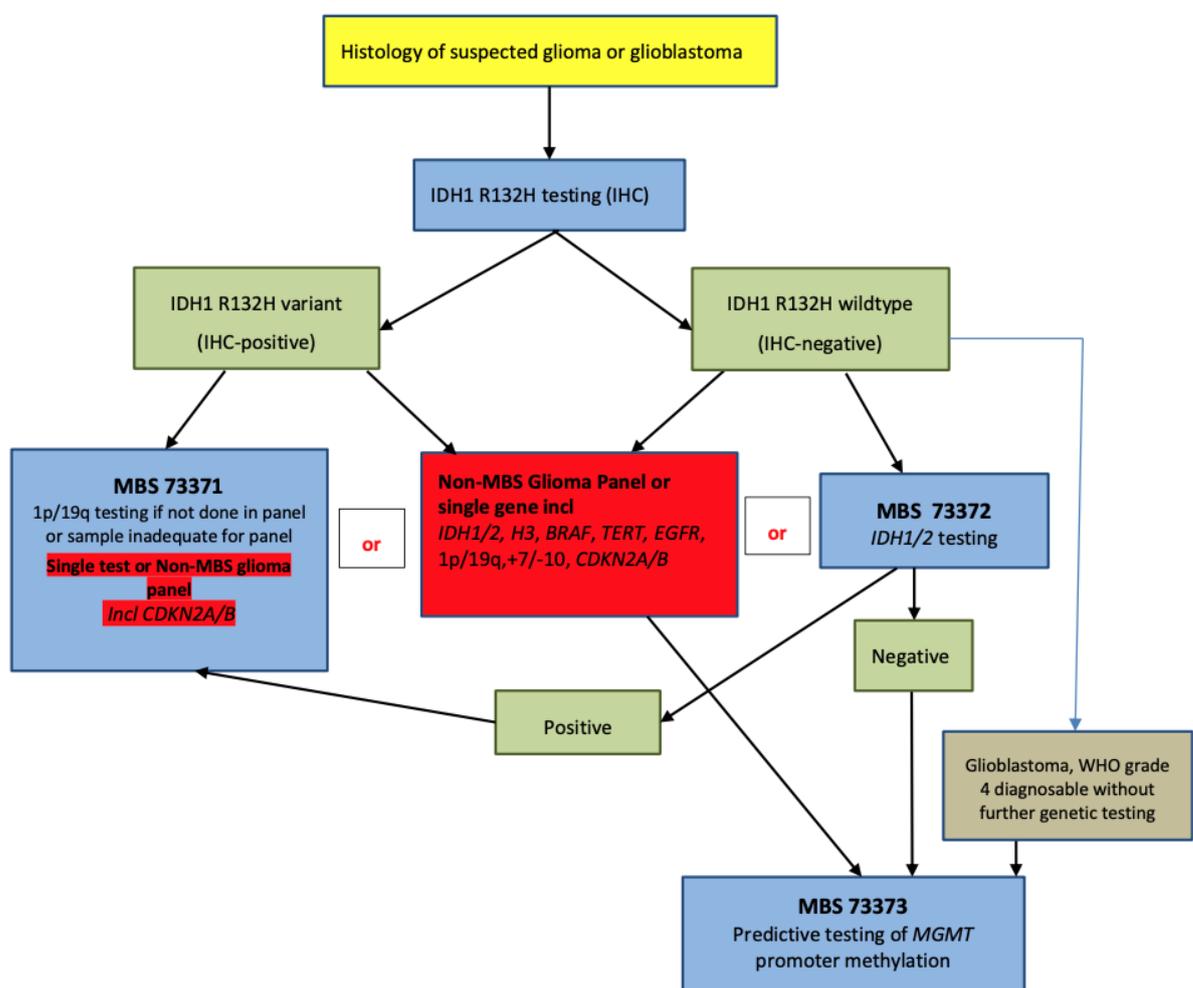
Overall, these very low numbers and the absence of billing for the services in first half of 2021 cannot be adequately explained. It is possible these tests were funded by an alternative source. From these data, it is not possible to determine the proportion of patients eligible for testing who actually received testing, as one patient may claim services under more than one MBS item and may have had this testing prior to panel testing.

