



Australian Government

Department of Health

MSAC Application 1709

Somatic gene testing of gliomas (resubmission)

This application form is to be completed for new and amended requests for public funding (including but not limited to the Medicare Benefits Schedule (MBS)). It describes the detailed information that the Australian Government Department of Health requires to determine whether a proposed medical service is suitable.

Please use this template, along with the associated Application Form Guidelines to prepare your application. Please complete all questions that are applicable to the proposed service, providing relevant information only. Applications not completed in full will not be accepted.

Should you require any further assistance, departmental staff are available through the Health Technology Assessment Team (HTA Team) on the contact numbers and email below to discuss the application form, or any other component of the Medical Services Advisory Committee process.

Email: hta@health.gov.au

Website: www.msac.gov.au

PART 1 – APPLICANT DETAILS

1. Applicant details (primary and alternative contacts)

Corporation / partnership details (where relevant):

Corporation name: The Royal College of Pathologists of Australasia

ABN: REDACTED

Business trading name: The Royal College of Pathologists of Australasia

Primary contact name: REDACTED

Alternative contact numbers

Business: REDACTED

Mobile: REDACTED

Email: REDACTED

Alternative contact name: REDACTED

Alternative contact numbers

Business:

Mobile: REDACTED

Email: REDACTED

2. (a) Are you a lobbyist acting on behalf of an Applicant?

Yes

No

(b) If yes, are you listed on the Register of Lobbyists?

Yes

No

PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

3. Application title

Somatic gene testing for the diagnosis of glioma, including glioblastoma.

4. Provide a succinct description of the medical condition relevant to the proposed service (no more than 150 words – further information will be requested at Part F of the Application Form)

Brain cancer in Australia is relatively rare with a 2021 incidence of approximately 6.5 per 100,000 individuals.¹ The most prevalent brain tumours are brain metastases, meningiomas (which are mostly benign), and the most common tumour of the central nervous system, gliomas. Gliomas include astrocytomas, oligodendrogliomas, ependymomas, and other rare histologies. Glioblastomas are the most common and most aggressive type of astrocytoma, representing 45% of malignant primary brain tumours. Patients usually present with headaches, seizures, or focal neurological symptoms and due to its aggressive nature, symptoms tend to develop rapidly. Ongoing symptoms include medical and neurologic complications including seizures and cerebral oedema, neurocognitive decline, depression, fatigue, endocrinopathies, and venous thromboembolism.² In Australia, the average 5-year survival rate for persons diagnosed with brain cancer is only 22.3 per cent.¹

According to the 2021 the World Health Organization (WHO) classification of brain tumours, accurate classification and grading of gliomas requires a combination of histological and molecular features identified on samples obtained through biopsy or surgical resection to arrive at an “integrated diagnosis”.^{2,3}

5. Provide a succinct description of the proposed medical service (no more than 150 words – further information will be requested at Part 6 of the Application Form)

Small to medium sized gene panel (up to 25 genes) testing in patients who have been pathologically diagnosed with a glioma or glioneuronal tumour, and who are immune-negative for IDH1 (R132H). In accordance with the WHO classification, the panel must be able to detect at least, but not limited to: *IDH1/2*, *BRAF*, H3 K27 and G34 mutation status, *TERT* promoter mutation status, *EGFR* amplification, *CDKN2A/B* deletion and 1p/19q codeletion.

The latest WHO classification of brain tumours highlights the critical importance of molecular diagnostics in the accurate diagnosis and accurate classification of brain tumours. For some entities, molecular information is required to provide an “integrated” diagnosis and only a descriptive histological diagnosis is acceptable if no molecular diagnostic testing is available. Identification of co-deletion of chromosome 1p/19q regions is important for accurate diagnosis of oligodendrogial tumours, and *IDH1/2* mutations and *MGMT* promoter methylation add important prognostic and predictive information to the histopathological diagnosis of gliomas.³⁻⁵

6. (a) Is this a request for MBS funding?

- Yes
 No

(b) If yes, is the medical service(s) proposed to be covered under an existing MBS item number(s) or is a new MBS item(s) being sought altogether?

- Amendment to existing MBS item(s)
 New MBS item(s)

(c) If an amendment to an existing item(s) is being sought, please list the relevant MBS item number(s) that are to be amended to include the proposed medical service:

N/A

(d) If an amendment to an existing item(s) is being sought, what is the nature of the amendment(s)?

N/A

(e) If a new item(s) is being requested, what is the nature of the change to the MBS being sought?

- i. A new item which also seeks to allow access to the MBS for a specific health practitioner group
- ii. A new item that is proposing a way of clinically delivering a service that is new to the MBS (in terms of new technology and / or population)
- iii. A new item for a specific single consultation item
- iv. A new item for a global consultation item(s)

(f) Is the proposed service seeking public funding other than the MBS?

- Yes
- No

(g) If yes, please advise:

N/A

7. What is the type of service:

- Therapeutic medical service
- Investigative medical service
- Single consultation medical service
- Global consultation medical service
- Allied health service
- Co-dependent technology
- Hybrid health technology

8. For investigative services, advise the specific purpose of performing the service (which could be one or more of the following):

- i. To be used as a screening tool in asymptomatic populations
- ii. Assists in establishing a diagnosis in symptomatic patients
- iii. Provides information about prognosis
- iv. Identifies a patient as suitable for therapy by predicting a variation in the effect of the therapy
- v. Monitors a patient over time to assess treatment response and guide subsequent treatment decisions

9. Does your service rely on another medical product to achieve or to enhance its intended effect?

- Pharmaceutical / Biological
- Prosthesis or device
- No

10. (a) If the proposed service has a pharmaceutical component to it, is it already covered under an existing Pharmaceutical Benefits Scheme (PBS) listing?

N/A

(b) If yes, please list the relevant PBS item code(s):

N/A

(c) If no, is an application (submission) in the process of being considered by the Pharmaceutical Benefits Advisory Committee (PBAC)?

N/A

(d) If you are seeking both MBS and PBS listing, what is the trade name and generic name of the pharmaceutical?

N/A

11. (a) If the proposed service is dependent on the use of a prosthesis, is it already included on the Prostheses List?

