

# Medical Services Advisory Committee (MSAC) Public Summary Document

## *Application No. 1684 – Genetic testing for variants associated with haematological malignancies*

**Applicant:** Royal Australasian College of Pathologists

**Date of MSAC consideration:** 24-25 November 2022

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

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

An application requesting Medicare Benefits Schedule (MBS) listing of genetic testing for variants associated with haematological malignancies was received from the Royal College of Pathologists of Australasia (RCPA) by the Department of Health and Aged Care.

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

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC supported the creation of new Medicare Benefits Schedule (MBS) items for next-generation sequencing (NGS) gene panel testing for genetic variants associated with haematological malignancies. These items should specify testing methodology using 1) DNA and RNA, and 2) DNA only, to reflect laboratories different testing capabilities; and a practice note be included referring to “appropriate international guidelines” rather than specifying particular gene variants.

MSAC noted limitations in the clinical evidence but considered that NGS panel testing had superior effectiveness and non-inferior safety compared with no NGS panel testing. MSAC accepted that NGS panel testing had been demonstrated to have diagnostic and/or prognostic and/or predictive utility, with acceptable cost-effectiveness. MSAC considered there was uncertainty in the estimated financial impact as utilisation may be underestimated but noted that there could be likely significant cost offsets due to this testing replacing other types of tests currently reimbursed on the MBS.

The MSAC supported item descriptors and draft explanatory note are provided below.

Category (6) – Pathology services – Group P7 Genetics
<p>MBS item AAAA</p> <p>Characterisation of variant(s) in a panel of at least 25 genes using DNA and RNA, requested by a specialist or consultant physician, to determine the diagnosis, prognosis and/or management of a patient presenting with a clinically suspected haematological malignancy of myeloid origin</p> <p>Applicable once per diagnostic episode at diagnosis, disease progression or relapse</p>
Fee: \$1,100 Benefit: 75% = \$825 85% = \$1,006.80
Category (6) – Pathology services – Group P7 Genetics
<p>MBS item BBBB</p> <p>Characterisation of variant(s) in a panel of at least 25 genes using DNA and RNA, requested by a specialist or consultant physician, to determine the diagnosis, prognosis and/or management of a patient presenting with a clinically suspected haematological malignancy of lymphoid origin</p> <p>Applicable once per diagnostic episode at diagnosis, disease progression or relapse</p>
Fee: \$1,100 Benefit: 75% = \$825 85% = \$1,006.80
Category (6) – Pathology services – Group P7 Genetics
<p>MBS item CCCC</p> <p>Characterisation of variant(s) in a panel of at least 25 genes using DNA, requested by a specialist or consultant physician, to determine the diagnosis, prognosis and/or management of a patient presenting with a clinically suspected haematological malignancy of myeloid origin</p> <p>Applicable once per diagnostic episode at diagnosis, disease progression or relapse</p>
Fee: \$927.90 Benefit: 75% = \$725 85% = \$840
<p>MBS item DDDD</p> <p>Characterisation of variant(s) in a panel of at least 25 genes using DNA, requested by a specialist or consultant physician, to determine the diagnosis, prognosis and/or management of a patient presenting with a clinically suspected haematological malignancy of lymphoid origin</p> <p>Applicable once per diagnostic episode at diagnosis, disease progression or relapse</p>
Fee: \$927.90 Benefit: 75% = \$725 85% = \$840

85% benefit reflects the 1 November 2022 Greatest Permissible Gap (GPG) of \$93.20. All out-of-hospital Medicare services that have an MBS fee of \$621.50 or more will attract a benefit that is greater than 85% of the MBS fee – being the schedule fee less the GPG amount. The GPG amount is indexed annually on 1 November in line with the Consumer Price Index (CPI) (June quarter).

<b>TN.PN.X.XX</b>
<i>Testing should include, but not be restricted to, genes described in the current World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms or other appropriate international guidelines.</i>

## Consumer summary

This application from the Royal College of Pathologists of Australasia (RCPA) was for Medicare Benefits Schedule (MBS) listing of genetic testing for variants associated with haematological malignancies (blood cancers) using gene panels. This application was for two gene panels, to look for the genetic causes of two different types of blood cancers. One gene panel was proposed for myeloid cancers and one for lymphoid cancers. A gene panel is when many genes are tested at the same time.

Blood cancers are a diverse group of diseases, and include cancers such as lymphoma, myeloma and leukaemia. Blood cancers can be broadly categorised based on their cell of origin (lineage) into myeloid or lymphoid cancers. The cancer actually involves a special cell, called a “progenitor cell”. This is an ancestor cell that has the potential to become several different types of cells in the one lineage. Myeloid cancers are due to cancers in cells that come from the bone marrow. These cells eventually turn into red blood cells, platelets and some white blood cells. Lymphoid cancers are due to cancers in cells that come from the lymphatic system. These cells eventually turn into white blood cells that fight infections.

The proposed genetic tests can help haematologists (blood cancer doctors) work out what specific type of blood cancer a patient has. This information can help a haematologist work out what is the right treatment for that patient. The information would also help doctors understand what the patient’s chances of recovery might be and whether the cancer might come back again.

There are currently gene tests that look for variants in only a single gene for some blood cancers, available on the MBS. The proposed gene panels will include more genes than what is currently available. Using gene panels therefore increases the chance of finding relevant genetic variants and being able to make an accurate diagnosis. The World Health Organization recommends using genetic testing to accurately diagnose haematological malignancies.

MSAC considered this type of genetic testing to be important for patients to receive; MSAC considered it to be safe, effective and good value for money. MSAC noted that this genetic testing may find an acquired variant in tumour tissue (called somatic variant) or blood cancer variants that can be passed down through families (called germline variants). The application only covered testing for somatic variants, so MSAC encouraged the applicant to submit a future application for genetic testing for relatives of people who have been found to have a germline genetic cause of their blood cancer.

### **MSAC’s advice to the Commonwealth Minister for Health and Aged Care**

MSAC supported listing gene panel testing for variants associated with haematological malignancies (blood cancers) on the MBS. MSAC considered the testing to be safe, effective, good value for money, and to have an acceptable cost to the MBS.

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

MSAC noted that this application from the RCPA was for MBS listing of two large multigene panels for genetic testing for variants associated with haematological malignancies. MSAC noted that it has not previously considered these specific panels, but has considered applications for single somatic genetic tests for a small number of specific haematological malignancies, for example:

- Application 1526 – diffuse large B cell leukaemia, high-grade B cell lymphoma, mantle cell lymphoma, hepatosplenic T cell lymphoma, T cell prolymphocytic leukaemia, myeloma
- Application 1532 – myeloproliferative neoplasms.

MSAC also recalled that it has previously considered applications for large multigene panels for the characterisation of variants in inherited conditions (i.e. germline testing; Applications 1585, 1598 and 1600), as well as multigene somatic testing for the diagnosis of glioma, including glioblastoma (Application 1709).

MSAC noted that haematological malignancies account for 9% of all cancers in Australia (18,485 cases in 2021) and are a heterogeneous group of disorders. Some malignancies have a long natural history, others behave aggressively from the point of diagnosis. The 5-year survival in both males and females is approximately 66%. MSAC noted that the loss or gain of genetic aberrations, including during treatment, can change the phenotype of the malignancy over the course of disease. These genetic aberrations influence the clinical course of the condition (including changing the diagnostic classification) and management decisions (due to the development of treatment resistance).

MSAC acknowledged the clinical need for the proposed molecular testing. For patients with clinical or laboratory evidence of a suspected haematological malignancy, a NGS gene panel test during the initial work-up or at suspected disease progression/relapse would assist diagnosis and/or management. MSAC noted that genetic testing is now standard of care for patients with these types of malignancies, and that the [5th edition of the World Health Organization \(WHO\) Classification of Haematolymphoid Tumours: Lymphoid Neoplasms](#) (2022) recommends molecular testing for establishing a comprehensive diagnosis. MSAC noted that without genetic testing, patients may be incorrectly diagnosed and potentially receive ineffective or incorrect treatment. MSAC also considered subsidy of molecular testing would address an area of unmet need since only one laboratory in Australia (the Peter MacCallum Cancer Centre) currently offers an NGS panel for patients (but at high out-of-pocket costs).

MSAC noted that this application builds on existing MBS items by creating two new MBS items for multigene NGS panels (one myeloid panel, one lymphoid panel) with broader gene coverage than what is currently provided by the existing MBS items. Gene panel testing is not publicly funded in this setting.

MSAC noted that the application addressed DNA testing only, and considered that there will be an increasing need for RNA-based detection of fusions in the very near future. MSAC also noted that many diagnoses cannot be made without analysis for RNA-fusion variants. MSAC referenced the WHO guidelines which specify RNA-fusion variants as diagnostic biomarkers in haematological malignancy testing. Thus, MSAC advised that testing methodology using:

- DNA and RNA should be specified in the MBS item descriptors for NGS panel testing (myeloid: AAAA; and lymphoid: BBBB), and agreed to increase the 85% benefit from the proposed \$840 to \$1,006.80 (Fee=\$1,100) to reflect the increased scope of testing
- DNA should be specified in the MBS item descriptors for NGS panel testing (myeloid: CCCC; and lymphoid: DDDD) at the agreed revised fee of \$927.90 (85% Benefit=\$840).

MSAC considered that by providing a subsidy for two options (DNA and RNA OR DNA only) it would allow laboratories time to develop testing capability for both DNA and RNA. MSAC also considered that access to DNA-only testing items could be time-limited to permit laboratories to upscale capability. The greater complexity of DNA and RNA testing justified the higher benefit than DNA only testing.

MSAC acknowledged that many laboratories would not yet have the capacity to perform RNA-fusion testing, but noted the technology is improving rapidly and considered it would not take long for laboratories to adopt this technique. MSAC also acknowledged that RNA can be more difficult to isolate from sources such as solid tissue and paraffin-embedded tissue, but did not consider this to be a valid reason to exclude the option of RNA testing from the MBS items.

MSAC considered that a pathology laboratory would follow a standardised test directory and proposed the inclusion of a practice note referring to 'appropriate international guidelines' (such as the WHO 5<sup>th</sup> edition) to determine which genes to include on each panel. MSAC did not consider it appropriate to specify particular genes given the rapid evolution of knowledge in this field. It was

assumed that clinicians will send samples to a laboratory that offers a gene panel best suited to a patient's clinical situation.

MSAC considered that the MBS items should not be pathologist-determinable, as the genetic testing should be determined by the treating clinician in discussion with the patient. MSAC also considered that utilisation would be higher if the MBS item was pathologist-determinable. MSAC advised reviewing the utilisation of these items in two years to ensure that testing was being adopted at the expected rate.

MSAC accepted the clinical management algorithm, noting that NGS panel testing may be performed earlier (given it provides more diagnostic certainty) or later in the treatment algorithm, but this would depend on the clinical context.

MSAC noted that the comparator was not NGS panel testing. MSAC noted that there are existing MBS items for genetic testing including cytogenetic testing including fluorescent in situ hybridisation [FISH] in the setting of haematological malignancy. MSAC noted the lack of direct comparative evidence for cumulative yield from other existing genetic tests that are MBS reimbursed and that the cost of the comparator would depend on the clinical context, which is complicated due to the heterogenous patient population. MSAC considered it pragmatic to assume that the costs of any comparative profiling would be considerable.