A conservative approach has therefore been taken, assuming all eligible patients access molecular testing (compared with the uptake in 2021 among 659/1060 (62%) eligible patients), providing an upper limit of the likely financial impact on the MBS. If the panel is expanded to be comprehensive, and includes predictive biomarkers, a proportion of the patients with *IDH*-wildtype WHO grade 4 glioblastoma may seek testing, but the conservative approach taken in calculating the financial impact is considered likely to capture the small proportion of these patients who might access testing should it be publicly funded under the MBS.

## 8. Comparator

The comparator is testing undertaken using Items 73371 and 73372, compared with replacement of Item 73372 and a reduction in the usage of Item 73372 usage with the introduction of the Glioma Panel.

The Applicant described the current diagnostic process with the currently approved Items 73371, 73372 and 73373 after a brain tumour is identified and a biopsy taken, and depicted the algorithm if the proposed genetic testing were not available. Given the current clinical management pathway already incorporates the proposed genetic testing as the standard of care (659/1060 (62%) patients estimated to be eligible in 2021 had panel testing), the HTA group revised this algorithm to reflect current clinical practice and utilisation (Figure 1). The applicant provided a more detailed proposed algorithm with the panel testing intervention included (Figure 2).



**Figure 1 Current clinical algorithm for the diagnosis of brain cancer.** Genetic testing currently available under the MBS item numbers 73371, 73372 and 73373 is shown in blue boxes, and non-MBS-funded single genetic testing or Glioma Panel testing is shown in red boxes or red highlight.

Source: adapted from Application form 1709 p.15.

The Applicant indicated the appropriate comparator would be histological examination of a biopsy or tumour resection sample, immunohistochemistry for IDH1 (R132H), followed by sequential gene

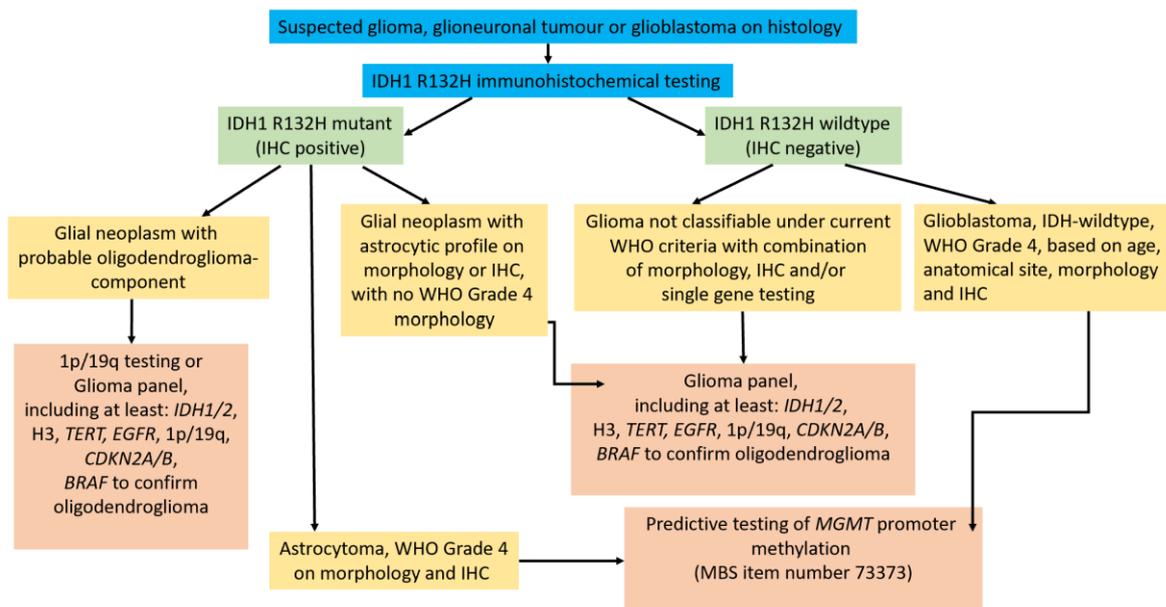
testing for non-canonical *IDH1* or *IDH2* mutations, and 1p/19q co-deletion testing. In glioblastomas *MGMT* promoter methylation status would follow.