N/A

(b) If yes, please provide the following information (where relevant):

N/A

(c) If no, is an application in the process of being considered by a Clinical Advisory Group or the Protheses List Advisory Committee (PLAC)?

N/A

(d) Are there any other sponsor(s) and / or manufacturer(s) that have a similar prosthesis or device component in the Australian market place which this application is relevant to?

N/A

(e) If yes, please provide the name(s) of the sponsor(s) and / or manufacturer(s):

N/A

12. Please identify any single and / or multi-use consumables delivered as part of the service?

Single use consumables: General laboratory consumables

PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

The National Association of Testing Authorities (NATA) and the Royal College of Pathologists Australasia (RCPA) oversee the regulation of pathology testing for clinical purposes. Laboratories require accreditation by a joint NATA/RCPA process to ISO 15189, and 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.

Note: A non-commercial IVD is required to be regulated but not to be listed on the ARTG: testing using an IVD would be delivered only by Approved Practising Pathologists in NATA Accredited Pathology Laboratories (as defined in MBS Pathology table) by referral in line with other tests in the MBS Pathology Table.

- 13. (a) If the proposed medical service involves the use of a medical device, in-vitro diagnostic test, pharmaceutical product, radioactive tracer or any other type of therapeutic good, please provide the following details:**

Type of therapeutic good: N/A

Manufacturer's name: N/A

Sponsor's name: N/A

- (b) Is the medical device classified by the TGA as either a Class III or Active Implantable Medical Device (AIMD) against the TGA regulatory scheme for devices?**

- Class III
 AIMD
 N/A

- 14. (a) Is the therapeutic good to be used in the service exempt from the regulatory requirements of the *Therapeutic Goods Act 1989*?**

- Yes (If yes, please provide supporting documentation as an attachment to this application form)
 No

- (b) If no, has it been listed or registered or included in the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)?**

- Yes (if yes, please provide details below)
 No

ARTG listing, registration or inclusion number: N/A

TGA approved indication(s), if applicable: N/A

TGA approved purpose(s), if applicable: N/A

- 15. If the therapeutic good has not been listed, registered or included in the ARTG, is the therapeutic good in the process of being considered for inclusion by the TGA?**

- Yes (please provide details below)
 No

- 16. If the therapeutic good is not in the process of being considered for listing, registration or inclusion by the TGA, is an application to the TGA being prepared?**

- Yes (please provide details below)
 No

PART 4 – SUMMARY OF EVIDENCE

17. Provide an overview of all key journal articles or research published in the public domain related to the proposed service that is for your application (limiting these to the English language only). *Please do not attach full text articles, this is just intended to be a summary.*

Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research
Review/summary of WHO Guidelines (2017) ⁴	Molecular Testing of Brain Tumors	The World Health Organization (WHO) classification of central nervous system (CNS) tumours was revised in 2016 with a basis on the integrated diagnosis of molecular genetics. This paper reviews the guidelines for using molecular genetic tests in routine pathological practice for an accurate diagnosis and appropriate management.	https://pubmed.ncbi.nlm.nih.gov/28535583/
Review/summary of WHO Guidelines (2021) ³	The 2021 WHO Classification of Tumors of the Central Nervous System: a summary	The fifth edition of the WHO Classification of Tumors of the Central Nervous System (CNS), published in 2021, is the sixth version of the international standard for the classification of brain and spinal cord tumours. The fifth edition establishes some different approaches to both CNS tumour nomenclature and grading and it emphasizes the importance of integrated diagnoses and layered reports	https://pubmed.ncbi.nlm.nih.gov/34185076/
Level III-2 diagnostic accuracy, comparative cohort Australia (2021) ⁶	Next generation sequencing impacts the classification and management of primary brain tumours	75 gliomas underwent immunohistochemical analysis followed by molecular testing. The cohort included 46 high grade gliomas (HGG). Of these, 35 were diagnosed or favoured to be glioblastomas (WHO grade IV), and 11 were anaplastic gliomas (grade III). Twenty-five cases were low grade gliomas (LGG; grade I or II). A total of 15 cases (21%) had the histological diagnosis altered by additional molecular information. 37 cases (52%) were 'confirmed diagnoses' where NGS played an important role in excluding alternative diagnoses, but the molecular information did not alter tumour classification.	https://pubmed.ncbi.nlm.nih.gov/33858664/

Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research
Systematic review and meta-analysis (2016) ⁷	Role of chromosomal 1p/19q co-deletion on the prognosis of oligodendrogliomas: A systematic review and meta-analysis	A systematic review and meta-analysis to synthesize the results and provide insight on how 1p/19q co-deletion affects prognoses of WHO grade II/III oligodendrogliomas. The difference in median overall survival (OS) time is 0.24 and the weighted mean difference for 5-year OS rate is 6.87%, favouring patients with co-deletion. The pooled hazard ratio (HR) for mortality is 0.28, favouring 1p/19q co-deletion. For progression free survival (PFS), the standardised mean difference of median PFS time is 0.13, in favour of 1p/19q co-deletion. When comparing therapies among patients with 1p/19q co-deletion, we found that those receiving radiation therapy (RT) and chemotherapy (CT) had a significantly better prognosis than those who received RT only, with pooled HR of 0.64.	https://www.sciencedirect.com/science/article/pii/S2214751916300378
Cohort (2020) ⁸ Japan	TERT promoter mutation confers favorable prognosis regardless of 1p/19q status in adult diffuse gliomas with IDH1/2 mutations	560 adult patients with IDH-mutated glioma, 279 of whom had both <i>TERT</i> promoter mutation and 1p/19q codeletion, 30 had either <i>TERT</i> promoter mutation (n = 24) or 1p/19q codeletion (n = 6) alone. A univariable Cox proportional hazard analysis for survival using clinical and genetic factors indicated that a Karnofsky performance status score (KPS) of 90 or 100, WHO grade II or III, <i>TERT</i> promoter mutation, 1p/19q codeletion, radiation therapy, and extent of resection (90-100%) were associated with favourable prognosis (p < 0.05). A multivariable Cox regression model revealed that <i>TERT</i> promoter mutation had a significantly favourable prognostic impact (HR = 0.421, p = 0.049), while 1p/19q codeletion did not have a significant impact (HR = 0.648, p = 0.349). Analyses incorporating patient clinical and genetic information were further conducted to identify subgroups showing the favourable prognostic impact of <i>TERT</i> promoter mutation. Among the grade II-III glioma patients with a KPS score of 90 or 100, those with IDH- <i>TERT</i> co-mutation and intact 1p/19q (n = 17) showed significantly longer survival than those with <i>IDH1/2</i> mutation, wild-type <i>TERT</i> , and intact 1p/19q (n = 185) (5-year overall survival, 94% and 77%, respectively; p = 0.032).	https://pubmed.ncbi.nlm.nih.gov/33228806/

Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research
Cohort (2015) ⁹ China	TERT promoter mutations contribute to subset prognostication of lower-grade gliomas	<p>A cohort of 237 lower-grade gliomas comprising grades II and III astrocytomas, oligodendrogliomas, and oligoastrocytomas. Mutually exclusive mutations in <i>TERT</i> promoter, C228T and C250T, were identified in 16/105 (15%) diffuse astrocytomas, 16/63 (25%) anaplastic astrocytomas, 13/18 (72%) oligodendrogliomas, 3/3 (100%) anaplastic oligodendrogliomas, 17/45 (38%) oligoastrocytomas, and 2/3 (67%) anaplastic oligoastrocytomas. Mutations co-occurred with 1p/19q codeletion ($P < 0.001$) and are associated with oligodendroglial histology ($P < 0.001$). Kaplan-Meier's survival analysis showed that <i>TERT</i> promoter mutation ($P = 0.037$), Isocitrate dehydrogenase (<i>IDH1/2</i>) mutation ($P < 0.001$), and 1p/19q codeletion ($P < 0.001$) were associated with favourable overall survival (OS). In the subset of 116 IDH-mutated lower-grade gliomas lacking 1p/19q codeletion, 19 <i>TERT</i> promoter-mutated tumours exhibited longer progression-free survival (PFS) ($P = 0.027$) and OS ($P = 0.004$). The subset of 97 IDH-mutated astrocytomas, 14 <i>TERT</i> promoter-mutated tumours showed longer PFS ($P = 0.001$) and OS ($P = 0.001$). In the subset of 74 IDH-wild-type lower-grade gliomas with intact 1p/19q, <i>TERT</i> promoter mutation was associated with shorter PFS ($P = 0.001$) and OS ($P = 0.001$). Similarly, in the subset of 65 IDH-wild-type astrocytomas, 16 <i>TERT</i> promoter-mutated tumours exhibited unfavourable PFS ($P = 0.007$) and OS ($P = 0.008$). Our results indicate that when combined with IDH status, <i>TERT</i> promoter mutation contributes to prognostic subgroups of lower-grade astrocytic tumours or 1p/19q intact lower-grade gliomas and this may further refine future molecular classification of lower-grade gliomas.</p>	https://pubmed.ncbi.nlm.nih.gov/25081751/

Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research
(2017) ¹⁰ USA	Adult infiltrating gliomas with WHO 2016 integrated diagnosis: additional prognostic roles of ATRX and TERT	<p><i>TERT</i> promoter mutations and <i>ATRX</i> alterations have been shown to be associated with prognosis. The additional prognostic information provided by these markers was analysed in 1,206 glioma patients (infiltrative glioma, grades II-IV). All cases were assigned to one of 5 groups following the WHO 2016 diagnostic criteria based on their morphologic features, and IDH and 1p/19q codeletion status. (1) Oligodendroglioma, IDH-mutant and 1p/19q-codeleted; (2) Astrocytoma, IDH-mutant; (3) Glioblastoma, IDH-mutant; (4) Glioblastoma, IDH-wildtype; and (5) Astrocytoma, IDH-wildtype.</p> <p>Among Group 1 IDH-mutant 1p/19q-codeleted oligodendrogliomas, the <i>TERT</i>-WT group had significantly worse overall survival than the <i>TERT</i>-MUT group (HR: 2.72, p = 0.04). In Group 2, IDH-mutant astrocytomas and Group 3, IDH-mutant glioblastomas, neither <i>TERT</i> mutations nor <i>ATRX</i> alterations were significantly associated with survival. Among Group 4, IDH-wildtype glioblastomas, <i>ATRX</i> alterations were associated with favourable outcomes (HR: 0.36, p = 0.01). Among Group 5, IDH-wildtype astrocytomas, the <i>TERT</i>-WT group had significantly better overall survival than the <i>TERT</i>-MUT group (HR: 0.48, p = 0.02). Testing for <i>TERT</i> promoter mutations or <i>ATRX</i> alterations provides additional useful prognostic information.</p>	https://pubmed.ncbi.nlm.nih.gov/28255664/

18. Identify yet to be published research that may have results available in the near future that could be relevant in the consideration of your application by MSAC (limiting these to the English language only). *Please do not attach full text articles, this is just intended to be a summary.*

None identified

PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

- 19. List all appropriate professional bodies / organisations representing the group(s) of health professionals who provide the service (please attach a statement of clinical relevance from each group nominated):**

The Royal Australasian College of Physicians
The Royal Australasian College of Surgeons
Pathology Australia
Clinical Oncology Society of Australia (COSA)
Human Genetics Society of Australia

- 20. List any professional bodies / organisations that may be impacted by this medical service (i.e. those who provide the comparator service):**

N/A

- 21. List the consumer organisations relevant to the proposed medical service (please attach a letter of support for each consumer organisation nominated):**

Rare Cancer Group
Cancer Voices
Rare Cancers Australia
Cure Brain Cancer Foundation
Leukaemia Foundation
Without a Ribbon
Unicorn Foundation

- 22. List the relevant sponsor(s) and / or manufacturer(s) who produce similar products relevant to the proposed medical service:**

N/A

- 23. Nominate two experts who could be approached about the proposed medical service and the current clinical management of the service(s):**

Name of expert 1: **REDACTED**

Telephone number(s): **REDACTED**

Email address: **REDACTED**

Justification of expertise: **REDACTED** His main research interests revolve around the molecular and cellular biology of adult primary brain tumours, as well as immunological and degenerative diseases of the human central nervous system.

Please note that the Department may also consult with other referrers, proceduralists and disease specialists to obtain their insight.