MSAC noted that the Department-contracted assessment report's (DCAR's) data came from three studies comprising prospective and retrospective case series for the myeloid panel, and three studies comprising retrospective case series for the lymphoid panel. MSAC noted that the studies were at moderate risk of bias but demonstrated that NGS panel testing has superior effectiveness and non-inferior safety compared with no NGS panel testing.

MSAC noted that 'clinically informative' outcomes tended to be reported independently in studies, but considered it highly likely that many study subjects would have experienced one or more clinically informative outcomes (even for one gene variant). MSAC also considered that not all changes in management are equal: for example, in lymphoid NGS panel studies, malignant diagnoses were often overturned, and for myeloid malignancies the use of an NGS panel was associated with substantial changes in prognosis and treatment options.

MSAC considered that the main safety issue is the unintended identification of germline variants. Without NGS panel testing, clinically significant variants will not be detected and patients may be treated with therapies that are considered inferior. In addition, MSAC considered that panel testing a small number of genes could miss some very rare diagnoses and may also be a safety issue. However, MSAC considered that the benefits of NGS testing likely outweigh any safety issues.

MSAC noted that the economic evaluation was a cost-effectiveness analysis. MSAC noted that the DCAR did not attempt to model test-to-health outcomes; rather, the DCAR summarised "clinically informative" results. The reported incremental cost-effectiveness ratios (ICERs) were \$1,300 per result that altered diagnosis including subclassification, prognosis and/or treatment to \$63,000 per change in diagnosis alone (based on an MBS fee for DNA and RNA testing of \$1,100). MSAC noted that the ICERs were most favourable when diagnosis and prognosis and treatment/management were considered, but advised that the ICERs based on these *post hoc* combined outcomes were not reliable for decision-making as the numerator was not reported in any study but was derived by the DCAR as the sum of all the individually reported test results rather than the number of patients with at least one clinically informative result (i.e. the ICERs based on the 'combined outcome' did not account for multiple clinically informative results at a patient level). If the ICERs were based on "diagnostic yield" only and reporting the proportion of patients who experienced the relevant value, then they may be between \$3,019 and \$19,014 for myeloid neoplasms and \$1,758 to \$10,496 for lymphoid neoplasms (based on an MBS fee of \$1,100). If the ICERs were based on "impact on diagnosis, prognosis and/or treatment planning", then they are more favourable and may be between \$1,546 to \$2,126 for myeloid neoplasms and \$2,128 for lymphoid neoplasms (based on an MBS fee of \$1,100). However, MSAC considered the ICERs to be of limited value for decision making due to the heterogenous and overlapping populations,

and the lack of synthesised evidence, but noted the ICERs were consistent with the approach taken in other somatic gene panel applications, reflecting the multiplicity of test purposes.

MSAC noted that the net total cost of NGS-based gene panel testing for approximately 10,000 individuals in Year 1 is estimated to be \$6.8 million (based on the MSAC supported 85% MBS rebate of \$1,006.80). This reduces to \$5.3 million in Year 6 (estimate of 12,000 patients) due to the reduction in the prevalent pool of patients who may require testing, and the assumption that the extent of cost offsets at a national level can be inferred from the cost-offsets observed in Victoria (where gene NGS-panel testing for patients with haematological malignancies is currently philanthropically funded). MSAC noted that the key source of uncertainty in the estimation of the budgetary impact was the assumption that 50% of people with haematological malignancies would be eligible for and would access NGS panel testing; MSAC considered this uptake rate may have been underestimated. MSAC noted that there may be cost offsets due to gene panel testing replacing other types of tests and more appropriate use of therapeutics; however, MSAC agreed with ESC that these are highly uncertain. MSAC advised that a review of utilisation should be conducted in 2 years.

MSAC noted that the utilisation of current MBS items for genetic testing for haematological malignancies is relatively high in Queensland in comparison with other states and territories. MSAC considered that this may require further investigation by the Department to understand the cause of such a high utilisation. Of particular interest is whether high utilisation of testing reflects the fact that pathology services are reflexively testing all suspected haematological malignancies without requester input.

MSAC noted the pre-MSAC response that stated that NGS panel testing may also discover inheritable germline variants associated with blood cancer predisposition. MSAC considered that it can be inferred from an allele frequency of  $\geq 50\%$  that a variant may be a germline variant, but MSAC considered that the value of identifying germline variants and cascade testing was not captured in the application. MSAC agreed with the applicant that appropriate policy, systems, genetic counselling and consumer support must be in place when delivering such testing to ensure the patient is aware of the possibility of identifying germline variants. There is currently no MBS item for testing to confirm whether a variant detected in somatic testing is in fact a germline variant, nor for cascade testing of relatives for the vast majority of genes likely to be identified in haematological malignancies (only cascade testing for variants in *TP53* is currently MBS-funded). MSAC noted that NGS panel testing also has clinical relevance for screening relatives as potential stem cell transplant donors, as well as determining their personal risk of cancer and other conditions to inform risk-management and family-planning decisions. MSAC considered that where it can be identified that a patient's variant is a germline variant, then cascade testing is warranted. MSAC considered that cascade testing where a germline variant has been detected through somatic testing would ideally use a generic cascade testing item, in line with MSAC's previous support for generic items under application 1599. MSAC noted the Department would work with the RCPA to develop a future application for a generic cascade testing item in this specific context of somatic testing in haematological malignancies.

MSAC noted that, for the proposed NGS gene panel testing, laboratories are required to develop, validate, and seek accreditation and listing on the Australian Register of Therapeutic Goods (ARTG) as a class III in-house in vitro diagnostic medical device, due to a lack of commercially available tests approved by the Therapeutic Goods Administration. Laboratories require accreditation by a joint National Association of Testing Authorities, Australia (NATA)/RCPA process to ISO 15189, and are specifically accredited to provide genetic testing.

## 4. Background

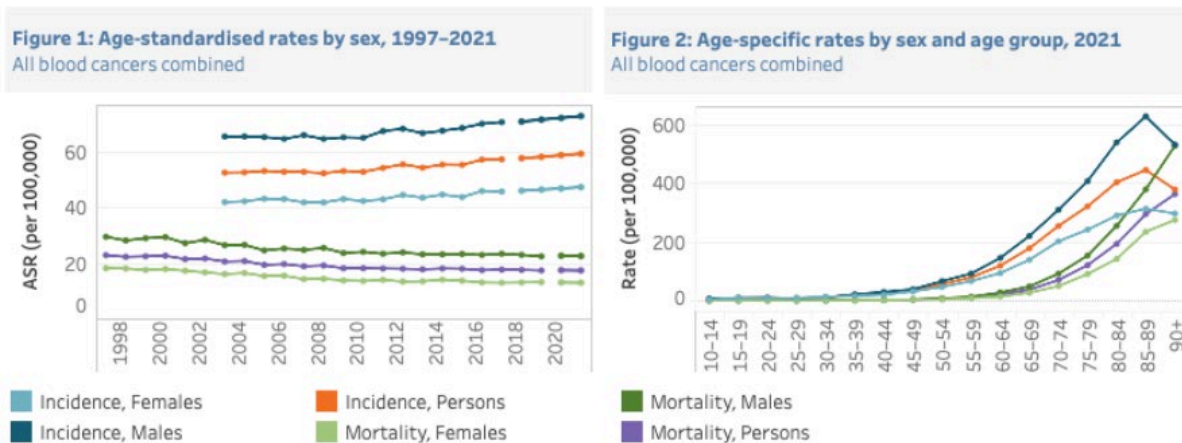
MSAC has not previously considered NGS panel testing for the characterisation of variants in haematological malignancies. MSAC has previously considered applications for single somatic genetic tests for small number of specific haematological malignancies (diffuse large B cell lymphoma, high-grade B cell lymphoma, mantle cell lymphoma, hepatosplenic T cell lymphoma,

T cell prolymphocytic leukaemia, myeloma) (Application 1526; [August 2019 Public Summary Document \[PSD\]](#)) and genetic tests for myeloproliferative neoplasms (Application 1532; [November 2020 PSD](#)). At the time of preparing this DCAR, MSAC had largely considered applications for large multigene panels for the characterisation of variants in inherited conditions (i.e., germline testing) as in Applications 1585, 1598 and 1600, and for multigene somatic testing for the diagnosis of glioma, including glioblastoma (Application 1709; [April 2022 PSD](#)).

Haematopoietic and lymphoid tissue neoplasms include lymphomas, leukaemias, myeloproliferative neoplasms, mast cell neoplasms, plasma cell neoplasms, as well as histiocytic tumours and dendritic cell neoplasms. Some of these are proliferative disorders with a propensity to transform to a malignant phenotype while others are diagnosed as malignant at the initial presentation. The continued acquisition or loss of genetic aberrations including during treatment, results in diverse combinations and permutations that contribute to a shift in phenotype over time and influence the clinical course of the condition (including changing the diagnosis) and management decisions (treatment resistance). In some instances, specific variant expression (alone or in combination with others) may define entities as a diagnostic biomarker, provide critical information about prognosis allowing risk stratification, inform potential familial predisposition and/or act as a therapeutic target.

In 2021 in Australia, 150,872 people were estimated to be diagnosed with cancer in Australia, including 18,485 with a haematological neoplasm using the AIHW's term 'All Blood Cancers combined.' Haematological malignancies account for 9% of all cancers in Australia.

When examined collectively, the majority of diagnoses of haematological neoplasms are made in adults in later life, with males consistently diagnosed at higher rates than females across all the ages and malignancies. The age-standardised incidence rate overall has been slowly increasing while mortality is slowly declining, and the 5-year survival in both males and females is approximately 66%. At any point in time, a substantial proportion will either have indolent disease under surveillance, be on treatment, in remission, or be cured – all of these contribute to the relatively high 5-year prevalence. Patient factors such as the age at diagnosis, comorbidities and personal preferences may influence the proportion of patients offered testing at diagnosis, while the high proportion who have been cured will have implications for the testing or re-testing rates among the prevalent pool.



Source: <https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/cancer-summary-data-visualisation> accessed June 7 2022

Figure 1 AIHW summary of projected incidence and mortality statistics in 2021 by sex ('All blood cancers combined')

## 5. Prerequisites to implementation of any funding advice

The proposed technology does not include a therapeutic good that requires Therapeutic Goods Administration (TGA) approval. However, there is a requirement for laboratories to develop, validate and seek accreditation and listing on the Australian Therapeutic Goods Register (ARTG) as a class III in-house IVD in many if not all applications in this area due to a lack of commercially available TGA approved tests.

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 or appropriately targeted to the most likely condition). The 2016 WHO classification provides a list of genes (the WHO HAEM5 has not yet been published so no comprehensive gene lists are available), and variants that define or characterise an entity by their presence or absence. Beyond the WHO classification, multiple additional genetic or genomic alterations with diagnostic, prognostic, familial and therapeutic implications are included in national and international clinical guidelines from bodies such as the European LeukemiaNet (ELN) and National Comprehensive Cancer Network (NCCN).