The application form indicated the multi-gene panel would be used both in addition to and instead of services provided under existing items 73371 and 73372.

The application form states,

*'Sequential, single gene testing using MBS item numbers 73371, 73372 or 73373 depending on tumour type can be conducted; however, stepwise testing would reflex to the panel, which combined with testing for other appropriate variants provides more comprehensive testing, providing results in a shorter timeframe. Single gene testing may still be requested by clinicians and conducted by some laboratories, particularly as some laboratories have spent time and resources establishing single gene or small NGS panels in combination with 1p/19q and EGFR FISH for glioma diagnosis'*

The Applicant proposes the following clinical management algorithm with incorporation of the Glioma panel (Figure 2). After tumour biopsy or resection and following initial histological review by a pathologist with IDH (R132H) immunohistochemistry, material from the biopsy (usually 5 x 10 micron sections of tumour) would be sent for NGS analysis. NGS analysis would usually be completed within 10 working days of receipt of specimen, and this would provide a 'molecular overview' of the tumour. Currently, this testing can be accessed by a proportion of patients through alternative funding means, but there are issues of equity and out-of-pocket cost to the patient.



**Figure 2 The proposed clinical management algorithm, including a multi-gene NGS panel for the investigation of patients with suspected glioma, glioneuronal tumour or glioblastoma**

Source: Application form 1709 p.19.

### Retention of Current Items

Note is made that the Applicant recommends all current MBS items for single genetic tests remain available.

#### **MBS item number 73371**

Analysis of tumour tissue, requested by a specialist or consultant physician, that:

(a) is for the detection of chromosome 1p/19q co-deletion; and  
(b) is for a patient with clinical or laboratory evidence, including morphological features, of glial neoplasm with probable oligodendroglial component

Applicable only once per lifetime

Fee: \$340.00 Benefit: 75% = \$255.00 85% = \$289.00

**MBS item number 73372**

Analysis of tumour tissue, requested by a specialist or consultant physician, that:

(a) is for the identification of IDH1/2 pathological variant status; and

(b) is for a patient with:

(i) negative IDH1 (R132H) immunohistochemistry; and

(ii) clinical or laboratory evidence, including morphological features, of glial neoplasm

Applicable only once per lifetime

Fee: \$340.00 Benefit: 75% = \$255.00 85% = \$289.00

**MBS item number 73373**

Analysis of tumour tissue, requested by a specialist or consultant physician, that:

(a) is for the characterisation of *MGMT* promoter methylation status; and

(b) is for a patient with clinical or laboratory evidence, including morphological features, of glioblastoma

Applicable only once per lifetime

Fee: \$400.00 Benefit: 75% = \$300.00 85% = \$340.00

The HTA group considers that retention of the genetic tests with items 73371 and 73373 are appropriate, as the latter is performed independently of the panel to provide information for patients identified as having a glioblastoma. Retention of the alternate methodologies such as FISH to detect 1p/19q codeletion (Item 73371) may be important where issues related to the biopsy or tumour sample specimen preclude ensure a reliable result (e.g., low tumour cell cellularity).

However, retaining standalone *IDH1/2* genetic testing (73372) when both genes are included as 'essential' in the proposed panel would not be favourable to patients because:

- a negative or positive result would mean further genetic testing is still required for diagnostic, prognostic or predictive information – proceeding directly to the panel would have achieved this more quickly
- it leads to a sequential approach, using up potentially very limited sample and lengthening the time to complete the required diagnostic tests
- it may be used instead of a panel, and is inferior
- it is included in the proposed panel essential gene list and therefore would be duplicated

The Applicant's cited reasons for retention of the existing item descriptors based on the investment in set-up costs and other resources are problematic from a patient perspective because this is an inferior test, and for the MBS as reflex from this test to the panel would duplicate services.