PART 6 – POPULATION (AND PRIOR TESTS), INTERVENTION, COMPARATOR, OUTCOME (PICO)

PART 6a – INFORMATION ABOUT THE PROPOSED POPULATION

24. Define the medical condition, including providing information on the natural history of the condition and a high level summary of associated burden of disease in terms of both morbidity and mortality:

The AIHW codes glioma and glioblastoma under ICD code C71: brain cancer. The four most common tumours of the central nervous system are meningioma, which are mostly benign (35.5%), pituitary tumours (18.7%), gliomas (15.1%), and nerve sheath tumours (10.3%).⁴ Gliomas include astrocytomas, oligodendrogliomas, ependymomas, and other rare histologies such as glioneuronal tumours. Glioblastomas are the most common and most aggressive type of astrocytoma, representing 35-45% of all gliomas.^{2,4} Patients usually present with headaches, seizures, or focal neurological symptoms and due to its aggressive nature, symptoms tend to develop rapidly. Ongoing symptoms include medical and neurologic complications including seizures and cerebral oedema, neurocognitive decline, depression, fatigue, endocrinopathies, and venous thromboembolism.²

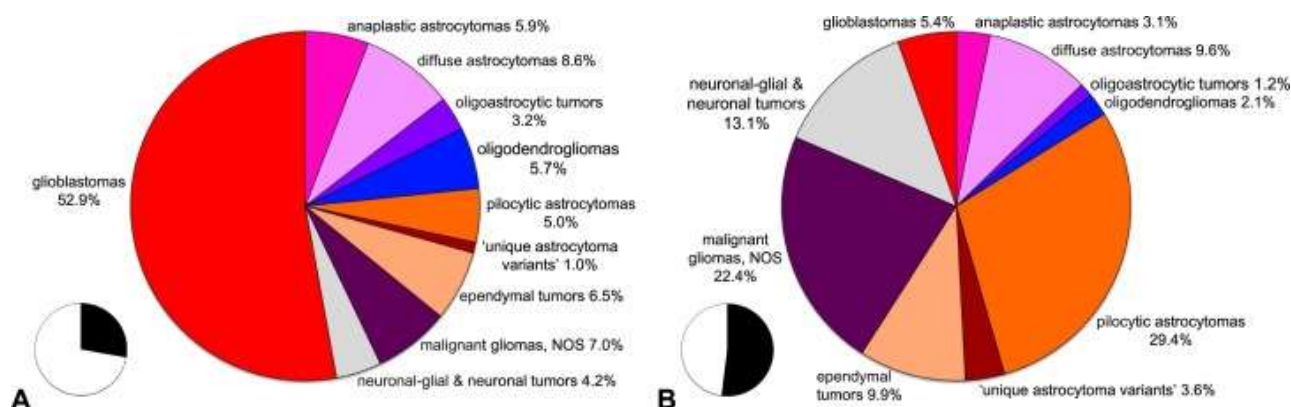


Figure 1 Relative frequency of tumour types within the overarching categories of glial, neuronal-glia, and neuronal central nervous system (CNS) neoplasms: (A) in the overall population; (B) in children and adolescents, ages 0–19 years. The black segment in the insets in the lower left corner of (A) and (B) represents the percentage of all primary CNS neoplasms diagnosed as glial, neuronal-glia, or neuronal tumours (> 25% in the overall population and >50% in children and adolescents). NOS, not otherwise specified¹¹

Brain cancer in Australia is relatively rare, and unlike many cancers, incidence has remained steady over the past 20 years. The age-standardised rate (ASR) for brain cancer is relatively low (6.7 per 100,000) in comparison to the most common cancers in Australia such as breast, prostate, lung, colorectal and melanoma (ASR ranging between 35 and 131 per 100,000) (Table 1). Incidence of brain cancer is higher in males (2017: 1,102 cases, ASR 8.4) compared to females (2017: 707 cases, ASR 5.0), with incidence increasing with age (Figure 2).^{1,12}

Table 1 Incidence (2017), mortality (2016) and 5-year relative survival (2011-2015) in Australia^{1,12}

	Incidence		Mortality		Survival
	Number	ASR*	Number	ASR*	Relative survival (%)
Brain cancer	1,809	6.7	1,439	5.3	22.1

*ASR = age standardised rate per 100,000 population

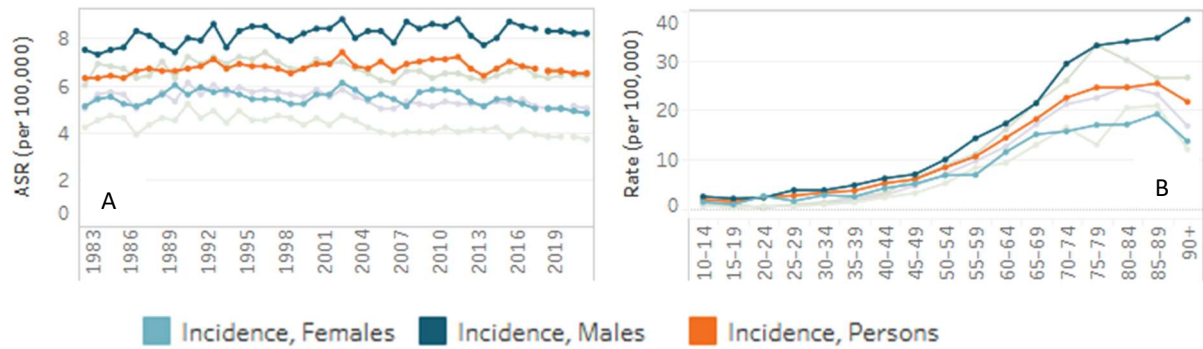


Figure 2 Incidence of brain cancer in Australia: A ASR 1982-2021 and B age-specific rates¹

Although incidence of brain cancer is low, it is associated with poor outcomes and significant mortality with an average 5-year survival rate of only 22.1 per cent (Table 1).¹² Corresponding rates of mortality are also higher in males (2017: 889 deaths, ASR 6.4) compared to females (2017: 581 deaths, ASR 3.8) (Figure 3).¹