### 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.

Whereas it may be possible to define core genes where an NGS gene panel is intended to diagnose and manage a specific type of cancer (as in Application 1709), given the proposed NGS panels are to diagnose and manage a broad range of conditions which are unrelated, inclusion of nominated genes in the item descriptor to convey which genes are required for the wide range of conditions captured within each panel is no longer feasible. A 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. While myeloid malignancies have some genes that are common across most of the conditions, lymphoid malignancies have very few. It is important that gene panel composition:

- aligns with the diagnostic WHO classification, especially where these are disease-defining
- incorporates wider test purposes e.g., prognostic genes for risk stratification, gene variants that confer potential treatment options.

It is recommended that consideration be given to:

1. Establishing and maintaining a test directory, updated at intervals by Australian experts, with agreed genes within a panel test as is done in the National Health Service England



(NHSE) Genomic Test Directory, or similar to PanelApp Australia<sup>1</sup>. This would support equitable access to appropriate testing.

2. Provision of a detailed list of genes and regions analysed, similar to the Mayo Clinic, which provides such a list for each of its tests including the targeted DNA gene regions interrogated within their comprehensive 42-gene Onco-Heme NGS panel<sup>2</sup>. Although a NATA accreditation requirement, some websites lack sufficient detail to inform clinicians of the scope of testing.

## 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 by creating two new MBS items for two multi-gene NGS panel with broader coverage than currently provided.

The HTA group raises the following for MSAC's consideration:

1. Per discussion with the Applicant at a meeting on 6 May 2022, the currently proposed testing is costed for the analysis of DNA not RNA within NGS targeted multigene panel testing. RNA analysis is not currently routinely available in Australia for haematological malignancies (but is evolving rapidly) and will require resourcing and development of services. This would substantially expand the scope of testing (e.g., to include structural variants), clinical utility and diagnostic/prognostic/therapeutic information yield and further reduce the need for other genetic tests. It is likely this would require a new item or amendment of the fee for the currently proposed items (if they are supported and implemented at the time of any such application).
2. The Applicant nominated a panel size of at least 25 genes each for the myeloid and lymphoid panels, with a list of 'exemplar' genes for each from which candidate genes could be drawn. The exact composition of a panel could be at the discretion of the provider but this may not be consistent in the absence of a test directory.
3. The application lacks detail about the genes and the types of variants that are required to be tested to be fit for purpose. This reflects the breadth and heterogeneity of the conditions captured within the terms 'myeloid malignancy' and 'lymphoid malignancy' and also the lack of a test directory to accompany the application, and guide providers, requesters and patients.
  - a. Currently, no genes or copy number variants are nominated as essential in the Applicant's proposed panel and the intended scope and costing allow for at least 25 genes in total; however, the Applicant's experts included only a subset of WHO list 81 genes where variants would be detectable using DNA analysis within an NGS panel. Which 25 genes are to be included? 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 classification and other prognostic genes are provided for. Testing limited to just the Applicant's candidate genes might meet the requirements for the claiming the fee but not necessarily adequately characterise all haematological malignancies.
  - b. The application does not define the diagnostic pathway or funding source for further investigations for patients still without a diagnosis after being tested with

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<sup>1</sup> <https://panelapp.gha.umccr.org> accessed 12 June 2022

<sup>2</sup> [https://www.mayocliniclabs.com/~media/it-mmfiles/special-instructions/Targeted\\_Genes\\_Interrogated\\_by\\_OncoHeme\\_Next-Generation\\_Sequencing.pdf](https://www.mayocliniclabs.com/~media/it-mmfiles/special-instructions/Targeted_Genes_Interrogated_by_OncoHeme_Next-Generation_Sequencing.pdf) accessed 12 June 2022

- the proposed panel size, which may lead to a higher undiagnosed rate and require other additional testing and potentially lead to equity issues.
4. Germline variants are found in approximately 10% of all MDS/AML<sup>3</sup>, with higher rates where enriched by personal history of a prior malignancy, prior cancer treatment<sup>4</sup> or family history.<sup>6</sup>
    - a. WHO HAEM5 has a specific new chapter for haematological malignancies with a germline pathogenic variant. Germline pathogenic variants in the haematological cancer predisposition genes – in order of decreasing frequency *RUNX1*, *DDX41*, *GATA2*, *CEBPA*, *SAMD9L* and *TP53* (frequency order may vary according to test population<sup>5</sup>) – have been identified across a range of myeloid and lymphoid malignancies in an Australian patient cohort<sup>6</sup> and may independently determine risk stratification in some malignancies otherwise considered low-risk<sup>7</sup>.
    - b. This already meets MSAC’s previously outlined threshold of a 10% diagnostic yield to support funded access to germline testing.
    - c. Broad somatic testing strategies for haematological malignancies will identify potential germline variants requiring access to genetic counselling and further genetic testing to clarify and manage any associated risks for the individual and their family.
    - d. There is currently no MBS item for testing to confirm germline pathogenic variant status, nor for cascade testing for the vast majority of genes likely to be identified in haematological malignancies (only cascade testing for *TP53* would be eligible for MBS-funded testing). This has immediate/urgent clinical relevance for screening relatives as potential stem cell transplant donors as well as determining their personal risk of cancer/other conditions to inform risk management and family planning decisions for relatives.

This application has been amended 4 times since lodgement, variously including:

- 3 amendments to the proposed MBS items
  - A single MBS item was proposed for all haematological malignancies in the application and Ratified PICO confirmation, but subsequently the applicant proposed three new MBS items: a myeloid panel (AAAA), a lymphoid panel (BBBB) and a larger, combined lymphoid/myeloid panel at a higher proposed fee of \$1200 (CCCC). The proposed larger combined panel (40+ genes) was withdrawn on June 30<sup>th</sup> 2022, with the Applicant citing the likely low utilisation and “difficulty in identifying evidence supporting the increased benefit of a combined approach vs myeloid/lymphoid. Most patients will get the genetic test they require with AAAA and BBBB.”
  - The Applicant removed the restriction ‘Applicable once per diagnostic episode’ on the frequency of testing from the Ratified PICO confirmation – no justification was

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<sup>3</sup> 1. Tawana K, Brown AL, Churpek JE. Integrating germline variant assessment into routine clinical practice for myelodysplastic syndrome and acute myeloid leukaemia: current strategies and challenges. *British Journal of Haematology*. 2022;196(6):1293-310.

<sup>4</sup> 2. Singhal D, Hahn CN, Feurstein S, Wee LYA, Moma L, Kutyna MM, et al. Targeted gene panels identify a high frequency of pathogenic germline variants in patients diagnosed with a hematological malignancy and at least one other independent cancer. *Leukemia*. 2021;35(11):3245-56.

<sup>5</sup> The applicant advised that experience at the Peter MacCallum Centre has shown that mutations in *DDX41* are more common than *RUNX1*

<sup>6</sup> 3. Hahn CN, Babic M, Brautigam PJ, Venugopal P, Phillips K, Dobbins J, et al. Australian Familial Haematological Cancer Study - Findings from 15 Years of Aggregated Clinical, Genomic and Transcriptomic Data. *Blood*. 2019;134:1439.

<sup>7</sup> 4. DeZern AE, Dalton WB. How low risk are low risk myelodysplastic syndromes? *Expert Review of Hematology*. 2022;15(1):15-24.

provided. The Applicant subsequently advised in its pre-ESC response that this was unintentional and its preferred text is: *"Applicable once per diagnostic episode at initial diagnosis or at disease relapse"*

- 3 amendments to the requested fee
  - The 85% benefit being sought was revised in the applicant comments on the Ratified PICO confirmation (\$800), and after seeking a corresponding fee that did not account for the Greatest Permissible Gap, subsequently revised again to \$852.10 to align with that requested fee. No amended costing or justification was provided for the second increase in 85% benefit being requested.

**Table 1 Applicant's revised newly proposed MBS item AAAA for an NGS panel for characterising variants in suspected haematological malignancies of myeloid origin; amendments from Ratified PICO confirmation marked up**

<b>Category 6 – PATHOLOGY SERVICES –Group P7 Genetics</b>
<p>Characterisation of gene variant(s) <del>by a gene panel consisting of at least 25 genes</del>, requested by a specialist or consultant physician, in a patient presenting with a <del>clinically suspected</del> haematological malignancy <i>of myeloid origin that includes at least 25 genes from the exemplar list</i></p> <p>Applicable once per diagnostic episode at initial diagnosis or at disease relapse</p>
<p>Fee: \$940 Benefit: 75%=\$705 85%=\$852.10 (Revised 85% rebate to account for Greatest Permissible Gap)</p>

Proposed gene list (44 genes): ASXL1, BRAF, CALR, CBL, CD274, CEBPA, CSF3R, DDX41, DNMT3A, ETNK1, ETV6, EZH2, FGFR1, FLT3, GATA1, GATA2, IDH1, IDH2, IKZF1, JAK1, JAK2, JAK3, KIT, KMT2A, KRAS, MPL, NF1, NPM1, NRAS, PDCD1LG2, PDGFRA, PDGFRB, PHF6, PTPN11, RAD21, RUNX1, SETBP1, SF3B1, SRSF2, TET2, TP53, U2AF1, WT1, ZRSR2

The HTA group does not consider these genes to be exemplars (per the MSAC Guidelines exemplar/facilitated HTA approach) but more as an advisory list of core genes that could form the basis of a reference list, and in some way, inform the item descriptor. It may be confusing to retain the term 'exemplar' given the MSAC guidelines use of this term as genes that are in some way representative of the clinical utility or as a proxy for the effectiveness of other genes. In somatic testing in general, there are no such exemplars and, in these conditions, these genes are not necessarily related in any way, although some co-occur and others are mutually exclusive. However, the principle of establishing a core list of genes with strong clinical utility is very important. The HTA group considers the following genes in red, from the 2016 WHO classification and/or the NHSE Test Directory, the IPSS-M (31 genes), and some from the large case series reported by Rosenthal et al (2021) could be added to the Applicant's proposed list. This is referred to the Applicant and MSAC for further consideration. Once a comprehensive list of the genes is available for WHO HAEM5, consideration could be given to including these to ensure the list is up to date.

The HTA group's suggested item descriptor is below with proposed amendments to the wording and additional genes not currently in the candidate list. Those highlighted in black are potential germline predisposition genes.

The Applicant provided a costing in the Application and has not provided additional, updated costing with subsequent adjustments to justify the fee being sought. An expert in the HTA group reviewed the costing provided by the Applicant, and based on that, the HTA group suggests a fee of \$927.90. Details of the costing are contained in the body of the report.

For the myeloid NGS panel, the HTA group considers it reasonable to include reference to a list of genes. How this is implemented is referred to MSAC/MBD as a policy consideration. Given there is a range of genes for the different myeloid neoplasms, this item descriptor would be best supported by a test directory, outlining the genes required to be tested for each condition. This would ensure there is a reference list that can be readily maintained and updated and acts as a guideline for both requesters and providers regarding the current standard of care.

For both the myeloid and lymphoid panels, it is recommended that the test be available at initial diagnosis and also at suspected relapse or disease progression, given it informs the impact of clonal evolution with potential progression to new disease states (e.g., MDS to AML, MPNs to AML, Richter transformation of low-grade B cell neoplasms) or potentially identifies a new diagnosis or may rule out a malignancy. Beyond diagnosis, NGS panel testing at relapse may also inform prognosis, risk stratification and optimal management options. Only very rarely would a single patient require more than one repeat test after experiencing disease progression or relapse, i.e., a scenario where a patient is tested three times would be uncommon.