## 9. Summary of public consultation input

No public consultation information was available at the time of preparation of this DCAR, and this application was not considered by PASC.

At the time of MSAC consideration, public consultation feedback was received from seven organisations;

- Australian Pathology,

- Telethon Kids Institute,
- Cancer Australia,
- The Industry Genomics Network Alliance (InGeNA),
- The Neurosurgical Society of Australasia (NSA),
- Public Pathology Australia, and
- Cooperative Trials Group for Neuro-Oncology (COGNO)

Respondents noted that this type of testing is currently available in Australia, but often at the patient's own expense, thereby disadvantaging patients who cannot afford or access this testing. All organisations agreed that with the listing of this item on the MBS, patients will benefit from equity of access to fast and accurate diagnosis of their cancer which will lead to better patient outcomes as more precise clinical management decisions can be made in a timely manner. It was also noted that listing this item on the MBS would ensure public funding for what is considered the 'standard of care' in this area, and that public funding for the diagnosis of gliomas would fall in line with World Health Organization (WHO) recommendations for determining a diagnosis.

There were no major disadvantages perceived with the listing of this item on the MBS. It was noted by one organisation that gene panel testing is more efficient than single gene testing, and gene panels may overall be cost saving for the laboratory and the healthcare system. One organisation commented that gain of chromosome 7 and loss of chromosome 10 should also be encompassed by this testing.

Two organisations commented that the proposed fee was less than for *BRCA* testing, which is considered to have a similar amount of testing complexity.

## 10. Characteristics of the evidence base

The evidence cited in the Application is drawn from the 2021 WHO Classification of Tumours of the Central Nervous System, which is the reference standard for diagnosing gliomas. MSAC has previously accepted inclusion in WHO Classification as sufficient demonstration of diagnostic utility (e.g., Application 1532).

Two additional publications, including from one Australian centre, were cited by the Applicant as providing evidence of a change in the diagnosis with NGS testing for gliomas, including those sent for a specialist referral but also within a large series review in a Dutch service. Evidence of a change in health outcomes can be inferred from the rate of change of diagnoses but the impact cannot be directly measured by standard health outcomes and clinical endpoints such as progression-free or overall survival, nor readily by a linked analysis because the pathology service may not be aware of the outcomes of patients especially when consulted for a second opinion, and these tumours are rare, making a large study difficult to undertake.

## 11. Comparative safety

Performing the proposed NGS panel test does not directly alter the safety profile of the diagnostic process; however, the clinical benefits of its faster turnaround time, requiring less sample than sequential testing, the comprehensive information provided including accessing potentially effective or avoiding ineffective therapies, have the potential to impact safety.

## 12. Comparative effectiveness

In line with MSAC's consideration of Application 1527, the inclusion of biomarkers as essential for characterisation in the WHO criteria is assumed to be sufficient to justify the clinical utility, and therefore, this has not been re-examined in this report. Further supportive evidence of clinical utility can be derived from the inclusion of many of these biomarkers in the NHSE Genomic Test Directory.

Therefore, to evaluate the clinical effectiveness claims, the emphasis in this report was placed upon the impact of NGS panels in changing diagnosis and potential alteration in clinical management.

### Clinical claim

The publications cited by the Applicant support its claims that compared with the current testing available, publicly funding the Glioma panel via the MBS would:

- Negate the need for sequential gene testing which risks using all the available biopsy material
- Have a faster turnaround time: 2 weeks, vs 6 weeks with sequential testing
- Provide comprehensive test results
- Allow for treatment decisions to be made within clinically appropriate timeframes.
- Resolve diagnostic uncertainty for histologically ambiguous gliomas
- Subclassify some gliomas, that cannot be identified any other way
- Support a more efficient workflow for pathology laboratories
- Combine multiple tests into one MBS item number for an NGS panel, simplifying administrative/billing processes – but only if Item 73372 is removed.