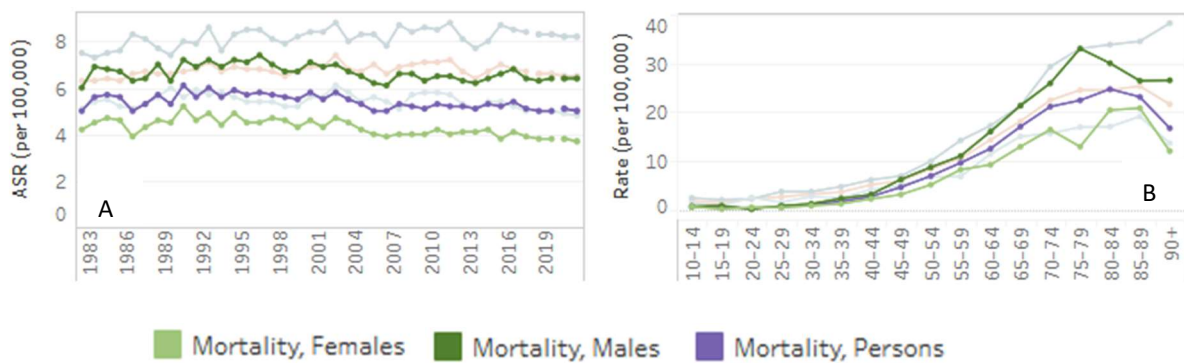


Figure 3 Rate of mortality associated with brain cancer in Australia: A) ASR 1982-2021 and B) age-specific rates¹

25. Specify any characteristics of patients with the medical condition, or suspected of, who are proposed to be eligible for the proposed medical service, including any details of how a patient would be investigated, managed and referred within the Australian health care system in the lead up to being considered eligible for the service:

Patients should be evaluated, and the treatment plan determined by a specialised multidisciplinary team including neurosurgeons, medical and radiation oncologists, but also an expert neuropathologist and neuroradiologist. Corticosteroids such as dexamethasone may be used for the reduction of tumour-associated oedema and to improve clinical symptoms but are not necessary in patients without increased intracranial pressure or with an absence of oedema-associated neurological deficits. Treatment with steroids can cease after tumour resection; however, discontinuation should be tapered to avoid toxicity associated with prolonged steroid exposure. Anti-epileptic therapy is indicated in patients presenting with seizures but should be re-evaluated after tumour resection. Glioma patients are at increased risk of thromboembolic events due to a tumour-induced hyper-coagulable state, but also as a consequence of neurological deficits, immobilisation and steroid use. However, prophylactic anticoagulation is not recommended but the use of standard anticoagulants in patients with proven thrombosis is not contraindicated.¹³

The initial therapeutic approach usually involves surgery for tumour debulking and obtaining tissue for diagnosis, with maximal tumour resection beneficial provided that neurological function is not compromised. Tissues samples obtained from resection will undergo histopathological or morphological review. Specific gene rearrangements, mutations and/or copy number changes are seen in a range of neoplasms and detection of these changes has become best practice to determine diagnosis, prognosis and for the appropriate selection of treatment for CNS tumours. Although a number of different molecular tests may be employed in the accurate diagnosis of glial tumours, the detection of co-deletion of 1p/19q chromosome regions (MBS item number 73371) is a baseline discriminator between oligodendroglial tumours and other glioma types.^{13, 14} Testing methods include in situ hybridisation (ISH),

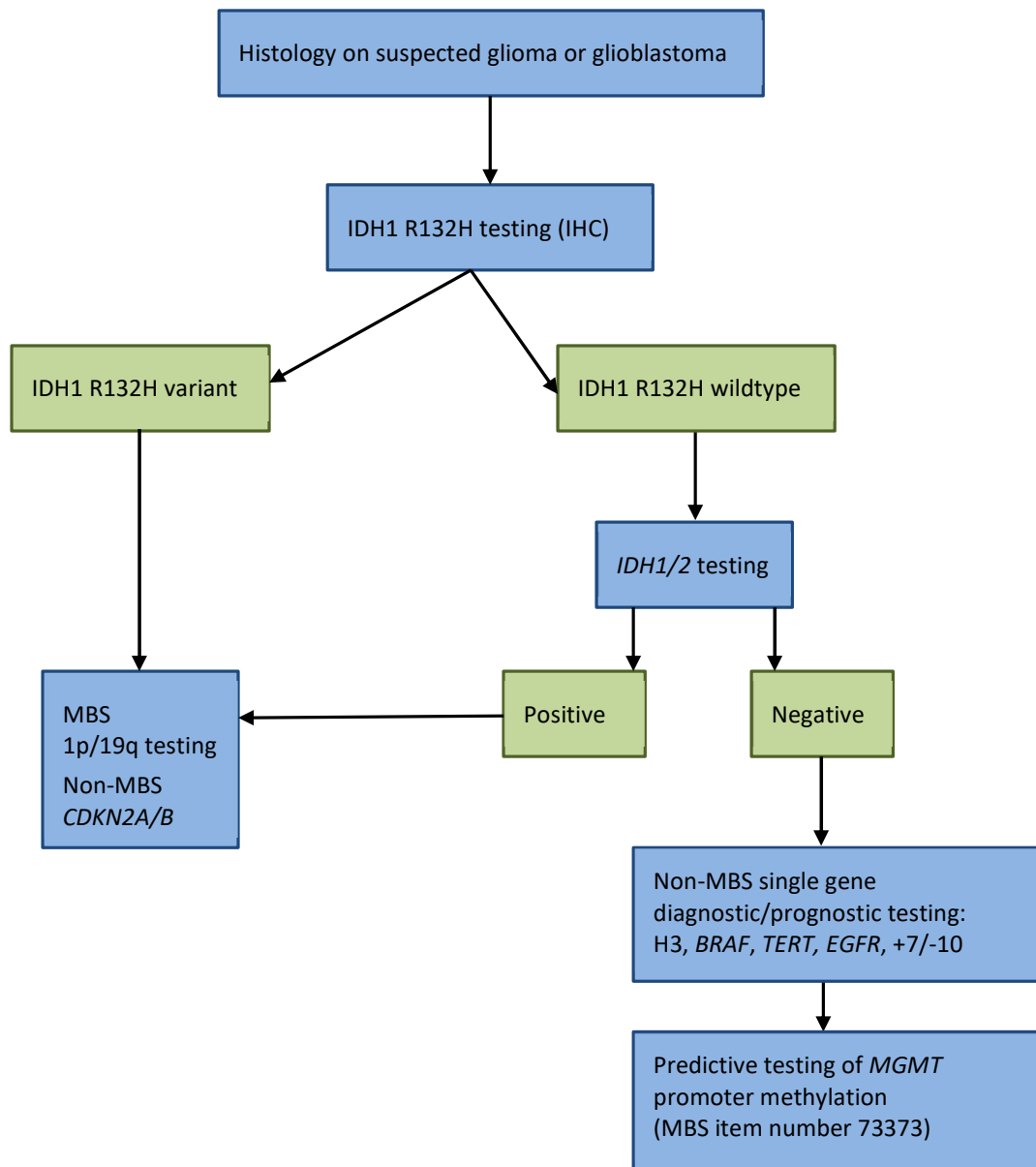
comparative genomic hybridisation (CGH) and next generation sequencing (NGS) methodologies amongst others. Single gene testing to determine *IDH1/2* mutation and *MGMT* promoter methylation status (MBS item numbers 73372 and 73373) in patients with a glioblastoma may be conducted with testing methods including in PCR, pyrosequencing and NGS methodologies amongst others.