Some genes with clinical utility appear to be missing and are presented in red for consideration by MSAC and the Applicant. Those highlighted in bold text in both the red and black lists of genes are potential germline predisposition genes.

**Table 2 HTA group's suggested MBS Item AAAA for an NGS panel for characterising variants in suspected myelofibrosis or haematological malignancies of myeloid origin; amendments from Applicant proposal marked up**

<b>Category 6 – PATHOLOGY SERVICES –Group P7 Genetics</b>
Characterisation of gene variant(s), requested by a specialist or consultant physician to determine the diagnosis, prognosis and management of a patient presenting with a suspected haematological malignancy of myeloid origin in at least 25 genes from the list  Applicable once per diagnostic episode at initial diagnosis or suspected disease progression/relapse
Fee: \$927.90 Benefit: 75%=724.50 85%=\$840

Suggested genes with established clinical utility (62 genes): ASXL1, BRAF, CALR, CBL, CD274, **CEBPA**, CSF3R, **DDX41**, DNMT3A, ETNK1, ETV6, EZH2, FGFR1, FLT3, GATA1, **GATA2**, IDH1, IDH2, IKZF1, JAK1, JAK2, JAK3, KIT, KMT2A, KRAS, MPL, **NF1**, NPM1, NRAS, PDCD1LG2, PDGFRA, PDGFRB, PHF6, PTPN11, **RAD21**, **RUNX1**, SETBP1, SF3B1, SRSF2, TET2, **TP53**, U2AF1, WT1, ZRSR2,

**ATM, BCOR, BCORL1, BCR-ABL1, CHEK2, CUX1, GNB1, HRAS, KDM6A, NFE2, NTRK3, PPM1D, PRPF8, RET, SH2B3, STAG2, STAT3, STK11**

Note: the HTA group has identified additional genes (highlighted in red) and potential hereditary predisposition genes (bold type).

**Table 3 Applicant's newly proposed MBS Item BBBB for an NGS panel for characterising variants in haematological malignancies of lymphoid origin; amendments from Ratified PICO confirmation marked up**

<b>Category 6 – PATHOLOGY SERVICES –Group P7 Genetics</b>
Characterisation of gene variant(s) by a gene panel consisting of at least 25 genes, requested by a specialist or consultant physician, in a patient presenting with a clinically suspected haematological malignancy of lymphoid origin that includes at least 25 genes from the lymphoid exemplar list  Applicable once per diagnostic episode at initial diagnosis or at disease relapse
Fee: \$940 Benefit: 75%=\$705 85%=\$852.10 (Revised 85% rebate to account for Greatest Permissible Gap)

Proposed exemplar gene list for lymphoid panel

ALK, ARID1A, ATM, BCL2, BCL6, BIRC3, B2M, BRAF, BTK, CARD11, CD274, CD79B, CDKN2A, CREBBP, CXCR4, DNMT3A, EP300, ETV6, EZH2, FOXO1, HAVCR2, ID3, IDH1, IDH2, IKZF1, JAK1, JAK2, JAK3, KLF2, KMT2A, KRAS, MEF2B, MYC, MYD88, NFKBIE, NOTCH1, NRAS, PDCD1LG2, PIM1, PTPRD, RHOA, RUNX1, SF3B1, SOCS1, STAT3, STAT5B, STAT6, TCF3, TET2, TNFAIP3, TP53, XPO1

The HTA group proposes the following amended item descriptor with altered/deleted text in strikethrough and proposed new wording in italics. The frequency restriction is recommended to allow testing at the initial diagnosis and then where there is suspected relapse or progression, noting that it would be uncommon or unlikely for a patient to access testing at every event of suspected or established disease progression or relapse, although in some instances this may be required and it would be reasonable to allow this where needed (e.g., second malignancy, where there is uncertainty surrounding the diagnosis).

As with the myeloid panel list, the HTA group does not consider these genes to be exemplars (per the MSAC Guideline exemplar/facilitated HTA approach) as they are not necessarily related in any way. The list was compared with other sources including the 2016 WHO Classification (a comprehensive list is not yet published for WHO HAEM5), the National Health Service England (NHSE) National Genomics Test Directory, consensus lymphoid gene panels proposed by French consensus groups (LYSA/GBMHGM)<sup>8</sup> and the key publications that inform the clinical and cost-effectiveness<sup>9</sup> and are of a comparable size and composition. The HTA group's suggested item descriptor is below with suggested amendments to the wording and additional genes not currently in the candidate list for the Applicant's and MSAC's consideration. Some genes with clinical utility appear to be missing. Those highlighted in black are potential germline predisposition genes.

A comparison was undertaken with the current 'ALLHAEM' panel offered at the Peter MacCallum Cancer Centre which includes 29 of the proposed 52 genes in the candidate list.

Given there is a much smaller pool of shared genes across the lymphoid malignancies compared with the myeloid malignancies, and the breadth of genes are required for a differential diagnosis between otherwise very similar entities, how a gene list would be specified in the item descriptor is more challenging so that genes for the diagnosis of rarer entities are not excluded. This is referred for MSAC's consideration.

**Table 4 HTA group's suggested MBS Item BBBB for an NGS panel for characterising variants in haematological malignancies of lymphoid origin; amendments from Applicant's proposal marked up**

<b>Category 6 – PATHOLOGY SERVICES –Group P7 Genetics</b>
<p>Characterisation of <b>gene</b> variant(s) <i>in at least 25 genes</i>, requested by a specialist or consultant physician to <i>determine the diagnosis, prognosis and management</i> of a patient presenting with a <i>suspected</i> haematological malignancy of lymphoid origin <i>that includes at least 25 genes from the lymphoid exemplar list</i></p> <p><i>Applicable once per diagnostic episode at initial diagnosis or suspected disease progression/relapse</i></p>
<p>Fee: \$927.90 Benefit: 75%=724.50 85%=\$840</p>

Suggested genes with established clinical utility for lymphoid panel

61 genes: ALK, ARID1A, **ATM**, BCL2, BCL6, BIRC3, B2M, BRAF, BTK, CARD11, CD274, CD79B, CDKN2A, CREBBP, CXCR4, DNMT3A, EP300, ETV6, **EZH2**, FOXO1, HAVCR2, ID3, IDH1, IDH2, **IKZF1**, JAK1, JAK2, JAK3, KLF2, KMT2A, KRAS, MEF2B, MYC, MYD88, NFKBIE, NOTCH1, NRAS, PDCD1LG2, PIM1, PTPRD, RHOA, **RUNX1**, SF3B1, SOCS1, STAT3, STAT5B, STAT6, TCF3, TET2, TNFAIP3, **TP53**, XPO1

**CCND1, CD79A, CD79B, FBXW7, NOTCH2, PLGC1, PLCG2, PRDM1, TRAF2**

Note: the HTA group has identified additional genes (highlighted in red) and potential hereditary predisposition genes (bold type).

<sup>8</sup> 5. Sujobert P, Le Bris Y, de Leval L, Gros A, Merlio JP, Pastoret C, et al. The Need for a Consensus Next-generation Sequencing Panel for Mature Lymphoid Malignancies. *Hemasphere*. 2019;3(1):e169.

<sup>9</sup> 6. Bommier C, Mauduit C, Fontaine J, Bourbon E, Sujobert P, Huet S, et al. Real-life targeted next-generation sequencing for lymphoma diagnosis over 1 year from the French Lymphoma Network. *Br J Haematol*. 2021;193(6):1110-22.

## Ambiguous lineage

Those patients with a suspected malignancy that cannot be ruled out with a single panel may require sequential testing with each panel. The requester is the specialist or physician so it is likely both will be ordered unless there is no urgency for the result. Expert clinical advice indicated this was uncommon, perhaps 1% of patients being tested per annum – mostly in patients with concurrent malignancies, or a suspected new malignancy or ambiguous lineage.

## 7. Population

The PICO confirmation's proposed population as "Patients/persons with clinically suspected myeloid or lymphoid neoplasm where accurate diagnosis sufficient for treatment planning is not achieved using conventional testing".

The HTA group has further defined the population eligible as "Patients with clinical or laboratory evidence of a suspected haematological malignancy where an NGS gene panel test during the initial work-up or at suspected disease progression/relapse would assist their diagnosis or management." This remains silent on the positioning of the test as the application covers a very broad range of conditions – for some, NGS panel testing is essential at diagnosis and has been the standard of care for more than 5000 Australians (e.g., myeloid malignancies, chronic lymphocytic leukaemia to test for clinically significant *TP53* variants) – whereas, for other conditions, NGS panel testing may be reserved for when all treatment avenues have been exploited (e.g., relapsed and refractory diffuse large B cell lymphoma) or those cases where a diagnosis cannot be made (e.g., lymphadenopathy of uncertain aetiology), or it may not be needed at all. From consultation with the Applicant's experts and with clinical experts providing advice to the HTA group, it is clear that NGS panel tests are used early in the diagnostic work-up, and where that occurs, there is a reduction in utilisation of other MBS items (Victorian utilisation data per capita is the 40% lower than in NSW). Kawata et al (2022) demonstrated that a coordinated use of 'NGS panel-first' approach reduced cytogenetic testing in myeloid malignancies and plasma cell malignancies by 76%<sup>10</sup>. This publication used an RNA and DNA NGS panel, had a clear clinical guideline in place in a state-based system and the observed 40% reduction in benefits paid in Victoria is consistent with the lower diagnostic yield with DNA analysis alone.

The Applicant presented an algorithm without NGS testing, and one with testing, and an algorithm was included in the ratified PICO confirmation - all positioned NGS panel testing after all other testing and in patients with a 'complete' malignant diagnosis, where it served largely to refine the diagnosis. The HTA group does not consider that a 'complete' malignant diagnosis/work-up can be achieved without NGS panel testing in myeloid malignancies, nor in many lymphoid malignancies (e.g., chronic lymphocytic leukaemia). In particular, the WHO HAEM5 does not include all the genes that inform prognosis and risk stratification or therapeutic choices. The HTA group, clinical advisers and the Applicant's experts (in May 6 2022 meeting) consider that NGS testing is not positioned after all other testing in the majority of settings and the HTA group has amended the algorithm without the test (Figure 2) and with the test included (Figure 3) to reflect this. The HTA also identified the potential for significant findings of a germline predisposition, and in a small proportion, clonal haematopoiesis of indeterminate potential (CHIP) (by definition, only in patients where no malignancy is found). Notably, both these entities are now prominent in WHO HAEM5: germline predisposition has its own chapter and any entity is now required to be defined according to the germline predisposition identified.

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<sup>10</sup> 7. Kawata E, Hedley BD, Chin-Yee B, Xenocostas A, Lazo-Langner A, Hsia CC, et al. Reducing cytogenetic testing in the era of next generation sequencing: Are we choosing wisely? *International Journal of Laboratory Hematology*. 2022;44(2):333-41.