Additional benefits of a comprehensive glioma panel including predictive biomarkers in this population with high unmet need would be:

- alignment with diagnostic criteria per the most recent WHO guidelines, which would facilitate a more accurate diagnosis and prognosis
- to expand treatment options including eligibility for investigational and approved therapies

## 13. Economic evaluation

The MSAC Executive advised on 28 January 2022 that a pragmatic economic analysis should be adopted in assessing this application. The MSAC Executive recalled its prior advice that 'cost per informative result' may be useful and that in the somatic context a negative result could also be informative. The MSAC Executive advised that the DCAR should include at least cost-effectiveness measures similar to 'cost per pathogenic or likely pathogenic variant identified' or 'cost per patient without any pathogenic or likely pathogenic variants'.

With NGS somatic testing to characterise gliomas, a result that does not identify a variant is still informative as part of the WHO integrated diagnosis, as some glioma entities are defined by the presence or absence of one or more variants; and therefore proposed the cost per patient where testing with an NGS Glioma panel yields an informative result was calculated on the basis of the test yielding information that alters the diagnosis and management (which includes ruling out potential differential diagnoses that remain after prior testing e.g., those tumour types that can only be diagnosed with molecular testing per WHO CNS5; or that eliminates a diagnosis of malignancy where there is uncertainty).

In a large retrospective series of 443 gliomas analysed with an NGS panel, survival outcomes were presented based on a molecular diagnosis alone according to the pattern of expression or diagnosis obtained. Prognostic information was obtained for different subgroups, including where no variants were identified, or where only variants that do not define a specific entity were identified<sup>23</sup>. Although used to identify predictive variants and eligibility for clinical trials, the diagnostic yield for this purpose was not presented separately.

In a smaller Australian dataset that focussed on diagnostic effectiveness (71 assessable test results with histological data for comparison) with prognostic information reported based on the variants identified (rather than from following patient outcomes as in the Dutch study above) and predictive value was not reported, Cheung et al (2021)<sup>24</sup> reported 93% of patients had a test result that informed the diagnosis using an NGS panel examining 26 genes or chromosomes that are frequently aberrant in gliomas. This predated the inclusion in the MBS of the Items 73371 and 73372.

Neither of the publications used NGS panels that incorporate all the biomarkers in WHO CNS5, nor all predictive variants reported in gliomas to date, and therefore there is likely to be additional clinical utility, and important decision-making information provided for a greater proportion of patients if expanded to incorporate these; however, determining the cost-effectiveness of an expanded panel requires the proposed panel composition to be defined and a costing that reflects the complexity of comprehensive testing.

To undertake a comparative cost-effectiveness analysis to provide a value proposition with listing of an NGS panel compared the currently listed items, the diagnostic, prognostic and predictive yield was analysed from the Australian study<sup>24</sup>. deWitt et al. (2017)<sup>25</sup> reported the diagnostic yield in patients with gliomas receiving just 1p/19q and *IDH1/2* testing (Items 73371 and 73372) and this was used to support calculation of testing outcomes where not reported in the Australian study. Based on the Australian dataset, which provided a list of altered or refined diagnoses, or where prognosis was altered using the NGS panel compared with histological assessment alone, it was possible to identify those cases which may have been detected with the single genetic tests currently funded by the MBS (i.e. the comparator). As the NGS panel was not designed to detect therapeutic targets and these were not reported, a literature-based approach was taken to determine from this Australian panel of genes and copy number variants, the likely detection of predictive targets and the ICER for NGS panel presented with the diagnostic, prognostic and predictive detection rates combined. Incremental cost-effectiveness ratios (ICERs) for the different test purposes are presented below (Table 6).

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<sup>23</sup> Synhaeve NE, et al. (2018). 'Clinical evaluation of a dedicated next generation sequencing panel for routine glioma diagnostics'. *Acta Neuropathol Commun*, **6**(1), 126.

<sup>24</sup> Cheung VKY, Buckland ME, et al (2021). Next generation sequencing impacts the classification and management of primary brain tumours. *Pathology*, **53**(6): 780-782.