After resection, patients may undergo radiotherapy concomitant with chemotherapy, depending on tumour type and age/frailty of the patient.¹³

26. Define and summarise the current clinical management pathway *before* patients would be eligible for the proposed medical service (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway up to this point):

The current clinical management pathway without genetic testing consists of:

- Patient presentation to general or medical practitioner with evidence or suspicion of a CNS tumour.
- Patient is referred to a specialist for investigations that would include radiology and pathology.
- Investigations would involve conducting histology on samples taken by biopsy or tumour resection, and a tentative diagnosis is made without specific molecular testing.
- Treatment for glioma and glioblastoma is based on histology and clinical judgement.



PART 6b – INFORMATION ABOUT THE INTERVENTION

27. Describe the key components and clinical steps involved in delivering the proposed medical service:

See Q25. Patients will undergo the same steps in evaluation; however, instead of single gene testing, panel testing will be conducted on resected tumour samples in accordance with the latest WHO classification of brain tumours. Identification of co-deletion of chromosome 1p/19q regions is important for accurate diagnosis of oligodendroglial tumours, *IDH1/2* mutations and MGMT promoter methylation add important prognostic and predictive information to the histopathological diagnosis of gliomas.

An update to the WHO classification, released in 2021, includes additional requisite molecular classifiers.³ The most important change is the entity of “diffuse glioma, IDH-wild type with molecular features of glioblastoma (WHO grade 4)”. This entity allows for a diagnosis of glioblastoma even when histological grading is of grade 2 or grade 3 astrocytoma, based on the presence of one of the following alterations:

- *TERT* promoter mutation,
- *EGFR* gene amplification, or
- Chr7 and Chr10 copy number changes.

This is particularly important for small biopsies, where under sampling of the tumour may lead to under grading of the histology. The molecular information required for the diagnosis of gliomas, including glioblastomas should include at least, but not be limited to, the following variants on a single small panel:

- *IDH1/IDH2* variant status (MBS item number 73371);
- 1p/19q co-deletion status (MBS item number 73372);
- *H3F3A* variant status, including H3 K27 and H3 G34 variants;
- *BRAF* variant status;
- *TERT* promoter variant status;
- *EGFR* amplification
- *CDKN2A/B* deletion
 - In the context of IDH-mutant astrocytoma, detection of *CDKN2A/B* homozygous deletion is also now a criterion for WHO grade 4 in the absence of necrosis and microvascular proliferation. This is also relevant to small biopsies which may not contain high grade features due to sampling issues. *CDKN2A/B* copy number assessment is currently not included in the MBS.

28. Does the proposed medical service include a registered trademark component with characteristics that distinguishes it from other similar health components?

N/A

29. If the proposed medical service has a prosthesis or device component to it, does it involve a new approach towards managing a particular sub-group of the population with the specific medical condition?

N/A

30. If applicable, are there any limitations on the provision of the proposed medical service delivered to the patient (i.e. accessibility, dosage, quantity, duration or frequency):

Testing should be pathologist determinable (able to be requested after a diagnosis of either CNS glioma, including glioneuronal tumours, or CNS glioblastomas is made) in order to provide definitive diagnosis/classification. Retrospective testing could also be requested by a treating clinician or pathologist and performed on archival material.

There is no role for repeat testing to monitor disease, however tumour recurrences may be tested to ensure there has been no change in molecular status.

31. If applicable, identify any healthcare resources or other medical services that would need to be delivered at the same time as the proposed medical service:

N/A

32. If applicable, advise which health professionals will primarily deliver the proposed service:

This service requires referral by a pathologist, oncologist, neurosurgeon or neurologist and collection of patient samples by a neurosurgeon under anaesthesia in hospital. Genetic testing will be delivered by trained scientists in a NATA accredited laboratory. Testing would be requested by the treating clinician and provided by Approved Practising Pathologists in line with other tests on the MBS Pathology Table.

33. If applicable, advise whether the proposed medical service could be delegated or referred to another professional for delivery:

N/A

34. If applicable, specify any proposed limitations on who might deliver the proposed medical service, or who might provide a referral for it:

Patients should be referred by a specialist neurologist/oncologist, consultant physician, neurosurgeon or pathologist.

35. If applicable, advise what type of training or qualifications would be required to perform the proposed service, as well as any accreditation requirements to support service delivery:

Testing would be delivered only by Approved Practising Pathologists in NATA Accredited Pathology Laboratories (as defined in MBS Pathology table) by referral only by registered Medical Practitioners (pathologists and non-pathologists – neurologists, neurosurgeons and oncologists) in line with other tests in the MBS Pathology Table.