The HTA group is in agreement with most aspects of the clinical algorithm without NGS testing but considers that the following are important for inclusion in the algorithm, depicting the diagnosis and management without (Figure 2) or with (Figure 3) the proposed NGS panel testing:

- Patients with symptoms and/or signs and/or investigation(s) (including incidental test results) suggesting a possible diagnosis of a haematological malignancy which may be an initial diagnosis or represent progression or relapse
- NGS panel testing is often performed alongside other tests for a broad range of haematological malignancies, rather than reserved for cases where there is uncertainty about the diagnosis
- NGS panel testing provides more information than just genomic subtyping and correction or refinement of a diagnosis and without it,
  - Per current guidelines and risk stratification models, there would be suboptimal/incorrect risk stratification e.g., in patients with myeloid neoplasms
  - Potential familial predisposition may not be identified
  - Treatment options may be suboptimal or restricted including limiting access to investigational therapies – these may be amended after initially commencing therapy as NGS testing takes approximately 3-4 weeks
    - Where more urgent results are required, single gene tests may be required
- Diagnostic uncertainties may be resolved with NGS panel testing shortening the diagnostic odyssey and avoiding delays in treatment or even incorrect treatment.

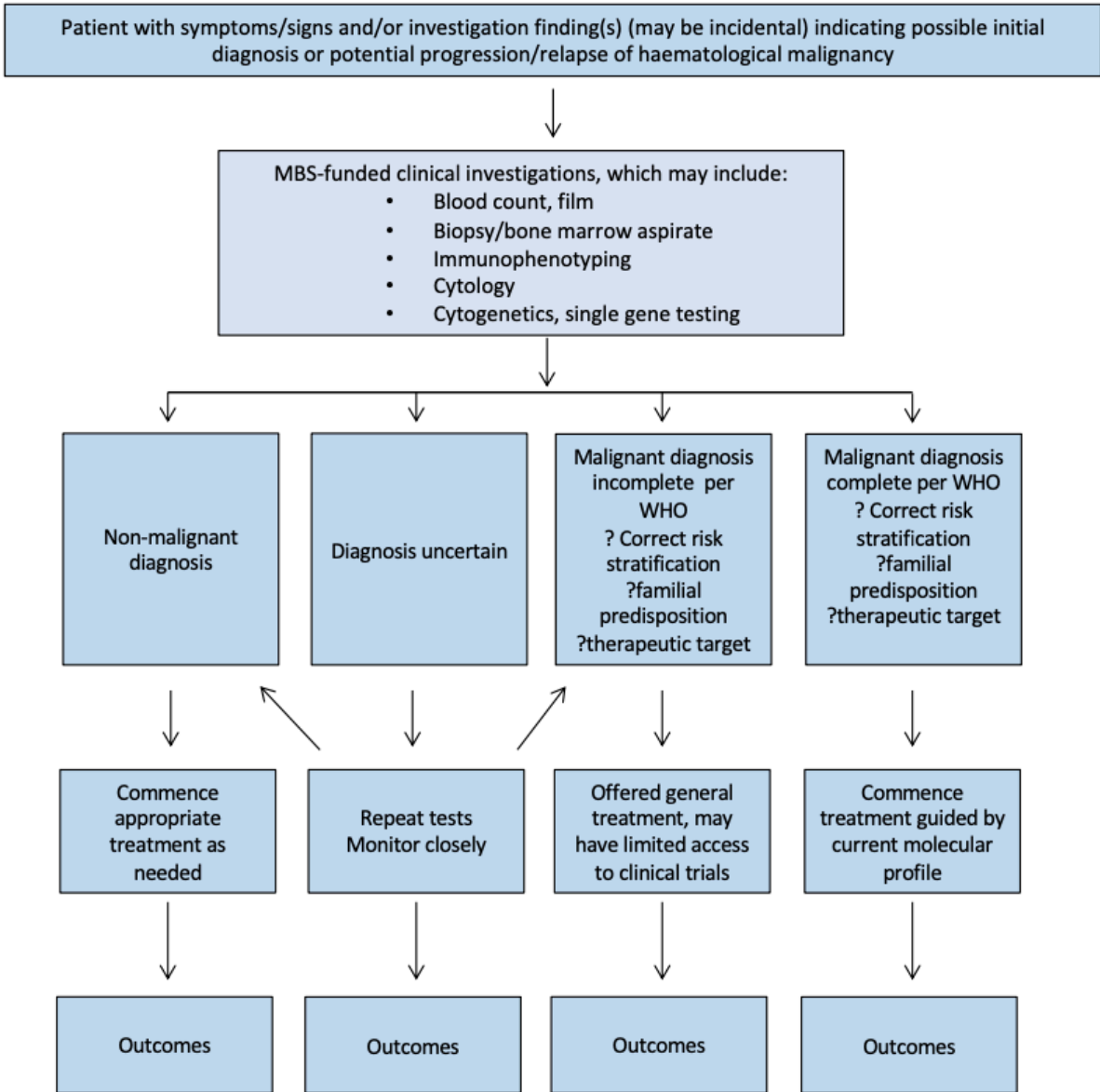
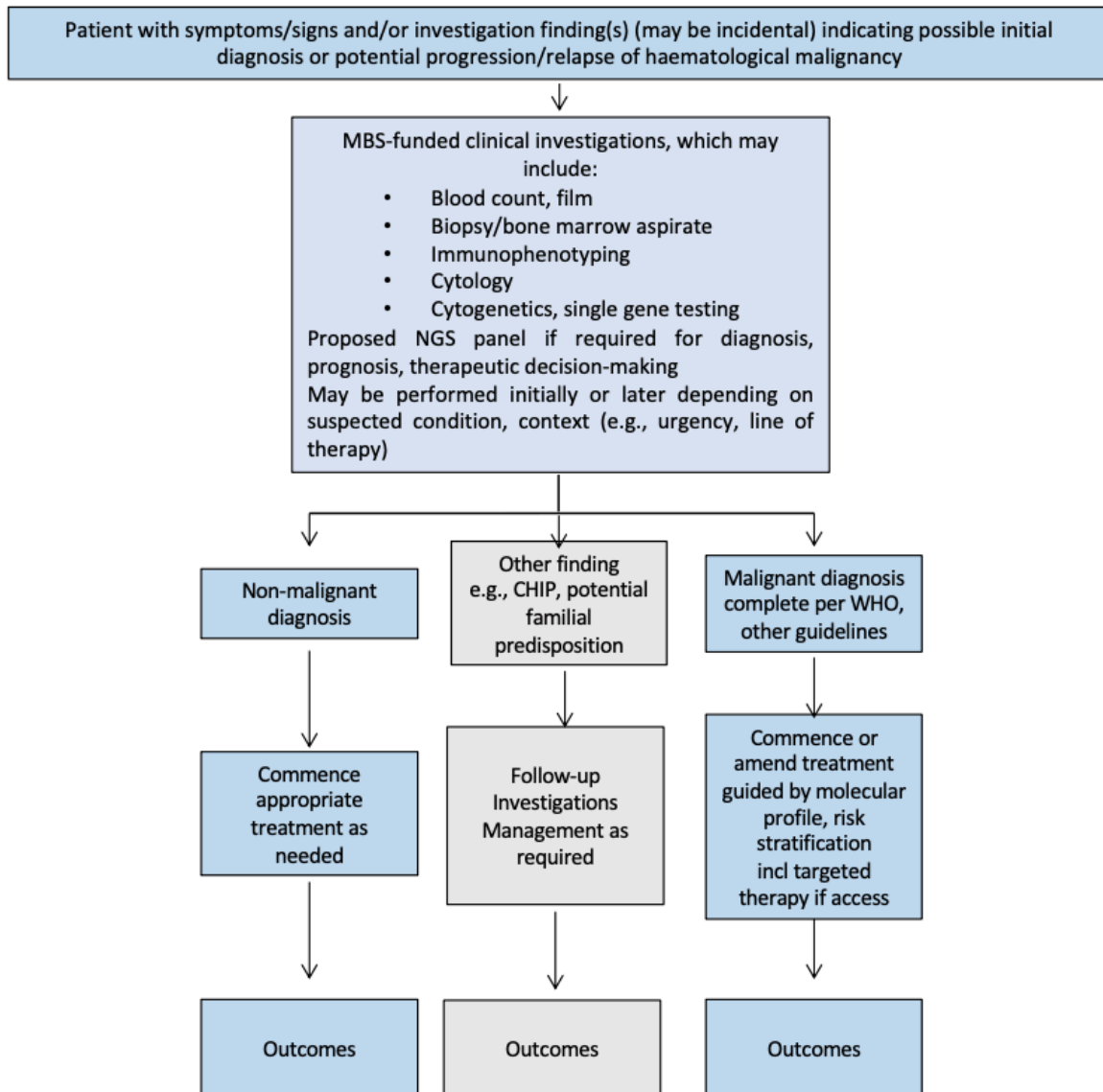


Figure 2 HTA group's algorithm for the diagnosis and management of patients with a possible diagnosis of a haematological malignancy in the absence of NGS panel testing





**Figure 3 HTA group's algorithm for the diagnosis and management of patients with a possible diagnosis of a haematological malignancy with the proposed NGS panel testing**

MBS items 73290, 73325, 73326, 73314, 73343, 73369, 73364, 73365, 73366, 73367, 73368, 73369, 77370, 73373, 73397, 73398 and 73399.

As above, an additional relevant population proposed by the HTA group to be tested are those with a suspected haematological malignancy but not found to have a malignancy. It is expected that this subpopulation will be relatively smaller for myeloid malignancies given their clinical presentation and prior tests might narrow down those needing a bone marrow aspirate/trephine; where reported, this accounted for approximately 1.65% of all cases tested.<sup>11</sup> The proportion is likely to be somewhat higher for those with a suspected lymphoid malignancy where the presentation may be with lymphocytosis or lymphadenopathy which requires exclusion of clonality/malignancy.

<sup>11</sup> 8. Carbonell D, Suárez-González J, Chicano M, Andrés-Zayas C, Triviño JC, Rodríguez-Macías G, et al. Next-Generation Sequencing Improves Diagnosis, Prognosis and Clinical Management of Myeloid Neoplasms. *Cancers (Basel)*. 2019;11(9).

## 8. Comparator

No NGS panel testing is the nominated comparator as there are existing MBS items for genetic tests that for some patients can provide supplementary information of a working diagnosis of haematological malignancy (e.g., flow cytometry, immunohistochemistry, cytogenetic testing including FISH and individual molecular genetic tests). PASC indicated any reduction in utilisation of existing items should be included in the assessment report.

## 9. Summary of public consultation input

Prior to consideration by PASC in December 2021, the Department received responses to the consultation survey from five organisations, all of whom were supportive of the application:

- Public Pathology Australia (PPA)
- Australian Genomics (AG)
- Myeloproliferative Neoplasm Alliance Australia (MPNAA)
- Leukaemia Foundation (LF)
- Australian Pathology (PA)

Advantages of the test stated in the feedback received were:

- The test would provide clarity of diagnosis as well as selection of the most appropriate treatment options, which would lead to better health outcomes.
- Access to the test through public funding will ensure patients have access to the standard of care in accordance with the World Health Organisation (WHO) guidelines.
- Equity of access to testing.

Disadvantages of the test stated in the feedback received were:

- Testing in some genes for tumour associated variants may also discover inherited variants associated with blood cancer predisposition (appropriate policy, systems, genetic counselling and consumer support must be in place when delivering such testing to ensure the patient is aware of this possibility).