<sup>25</sup> deWitt J, et al. (2017). Cost-effectiveness of IDH testing in diffuse gliomas according to the 2016 WHO classification of tumors of the central nervous system recommendations. *Neuro-Oncology*, **19**(12): 1640-50.

**Table 6 Cost-effectiveness of glioma gene panel testing for a range of effectiveness measures**

	Intervention	Comparator	Increment	ICER
Cost of testing	\$887.90	\$340	\$547.90	
Effectiveness measures:				
<i>Patients receiving a result that altered their diagnosis</i>	<i>0.211</i>	<i>0.001</i>	<i>0.210</i>	<i>\$2,609</i>
Patients receiving a result that altered their diagnosis or prognosis	0.296	0.079	0.217	\$2,527
Patients receiving a result that altered or refined their diagnosis or altered their prognosis	0.408	0.132	0.276	\$1,979
Patient receiving a result that altered or refined their diagnosis, altered their prognosis, or identified a potentially predictive* target	0.563	0.132	0.431	\$1,269
Patient receiving a result that altered diagnosis or prognosis, refined or confirmed diagnosis per WHO CNS5 (including removing uncertainties), or identified a potentially predictive* target	0.930	0.132	0.798	\$687

Source: Rejoinder Table 5A, with updates to correct rounding. Italics indicates additions by MSAC.

\* defined as targets with potential treatments (approved or investigational)

## 14. Financial/budgetary impacts

An epidemiological approach was taken to estimate the financial impact. Assumptions included inclusion in the MBS from 1 January 2023, all eligible patients accessing the Glioma Panel, a reduction in usage of Item 73371 and discontinuation of Item 73372 from the time of listing. These cost estimates are likely to be overestimated, as it is not certain currently what proportion of patients diagnosed with a glioma proceed to a biopsy or resection or have additional genetic testing.

The financial implications to the MBS resulting from the proposed listing of a Glioma Panel test over the 6 years following listing are summarised in Table 7. Key assumptions are that all eligible patients will access testing, that Item 73372 will be removed at the time the Glioma Panel is listed, and utilisation of Item 73371 will decline to 10% of prior usage.

**Table 7 Net financial implications of a Glioma Panel to the MBS**

Parameter	2022	2023	2024	2025	2026	2027	2028
<b>Estimated use and cost of the proposed health technology</b>							
Number of people eligible for Glioma Panel test	1,070	1,081	1,092	1,103	1,114	1,125	1,136
Number of people who undergo Glioma Panel test	0	1,081	1,092	1,103	1,114	1,125	1,136
Number of services of Glioma Panel (if more than one per person)	-	-	-	-	-	-	-
Cost to the MBS (85%=\$800)	\$0	\$864,779	\$873,427	\$882,161	\$890,983	\$899,893	\$908,892
<b>Change in use and cost of other health technologies</b>							
Change in use of Item 73372	\$0	-\$59,837	-\$60,436	-\$61,040	-\$61,651	-\$62,267	-\$62,890
Change in use of Item 73371	\$0	-\$35,819	-\$37,187	-\$37,559	-\$37,934	-\$38,314	-\$38,697
Net change in costs to the MBS (with appropriate copayments excluded)	\$0	-\$96,656	-\$97,623	-\$98,599	-\$99,585	-\$100,581	-\$101,586
<b>Net financial impact to the MBS</b>	\$0	\$768,123	\$775,804	\$783,562	\$791,398	\$799,312	\$807,305

Source: Rejoinder Table 6A, with updates to correct rounding, and Department edits in italics to correct changes in use of 73371 and 73372.

## 15. Other relevant information

Nil.

## 16. Applicant comments on MSAC's Public Summary Document

The College and Fellows would like to express their delight in MSAC approving public funding for the genetic testing of glioma, and to thank the Department for its assistance throughout the long application and assessment process. Public funding for this testing will result in better patient outcomes and significantly reduce inequity in access to genetic testing in this group of patients.

## 17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)