36. (a) Indicate the proposed setting(s) in which the proposed medical service will be delivered (select ALL relevant settings):

- Inpatient private hospital (admitted patient)
- Inpatient public hospital (admitted patient)
- Private outpatient clinic
- Public outpatient clinic
- Emergency Department
- Private consulting rooms - GP
- Private consulting rooms – specialist
- Private consulting rooms – other health practitioner (nurse or allied health)
- Private day surgery clinic (admitted patient)
- Private day surgery clinic (non-admitted patient)
- Public day surgery clinic (admitted patient)
- Public day surgery clinic (non-admitted patient)
- Residential aged care facility
- Patient's home
- Laboratory
- Other – please specify below

(b) Where the proposed medical service is provided in more than one setting, please describe the rationale related to each:

N/A

37. Is the proposed medical service intended to be entirely rendered in Australia?

- Yes
- No – please specify below

PART 6c – INFORMATION ABOUT THE COMPARATOR(S)

38. Nominate the appropriate comparator(s) for the proposed medical service, i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system (including identifying health care resources that are needed to be delivered at the same time as the comparator service):

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.

39. Does the medical service (that has been nominated as the comparator) have an existing MBS item number(s)?

Yes (please list all relevant MBS item numbers below)

No

Single gene testing using MBS item numbers 73371, 73372 or 73373 depending on tumour type can be conducted; however, this 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. In 2020, Melbourne's Austin Hospital had 54 glioma cases, with 20% (11/54) cases sent to the Royal Prince Alfred Hospital for panel testing with 30% (16/54) undergoing single gene tests at the Austin. The remaining 50% were diagnosed by histology and immunohistochemistry alone. The 20% of cases sent to RPA for NGS panel testing typically included those where a combination of histology, immunohistochemistry and single gene testing was not sufficient for a final integrated diagnosis.

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

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 73371

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

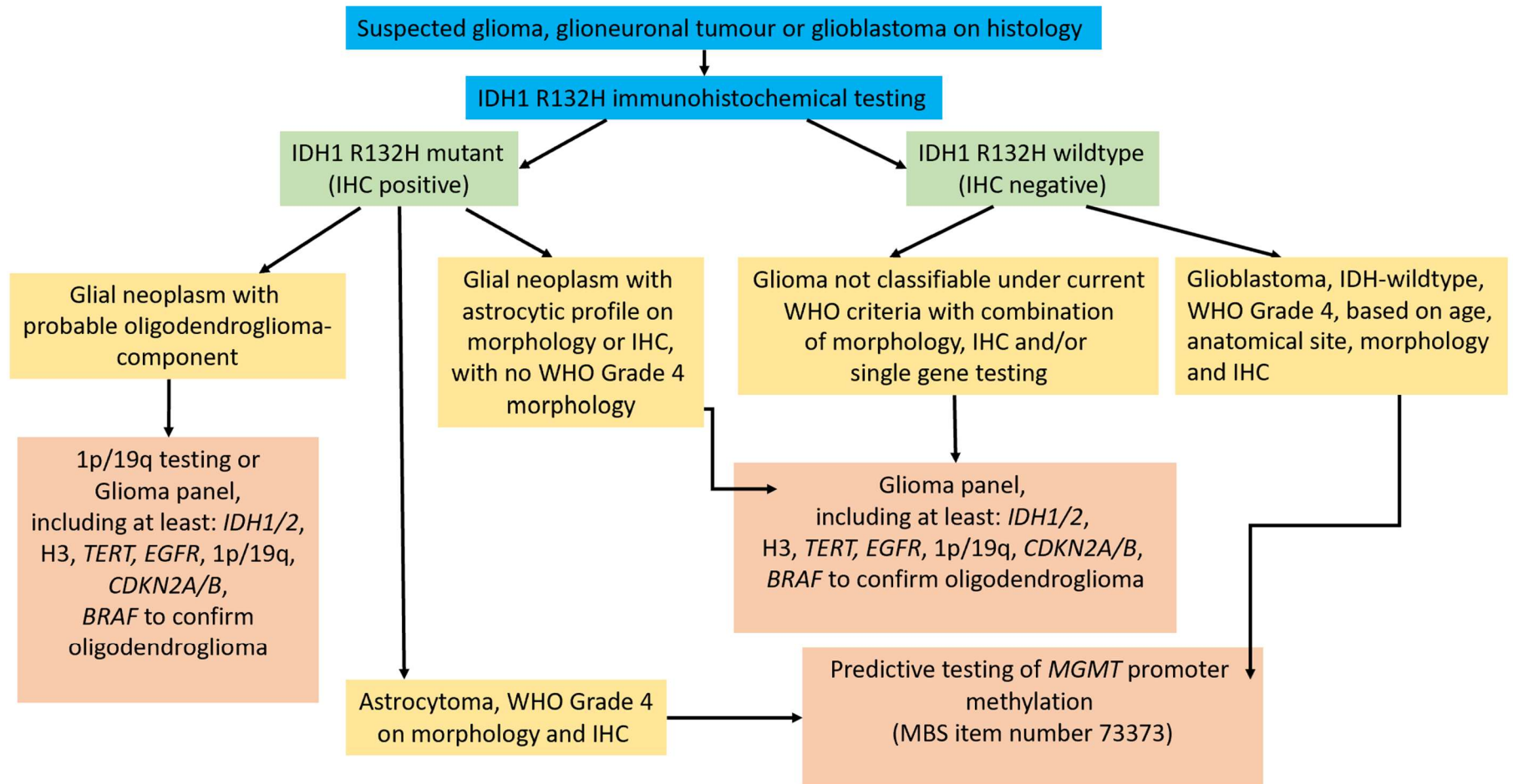
(a) is for the detection of chromosome 1p/19q co-deletion; and

(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

40. Define and summarise the current clinical management pathway/s that patients may follow *after* they receive the medical service that has been nominated as the comparator (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway that patients may follow from the point of receiving the comparator onwards, including health care resources):



41. (a) Will the proposed medical service be used in addition to, or instead of, the nominated comparator(s)?

- In addition to (i.e. it is an add-on service)
- Instead of (i.e. it is a replacement or alternative)

(b) If instead of (i.e. alternative service), please outline the extent to which the current service/comparator is expected to be substituted:

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.

42. Define and summarise how current clinical management pathways (from the point of service delivery onwards) are expected to change as a consequence of introducing the proposed medical service, including variation in health care resources (Refer to Question 39 as baseline):

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 is usually completed within 10 working days of receipt of specimen, and this would provide a 'molecular overview' of the tumour. This would negate the need for sequential gene testing, and allow for treatment decisions to be made within clinically appropriate timeframes. Reduced timeframe for molecular diagnosis of high-grade glioma on small biopsies and histologically ambiguous gliomas would expedite commencement of Stupp protocol or other appropriate clinical management.