Other comments provided in the consultation feedback was:

- The proposed MBS fee does not adequately reimburse the cost of the test.
- Public funding of the test would increase the knowledge base for myeloproliferative neoplasms and could inform clinical practice and best treatment pathways.
- Precision cancer care is emerging as standard of care and avoids the need for expensive therapies associated with treatment related side effects.

## 10. Characteristics of the evidence base

The HTA group has evolved an approach that has shifted with alterations in the application – initially requesting a single MBS item to characterise variants in a patient presenting with a haematological malignancy, with the item descriptor referencing an attached list presented in a large table of 235 candidate genes organised into ‘exemplar’ and ‘facilitated’, largely based on inclusion in the 2016 WHO classification. With the publication of the WHO HAEM5 summaries, and imminent release of the ‘blue book’ for WHO classification and other key publications (IPSS-M prognostic model for myelodysplastic syndrome (MDS), this list will require updating.

A literature search for NGS panel testing in haematological malignancies rapidly mapped that this process closely follows the WHO classification, clinical guidelines and clinical practice in specialist centres. These divide the diagnostic process according to whether these are suspected myeloid neoplasms and lymphoid neoplasms, with multiple NGS panels described for the former and relatively few for the latter – indeed, most of the studies in lymphoid malignancies are in the individual disease entities rather than as ‘lymphoid neoplasms’ approach. This is consistent with the Applicant’s proposed use of NGS panel testing downstream of other MBS-funded as well as non-MBS funded tests. By contrast, given the much more frequently mutated genes and their critical role in diagnosis, risk stratification and therapeutic selection in myeloid neoplasms, this essential testing is more likely to be used early and to complement or even replace other genetic tests. The approach to the assessment aimed to mirror these differences, and a meeting was held with the Applicant, the Applicant’s clinical experts and the Department early in the assessment process to define the NGS panel(s) being sought.

Following that meeting on May 6<sup>th</sup> 2022, on May 30<sup>th</sup> 2022, the application was altered to a request for 3 MBS items for 3 NGS panels, including the two now currently proposed plus a larger combined gene panel with a proposed list of 77 genes where a more comprehensive test was required. This larger panel was withdrawn from consideration by the Applicant on June 30<sup>th</sup> 2022.

The key issues have been to

- Define the test
- Compare with how the test is provided elsewhere (e.g., clinical guidelines, NHSE Genomic Test Directory)
- Allow a comparison with any published literature assessing clinical and cost-effectiveness.

The Applicant is requesting a very flexible approach by specifying a minimum of 25 genes, with a candidate list of 44 genes for the myeloid panel and 52 genes for the lymphoid panel. It is not clear how the composition and size of the lists were derived, and of the 11 references cited in the application, one was supportive and generalisable to the planned approach. No references were provided in support of lymphoid NGS panel testing. No rationale was provided to explain either the selection of the proposed genes, nor to explain the exclusion of other candidate genes. Essential genes have not been proposed that might form the core of any test panel, and perhaps inform an item descriptor. Essentially these are two tests seeking to characterise clinically significant variants in potentially more than 150 cancers.

Within these gene panels, there is considerable flexibility to alter the number of genes tested and/or to report potentially only those genes considered relevant to the condition being examined. How these genes would be selected by providers was not presented, nor the diagnostic algorithm for those patients who after testing with a subset of genes from these lists, remain without a diagnosis. This underscores the need for an Australian guideline to define what genes would be required to establish a diagnosis for each condition, and for providers to publish their test scope (e.g., Mayo Clinic descriptor) and allow requesters to determine whether different providers offer sufficient coverage within the test offered to support their reason for testing (e.g., to identify treatment options). The HTA groups does not consider these to be exemplar genes (per MSAC’s exemplar/facilitated HTA approach) as they are not related or informative for the use of other genes.

Following on from the approach to the DCAR for Application 1709, the HTA group has adopted a pragmatic approach of establishing clinical effectiveness using published literature wherever possible to identify examples where a similar NGS panel has been used. This was made more challenging because there is no clear test for comparison with the published literature. Given the two panels share no similarities, these have been presented separately.

A checklist was developed by the HTA group to focus the literature search and select the studies providing evidence of the kind required to address MSAC’s preferred approach for demonstrating cost-effectiveness of NGS panels. The key question is the clinical and cost-effectiveness of using

DNA analysis within an NGS panel to characterise variants for the diagnosis and manage patients presenting with a suspected haematological malignancy, either at initial diagnosis or relapse.

Inclusion and exclusion criteria were established to ensure that the findings from selected studies would be generalisable to the Applicant's proposed NGS panel tests.

A literature search was undertaken with the following selection criteria:

- Size of the gene panel: 25-55 genes given the Applicant listed 44 candidate genes for the myeloid panel and 52 genes for the lymphoid panel and proposed a 25-gene minimum in the MBS items;
  - The Applicant had also requested a 40+ gene panel for malignancies of indeterminate origin with a fee of \$1200 but withdrew this on 30 June 2022.
  - The upper limit of the number of genes likely to be tested under the proposed service have not been specified.
- Comparability of the genes tested: ideally these would be the same or a high proportion of genes the same as those on the proposed gene list (to ensure comparability of yield of informative results etc)
- NGS panel characterising DNA variants only or reporting DNA variants separately, as this is what the Applicant's experts identified as the proposed testing. Inclusion of RNA analysis would detect more variants (e.g., structural variants) than the proposed test, but is not currently available; therefore, inclusion of studies that used RNA and DNA analysis will overestimate the clinical and cost-effectiveness.
- Use in different settings to reflect the current usage in Australia:
  - at initial diagnosis/work-up of a patient with suspected haematological neoplasm
  - at suspected relapse or disease progression
- Publications from 1 January 2016 to April 14 2022, for the initial search, to ensure any diagnostic entities from the 2016 update of the 4<sup>th</sup> edition of the WHO classification were included (summaries for the upcoming WHO HAEM5 were only released in June 2022), with a preference for those published after 2017 to incorporate the latest prognostic models incorporating molecular data for risk stratification (e.g., European LeukemiaNet (ELN) for AML 2017<sup>12</sup>). Notably WHO HAEM5 summaries and IPSS-M for myelodysplastic syndromes and were published in June 2022<sup>13</sup>)
- Studies conducted in Australian laboratories/patients, where published or available to provide generalisable evidence.

Additional prespecified criteria for excluding retrieved studies during the review stage:

- the technology was not targeted NGS (excluded whole exome or whole genome analysis)
- gene panels were greater in scope (e.g., number of genes $\geq$ 55, RNA analysed) or design (e.g., to detect structural variants) – it is not clear in the application if copy number alterations are detected with the currently proposed technology and this will differ between providers
- DNA variants not reported separately
- the test purpose was for monitoring or establishing minimal residual disease status
- NGS panel testing was performed solely on cell-free circulating tumour DNA or not reported separately
- non-haematological cancers were included but not reported separately
- there was insufficient detail to
  - identify the genes tested or technology used
  - identify the clinically significant variant detection vs any variant detection

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<sup>12</sup> 9. Döhner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Büchner T, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood*. 2017;129(4):424-47.

<sup>13</sup> 10. Bernard E, Tuechler H, Greenberg PL, Hasserjian RP, Ossa JEA, Nannya Y, et al. Molecular International Prognostic Scoring System for Myelodysplastic Syndromes. *NEJM Evidence*. 2022;1(7):EVIDo2200008.

- determine outcomes from testing in all the patients
- study size too small.

The composition of the proposed gene lists were compared with those studies providing clinical effectiveness data, the NHSE Genomics National Test Directory for haematological neoplasms and other reference sources such as the Mayo Clinic laboratories.

The NGS panel tests themselves, the conditions evaluated and clinical setting are all different so no results could be combined.

## Myeloid NGS panel

The MSAC guidance indicates data should be summarised in tables with numbers only. However, given the complexities of the testing and the requirement to infer information from the published data to address the assessment question, it has been necessary to provide both a detailed summary and from that draw out the evidence to support the analysis, indicating where inferences and assumptions have been made. A summary of the key studies aligning the NGS panel criteria and usage are presented below, and the remainder in Section 2B Clinical Effectiveness.

In June 2022, two key articles were published: a summary of the changes to the myeloid malignancy classification proposed in the WHO HAEM5<sup>14</sup>, and a new molecular prognostic score for MDS (IPSS-M) which dramatically alters the prior risk categories which were based on patient factors and bone marrow findings<sup>15</sup> – all the currently published studies are therefore, likely to underestimate the impact on the diagnostic change in all patients with myeloid malignancies, and the prognosis of NGS panel testing in MDS patients.

The search strategy conducted led to the identification of 25 studies that reported outcomes using myeloid NGS panels of which 3 were considered key when matched to the checklist. Four studies were considered supportive of clinical utility of NGS gene panel testing in myeloid malignancies, but provided insufficient data to demonstrate cost-effectiveness. The remaining 17 studies were excluded during screening as the panels included:

- RNA and DNA analysis (8)
- Larger number of genes than the proposed minimum number of genes and/or number of exemplar genes (6)
- assessments of structural variants or copy number variants which are not currently proposed (2)
- insufficient data to assess the impact on the diagnosis or management (1)

As each study used either a different NGS panel or enrolled different populations and/or different malignancies, the patients and outcomes from these studies cannot be pooled.

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<sup>14</sup> 11. Khoury JD, Solary E, Abla O, Akkari Y, Alaggio R, Apperley JF, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. *Leukemia*. 2022;36(7):1703-19.

<sup>15</sup> 10. Bernard E, Tuechler H, Greenberg PL, Hasserjian RP, Ossa JEA, Nannya Y, et al. Molecular International Prognostic Scoring System for Myelodysplastic Syndromes. *NEJM Evidence*. 2022;1(7):EVIDoa2200008.

**Table 5 Key studies providing evidence for the clinical and cost-effectiveness of myeloid NGS panel testing in patients with a suspected haematological malignancy of myeloid lineage**

Authors	Risk of bias	NGS gene panel size; DNA or RNA analysis	Conditions	Number of patients	Comments on generalisability to proposed testing
Studies providing evidence in support of NGS panel testing in myeloid malignancies					
Patel 2021	Prospective case series, Observational study Moderate risk of bias (10/15 on modified <a href="#">IHE case series checklist</a> )	37 genes	Myeloid neoplasms  Consecutive enrolment patients with suspected haem malignancies	343	Larger gene panel than minimum proposed but within proposed size (included 8 genes not in proposed list) Consecutive enrolment, included follow-up with OS analysis Demonstrates NGS used for diagnosis, prognosis, treatment selection – no reporting of potential germline variant testing Real world estimate of impact with time taken for NGS
*Carbonell et al (2019)	Retrospective case series Moderate risk of bias (11/14 on HTA Group - modified <a href="#">IHE case series checklist</a> )	54 genes	Myeloid neoplasms Consecutive enrolment AML, PMF Selective enrolment MDS, MPNs if likely to change management	121	Larger gene panel than proposed (included 20 genes not in proposed list) Variants detected in 39 genes Had access to germline testing for followup which changed management May underestimate impact on diagnosis, prognosis Compared testing in AML at diagnosis and relapse in 10 patients
Rosenthal et al (2021)	Retrospective case series High risk of bias (3/15 on HTA Group - modified <a href="#">IHE case series checklist</a> )  See Appendix D Evidence Profile Tables	48 genes in total 47 analysed by NGS panel <i>FLT3</i> -ITD by PCR	Myeloid neoplasms  Consecutive enrolment of de-identified specimens from patients with AML, MDS, MPN referred for NGS testing	2053	Represents remote/offshore testing issues of not having access to patient information to provide integrated service. Main utility would potentially be treatment options. Larger gene panel than proposed in application (included 12 genes not in proposed list) Variants detected in 44 genes (8 not included in proposed list) Retrospective analysis of DNA variants in 2053 consecutive, de-identified unique patient specimens in a commercial laboratory Limited patient information, cannot integrate results, determine if treatment options appropriate Curation of results based on DNA variant alone without integration into risk stratification models so may underestimate prognostic impact No clinical follow-up data or outcomes including potential germline variants. US study so range of treatments, clinical trials available likely to be fewer in Australia

AML=acute myeloid leukaemia; PMF=primary myelofibrosis; MDS= myelodysplastic syndromes; MPNs myeloproliferative neoplasms  
Note: since these studies were published the IPSS-M for MDS has been published, incorporating molecular testing into prognostic score so these are likely to have underestimated prognostic value of testing

## Lymphoid NGS panel

Seven studies were identified that used lymphoid NGS panels or used a more comprehensive NGS panel in lymphoid malignancies, and restricted the genes reported to those of relevance. Three key studies were identified that support the clinical and cost-effectiveness of lymphoid NGS panel testing. A further 7 studies and a consensus statement with clinical evidence in support were excluded because:

- the specific genes were not proposed for inclusion in the proposed gene panel list which means the findings cannot be generalised (2)
- the gene panel size was too large (2)
- RNA and DNA were analysed and not presented separately (1)
- the data or genes tested were not presented in sufficient detail (1)
- The findings require validation (1).

**Table 6 Key studies providing evidence for the clinical and cost-effectiveness of lymphoid NGS panel testing in patients with a suspected haematological malignancy of lymphoid lineage; ESC amendments to include an additional study (Pillonel et al 2020) in italics**

Authors	Risk of bias	NGS gene panel size, RNA or DNA analysis	Conditions	Number of patients	Comments on generalisability to proposed testing
<b>Studies providing evidence in support of NGS panel testing in lymphoid malignancies</b>					
Bommier et al (2021)	Retrospective case series. Moderate risk of bias (11/14 on modified <a href="#">IHE case series checklist</a> )	46 genes DNA	Lymphomas	229	Highly screened population as only those with diagnostic uncertainty after centralised expert haematopathologist review tested – likely underestimates detection rate of NGS panel testing in less specialised centres or laboratories Used as final discriminator after all other tests Primarily diagnostic, no report on outcomes or prognostic, familial or predictive information Limitations: did not include <i>TP53</i> in NGS panel (not recommended at time study designed) Patients underwent molecular assessments of TCR, IGH which are currently not MBS-funded Did not assess all patients with lymphoma, just those with uncertainty regarding the diagnosis. Prognostic, therapeutic test purposes not explored or reported.
Jajosky et al (2021)	Retrospective case series. Moderate risk of bias (11/16 on modified <a href="#">IHE case series checklist</a> )	31 genes DNA	Low-grade lymphoproliferative disorder/malignancies	147	Study of routine use of NGS to identify differentiate low grade lymphoproliferative disorders from malignancies, including some where diagnosis not otherwise possible
Vicente-Garcés et al (2022)	Retrospective case series Moderate risk of bias (9/15 on modified <a href="#">IHE case series checklist</a> )	203 in broad panel 52 DNA reported separately from RNA	Paediatric/adolescent/young adult acute leukaemia  Selected on basis of	76	Limited to <25-year-olds at diagnosis or relapse with high quality samples, prioritising those without genetic Used pan-cancer Paediatric panel limited analysis to 52 genes relevant to haem malignancies DNA variants and outcomes reported separately RNA more impact on refining diagnoses vs DNA more impact on prognosis, treatment options

Authors	Risk of bias	NGS gene panel size, RNA or DNA analysis	Conditions	Number of patients	Comments on generalisability to proposed testing
			sample availability, and prioritised if no genetic results from prior tests		49% of patients had clinically relevant variants (Tier 1 or 2) in 33 genes Reported significant germline testing outcomes
<i>Pillonel et al (2020)</i>	<i>Retrospective case series</i>	<i>68 genes DNA</i>	<i>Lymphoid malignancies</i>	<i>80</i>	<i>Gene panel larger than proposed therefore not generalisable to this application Demonstrates resolution of diagnostic challenges Strongly supportive of the approach but key difference is the gene panel size</i>

TCR=T cell receptor; IGH=Immunoglobulin H.

## 11. Comparative safety

The safety of NGS panel testing for the characterisation of variants in patients with haematological malignancies would be non-inferior to management without the testing. Samples would have already been collected for other tests. The justification for not addressing the safety outcomes outlined in the Ratified PICO confirmation are presented

There is potential for the proposed technology to increase the safety of patients receiving treatment after NGS panel testing rather than clinical management without it. For example, the inclusion of genes such as *TPMT* may identify a patient with acute leukaemia who was at risk of toxicity from 6-mercaptopurine and NGS was demonstrated to be able to overturn diagnoses of a malignant condition, especially where no diagnosis was otherwise possible.

## 12. Comparative effectiveness

### Myeloid NGS panel

The evidence from the three studies below supports the clinical claim of superiority compared with no gene panel testing and can be used to demonstrate the cost-effectiveness of NGS panel testing to characterise variants in patients with a suspected myeloid neoplasm. This needs to be complemented by a test directory as currently it is not possible to present the range of genes, nor the range of conditions in a meaningful way in an item descriptor. The gene list currently lacks some critical genes and this is referred to MSAC for consideration.



**Table 7 Summary of NGS results and impact on diagnosis, prognosis and therapy selection**

<b>Patel et al (2021) NGS 37-gene panel testing <u>before</u> cytogenetic/other genetic testing</b>	<b>Number of patients (% of all patients)</b>
Number of patients tested	343
≥1 clinically significant variants (%)	244 (71%)
No variants detected	99 (29%)
2-4 variants in same gene	64 (19%)
Change in diagnosis	6 (1.7%)
Refinement in diagnosis	26 (7.6%)
Change/refinement in diagnosis	32 (9%)
Change in prognosis	211 (62%)
Worse prognosis <i>ASXL1, FLT3, TP53, RUNX1, NRAS, SRSF2, EZH2, ETV6</i>	157 (46%)
Better prognosis <i>JAK2, NPM1, SF3B1, CALR</i>	54 (16%)
Number who commenced initial treatment before NGS results available	223 (65%)
• Initial treatment changed once NGS results available	78 (23%)
○ Changed to clinical trial (11 targeted, 23 non-targeted)	34 (44%)
○ Changed to targeted therapy outside of trial	44 (56%)
Total number of patients offered HSCT	156 (46%)
• Based on bone marrow morphology, cytogenetics, clinical factors	89 (26%)
○ 38 actually received HSCT after induction (43%)	
• Additional patients recommended HSCT after NGS results	67 (20%)
○ 34 actually received HSCT after induction (51%)	
Proportion of patients whose treatment guided by NGS (initial or HSCT)	120 (35%)*
Number of treatment decisions guided by NGS (initial or HSCT)/total population	145 (43%)**

\* proportion reported in the discussion section, p1707 reflecting that a patient may have had their treatment selection altered more than once during the course of managing their disease

\*\* more than one treatment decision in an individual may have been guided by NGS (e.g., targeted therapy followed by haematopoietic stem cell transplant (HSCT))

**Table 8 Summary of clinical effectiveness of NGS 54-gene myeloid panel in patients with myeloid neoplasms<sup>16</sup>**

<b>Carbonell et al (2019) NGS 54-gene panel testing after cytogenetic/other genetic testing</b>	<b>Number of patients (% of total patients)</b>
<b>Effectiveness measures at initial diagnosis</b>	
Total number of patients tested in study	121
Number of patients where NGS identified ≥1 clinically significant variants	102 (84%)
Number of patients with NGS result that altered or refined/confirmed their diagnosis per 2016 WHO classification	7 (6%)
Number of patients where NGS results reclassified prior classification of prognostic group differently using ELN system (AML) or PMF MIPSS*	16 (13%)
Somatic test identified potential germline variant	21 (17%)
Somatic/germline assessment performed	17/21 (8%)
Germline pathogenic variant identified	3/17 (18%)
Number of patients eligible for clinical trial based on NGS results	44 (36%)
#*Number of informative results from NGS - diagnosis, prognosis, familial risk, treatment	70 (58%)
<b>Effectiveness measures at relapse (compared with diagnosis)</b>	
Total number of patients tested at relapse	10 (8%)
Patients with change of variant expression (gain, loss, both)	6 (60%)
Patients with change in treatment target at relapse likely to influence therapy	2 (20%)

Source Carbonell et al 2019

\* This may be an underestimate as this study was reported before the new risk stratification for MDS incorporating gene alterations

# Estimated by HTA group based on number of patients receiving an informative result within each domain

<sup>16</sup> 8. Carbonell D, Suárez-González J, Chicano M, Andrés-Zayas C, Triviño JC, Rodríguez-Macías G, et al. Next-Generation Sequencing Improves Diagnosis, Prognosis and Clinical Management of Myeloid Neoplasms. *Cancers (Basel)*. 2019;11(9).

**Table 9 HTA group compilation of clinical outcomes and information generated by NGS 47-gene@ myeloid panel testing in patients with a suspected myeloid neoplasm based on data presented**

<b>Rosenthal et al (2021) NGS 47-gene panel testing in addition to cytogenetic/other genetic testing</b>	<b>Number of patients (% of all patients)</b>
Number of patients tested	2053
≥1 clinically significant variants (%)	1142 (56%)
Patients receiving a result that changed diagnosis	748 (36%)
Patients receiving a result that changed prognosis	711 (35%)
Patients receiving a result that identified an approved therapeutic target or regimen	126/2053 (5%)
Patients receiving a result that identified an approved or off-label target	565/2053 (28%)
Patients receiving a result that identified an experimental therapy/clinical trial option	823/2053 (40%)
Patients receiving a result that changed their diagnosis, prognosis and/or treatment option(s)	1062 (52%)
<b>Number of informative, clinically significant results generated by NGS testing</b>	
#Number of informative, clinically significant results generated by NGS that identified any therapies (approved, off-label or investigational)	1388/2053 (68%)
*Number of informative results from NGS regarding diagnosis, prognosis, treatment with <i>approved</i> therapies or regimens	1585/2053 (77%)
*Number of informative results from NGS diagnosis, prognosis, treatment with <i>any</i> therapies (approved, off-label, investigational)	2847/2053 (139%)

@FLT3-ITD analysed by another method

# Sum of patients with a result informing options for an approved targeted therapy, off-label targeted therapy or experimental therapy – a single patient may receive more than one informative result or change

\*Sum of patients with a change in diagnosis, prognosis, treatment with approved therapies – a single patient may receive more than one informative result or change, and a single variant may inform more than one domain

## **Lymphoid NGS panel**

The clinical effectiveness of a lymphoid panel was demonstrated across all four domains (diagnostic, prognostic, potential familial predisposition and therapeutic) across a range of different lymphoid malignancies in the three key studies summarised below (there was also a sub-study of NGS panel testing of patients with chronic lymphocytic leukaemia by Jajosky et al (2021)).