Sequential testing of genes runs the risk of using all available biopsy tissue sample, whereas panel testing will use significantly less material, and allows tissue preservation for other testing or treatment options for the patient. In addition, by combining multiple tests into one MBS item number for an NGS panel, administrative/billing processes will also be simplified.

PART 6d – INFORMATION ABOUT THE CLINICAL OUTCOME

43. Summarise the clinical claims for the proposed medical service against the appropriate comparator(s), in terms of consequences for health outcomes (comparative benefits and harms):

Testing with a 'glioma panel' enables a more efficient and cost-saving workflow for pathology laboratories, in so doing delivering significant cost-savings to the health system. More importantly, however, small panel testing delivers significant patient benefits by reducing the size of the biopsy required and reducing the time to diagnosis (2 weeks versus an average of 6 weeks with stepwise testing). Providing a faster, more accurate diagnosis informs clinical decision-making, resulting in a change in patient management by enabling the appropriate choice of therapeutic intervention, resulting in improved outcomes for at least 20 percent of patients.

The presence of chromosome 1p/19q-co-deletion has predictive value for response to chemotherapy in anaplastic oligodendrogliomas. Randomised clinical trials have demonstrated survival advantages for these patients when treated with combined procarbazine/lomustine/vincristine (PCV) chemotherapy and radiotherapy compared with radiotherapy alone.¹⁴

Data from a recent Australian publication described the clinical utility of glioma gene panel testing in a cohort of 75 patients diagnosed with a glioma or glioblastoma.⁶ A total of 15 cases (21%) had the histological diagnosis changed by additional molecular information leading to a change in tumour classification/grading. In addition, 14 cases had the original diagnosis refined (20%) encompassing tumour categories that were suspected on morphology but required molecular confirmation. Although molecular information did not alter tumour classification, NGS played an important role in excluding alternative diagnoses in 37 cases (52%) by confirming the diagnosis.⁶ A small proportion of patients will have a change in diagnosis that will then make them eligible for PBS drugs; however, the impact on the PBS will be minimal. These results align well with overseas experience.⁵

44. Please advise if the overall clinical claim is for:

- Superiority
 Non-inferiority

The clinical claim is that panel testing of glioma patients will be non-inferior in terms of safety and superior in terms of clinical effectiveness compared to stepwise, single gene testing.

45. Below, list the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be specifically measured in assessing the clinical claim of the proposed medical service versus the comparator:

Safety Outcomes:

- Test adverse events
- Adverse events from treatment
- Adverse events from change in patient management

Clinical Effectiveness Outcomes:

Direct evidence:

- Change in patient health outcomes: mortality, morbidity, quality of life

Indirect evidence

- Change in management/treatment resulting in change in patient outcomes: mortality, morbidity, quality of life

Health system resources:

- Cost of gene panel
- Cost of targeted therapies
- Cost per quality-adjusted life year
- Total Australian Government healthcare costs

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

46. Estimate the prevalence and/or incidence of the proposed population:

The AIHW codes glioma and glioblastoma under ICD code C71: brain cancer, with approximately 40% of these being gliomas (and approximately 48% of these are glioblastomas) (Table 2)

Table 2 Incidence (2017), mortality (2016) and 5-year relative survival (2011-2015) in Australia^{1, 12}

	Incidence		Mortality		Survival
	Number	ASR*	Number	ASR*	Relative survival (%)
Brain cancer	1,809	6.7	1,439	5.3	22.1

*ASR = age standardised rate per 100,000 population

47. Estimate the number of times the proposed medical service(s) would be delivered to a patient per year:

Once per episode of disease.

48. How many years would the proposed medical service(s) be required for the patient?

Once per episode of disease

A tumour recurrence may require re-testing to determine if the tumour status has changed.

49. Estimate the projected number of patients who will utilise the proposed medical service(s) for the first full year:

Approximately 40% of the incident cases of brain cancer will be a glioma, equating to approximately 723 cases that may require panel testing, of which 347 will be a glioblastoma. Based on current utilisation of panel testing in Australia, it is unlikely that all of these patients will undergo panel testing.

50. Estimate the anticipated uptake of the proposed medical service over the next three years factoring in any constraints in the health system in meeting the needs of the proposed population (such as supply and demand factors) as well as provide commentary on risk of 'leakage' to populations not targeted by the service:

The number of incident cases of brain cancer has remained relatively steady over the past 20 years; however, it may be reasonable to factor in a 1% increase in incidence (Table 3). Leakage to populations not targeted by the service will be constrained by the MBS item number descriptors to ensure testing is applied only where clinically indicated.

Table 3 Expected number of new patients with brain cancer* in Australia

	2021**	Expected 2022	Expected 2023	Expected 2024
Brain cancer	1,896	1,915	1,934	1,953
Glioma	758	766	773	781

* Gliomas account for approximately 40% of all brain cancers, and glioblastoma approximately 48% of gliomas

** Based on expected numbers¹

PART 8 – COST INFORMATION

51. Indicate the likely cost of providing the proposed medical service. Where possible, please provide overall cost and breakdown:

Equipment and resources	Gilomas
DNA extraction, library preparation and Next generation sequencing	\$456
Labour medical (consultant pathologist)	\$75.00
Labour scientific	\$175.00
Total costs per Test	\$706.00

Note: Total cost of \$706 does not include repeats for failed library preparation or equipment maintenance

52. Specify how long the proposed medical service typically takes to perform:

7 -10 working days

53. If public funding is sought through the MBS, please draft a proposed MBS item descriptor to define the population and medical service usage characteristics that would define eligibility for MBS funding.

Category 6 –Genetics P7
<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"> • <i>IDH1</i>, <i>IDH2</i> variant testing • 1p/19 co-deletion assessment. • <i>H3F3A</i> K27 and <i>H3F3A</i> G34 mutation status • <i>TERT</i> promoter mutation status, and • <i>EGFR</i> amplification • <i>CDKN2A/B</i> deletion • <i>BRAF</i> mutation status <p>Maximum one test per episode of disease Fee: \$800 (85%)</p>

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