**Table 10 Summary of outcomes after testing with lymphoid NGS panel used to establish diagnosis where there was uncertainty after expert review, centralised review**

<b>Bommier et al (2021)</b> <b>NGS 46-gene panel after all other tests, expert review</b>	<b>Number of patients (% of all patients)</b>
Number of patients tested	229
Change in diagnosis	24 (11%)
Malignancy diagnosis overturned	2 (0.9%)
NGS strengthened the suspected histological diagnosis	144(63%)
Change or confirmation of diagnosis	168 (73%)
NGS result non-contributory	61 (27%)
Management altered where change in diagnosis	19/24 (80%) 8.3% overall
Confirmed exclusion of malignancy where residual uncertainty	18/23 (78%) 7.9% overall

**Table 11 Summary of findings with routine lymphoid NGS panel testing for the diagnosis and management of suspected low-grade lymphoid malignancies, including 16 cases lacking distinctive features**

<b>Jajosky et al (2021)</b> <b>NGS 31-gene panel testing used routinely in initial diagnostic work-up</b>	<b>Number of patients (% of all patients)</b>
Number of patients tested	147
Samples with $\geq 1$ clinically significant variant	92 (64%)
Patient receiving a diagnosis where not previously possible	10 (7%)
Patient where diagnosis assisted (new or increased certainty)	37 (25%)
Patients receiving prognostic information	50 (34%)
Patients receiving result identifying an approved therapy	27 (18%)
Patients receiving result identifying an off-label or investigational therapy	26 (18%)
Management altered where change in diagnosis	76 (52%)
<b>Number of informative results</b>	
*Number of informative results from NGS – diagnosis, prognosis, approved therapy	114 (78%)
*Number of informative results from NGS – diagnosis, prognosis, any therapy	140 (95%)

\*Sum of patients with a change in diagnosis, prognosis, treatment with approved therapies – a single patient may receive more than one informative result or change, and a single variant may inform more than one domain

**Table 12 Summary of findings of routine use of lymphoid NGS panel testing for the management of patients with chronic lymphocytic leukaemia**

<b>Jajosky et al (2021)</b> <b>NGS 31-gene panel testing used routinely in initial work-up of chronic lymphocytic leukaemia</b>	<b>Number of patients (% of all patients)</b>
Number of patients tested	43
Samples with $\geq 1$ clinically significant variant	28/43 (65%)
Patient receiving a change in diagnosis	0
Patients receiving prognostic information	27/43 (63%)
Patients receiving result directing therapy	6/43 (14%)
Patients receiving result identified an investigational therapy	14/43 (33%)
Total number of informative NGS results/total number of patients – diagnosis, prognosis, therapy	*47/43 (109%)

\*An individual patient may have more than one informative variant, and a single variant may be informative across more than one domain so the total may exceed 100%

**Table 13 Clinical impact of Tier 1 or 2 variants identified in NGS 52-gene panel testing of patients under the age of 26 years with acute leukaemia (myeloid or lymphoid)**

<b>Vicente-Garces et al (2022) NGS 52-gene panel testing after other diagnostic tests</b>	<b>Number of patients (% of all patients)</b>
Number of patients tested	76
Samples with $\geq 1$ clinically significant variant	52 (68%)
Patient where diagnosis refined	31 (41%)
Patients receiving prognostic information	53 (70%)
Patients with potential germline variant detected	5 (6%)
Patients receiving result that identified an approved therapy, off-label or investigational therapy	31 (41%)
Number of informative NGS results (diagnostic, prognostic, familial, predictive) – derived from supplementary table 3	*134 (176%)

\*An individual patient may have more than one informative variant, and a single variant may be informative across more than one domain so the total may exceed 100%

The studies demonstrate the clinical utility and clinical effectiveness of lymphoid gene panels in the diagnostic process, either after extensive review and prior testing (Bommier et al, 2021; see Table 10); or when used upfront as an adjunct in the diagnosis of lymphoid conditions where a substantial proportion will be difficult to diagnose (Jajosky et al, 2021; see Table 11) or to provide additional information over and above conventional testing, particularly for prognostic, familial and predictive purposes (Jajosky et al, 2021; see Vicente-Garces et al, 2022). The overturning of prior diagnoses of malignancy and to establish a definitive diagnosis is evident, regardless of whether it is used earlier (Jajosky et al, 2021) or later in the diagnostic process (Bommier et al, 2021). Furthermore, the detection of a germline variant conferring an increased risk of toxicity with mercaptopurine broadens the clinical claim to include enhanced safety if such genes are included (Vicente-Garces et al, 2022; see Table 13)- these are not currently proposed but the permissive approach of an advisory candidate gene list does not preclude their inclusion.

Both Bommier (2021) and Jajosky emphasise the value of NGS panel testing to assist in difficult diagnoses, and Jajosky et al (2021) also demonstrate the value of the prognostic and therapeutic information gained when testing patients with chronic lymphocytic leukaemia - a condition that can be readily diagnosed by other means (see Table 12). Vicente-Garces et al (2022) tested patients after all other tests had been completed, and their findings indicate that DNA analysis within NGS panel testing assisted most with prognostic, familial predisposition and therapeutic selection.

The use of multigene panel testing to characterise variants in suspected haematological malignancies of myeloid, lymphoid or uncertain lineage results in superior effectiveness compared with no gene panel testing.

The use of multigene panel testing to characterise of variants in suspected haematological malignancies of myeloid, lymphoid or uncertain lineage may result in superior safety compared with no gene panel testing.

### 13. Economic evaluation

The MSAC Executive advised that a pragmatic economic evaluation was required.

**Table 14 Summary of the economic evaluation; ESC amendments marked up in italics**

Component	Description
Perspective	Health care system perspective
Population	Patients with a suspected initial diagnosis of a haematological malignancy, or with suspected relapse or progression
*Prior testing	Any of the following (although not included in economic model): Blood count, film Biopsy/bone marrow aspirate Immunophenotyping Cytology Cytogenetics, single gene testing Radiological imaging where indicated
Comparator	No NGS panel testing
Type(s) of analysis	Cost-effectiveness analysis
Outcomes	Diagnostic (alteration or refinement)/prognostic/familial predisposition/therapeutic
Time horizon	<i>Time to diagnosis/prognosis/management</i>
Computational method	<i>Decision analytic. No translation of clinical evidence</i>
Generation of the base case	<i>Modelled analysis, separately to distinguish the effect of each of these on the results</i>
Health states	NA
Cycle length	NA
Transition probabilities	NA
Discount rate	NA
Software	Excel

NA = not applicable; \* will vary according to the malignancy and availability of NGS testing

The HTA group has evolved an approach to reflect that NGS testing is many tests within a single test, may have multiple purposes and therefore can potentially provide multiple informative results of immediate relevance or perhaps for future management decisions. The cost-effectiveness of an NGS panel is an intersection of its ability to identify genetic alterations to diagnose and classify those malignancies according to the WHO diagnostic criteria as well as to identify the individual or clusters of gene variants that predict outcomes, familial predispositions and direct therapy. The HTA group’s approach has been to assess cost-effectiveness using two approaches that acknowledges the changes to the population in the study, and also the multiplicity of test purposes and potential to provide results across 4 domains (diagnostic, prognostic, familial predisposition (where reported) and therapeutic) and that there may be more than one informative result in each domain for individual patients (e.g., a clinical trial option and an approved therapy). These results

may inform multiple management decisions over time, representing the potential 'value-add' of a broader testing approach, particularly compared with a single gene testing strategy.

Thus, wherever possible, the cost-effectiveness results are presented in the following analyses as:

- alterations as reported in outcomes in terms of numbers of patients with a result that changes thinking or management in each of the 4 domains as reported;
- the number of informative outcomes provided by the test overall to acknowledge the depth of information provided, to acknowledge and attach a value where:
  - there may be more than one informative result in a given domain or in a patient that influences their management
  - results may influence management decisions in a multiplicity of ways (e.g., provide choice by identifying both approved and clinical trial options)
  - results influence treatment in an ongoing way beyond the immediate decisions and may be used for later decision-making e.g., subsequent lines of therapy.

Additional considerations are whether this approach allows an efficient assessment of the malignancy which would otherwise result in extensive serial testing, which may not be possible, feasible or currently available for some rarer malignancies

Where the test yields more than one informative result in an individual patient, there is seldom sufficient granularity to determine this for the individual patients in the publications assessed. Therefore, a simplistic approach has been adopted of adding together those results considered informative in each domain to present a net outcome of the results that are informative. The number of patients tested will influence this so that is retained as a denominator – this yields a value assessment of the cost per informative result rather than cost per reported change in management. Weighting of the value of the individual results is not possible and some of the reported options are not presented in sufficient detail to evaluate or consider for the Australian context. However, this approach aims to address that limiting the presentation to a single patient receiving a single benefit underestimates the value of the test, when multiple results are likely to have informed that outcome.

It would be valuable to evolve a weighting scale for the value of a certain test result. In the lymphoid NGS panel studies in particular, malignant diagnoses were often overturned, which is a critical change. This will only be represented as a single change in management in a single patient – the value of an outcome like that, particularly where there may not be niche specialists would be diluted if the test were used often where there was uncertainty – but that may be its value.

The following tables correspond with the studies above and present the cost-effectiveness analyses corresponding to the clinical effectiveness data.

The value of NGS testing is not always related to the diagnostic outcome – the value of NGS testing for myeloid malignancies is evident from the substantial change in prognosis and treatment options with somatic variants of clinical significance. These analyses are likely to underestimate the benefit because the IPSS-M which integrates molecular findings into a prognostic score for patients with MDS has dramatically altered risk stratification, was only published last month.

Few studies reported germline variants and test outcomes – these were included by Carbonell (2019) and Vicente-Garces, and both influenced management including offering a bone marrow transplant to one patient who would have otherwise received no treatment, due to the poor prognosis associated with MDS harbouring germline variants, (Carbonell, 2019) as well as screening family members as potential donors and for their own personal risk assessment and management.

The clinical context is critical and this is particularly evident in the analyses for Bommier (2021) where extensive prior testing was done and NGS testing was only ordered when central review expert pathologists required it to resolve residual diagnostic uncertainty – in less skilled hands, the diagnostic yield would be higher. The value of a correct diagnosis is not captured within these

analyses. These authors are pathologists and the focus of the study was the change in diagnostic rate so any other benefits or informative results would not have been captured.

The incorporation of all variants providing information is evident in the analyses for Jajosky (2021) where patients received NGS testing as a routine investigation. The value proposition for CLL is different when the array of possible outcomes are considered given these inform prognosis and treatment options, but are not required in most instances for a diagnosis.

The cumulative yield was difficult to ascertain in most studies as it was not necessarily reported the proportion of patients received results that informed diagnostic, prognosis, familial predisposition and therapeutic options. Most of these studies reported those domains independently.

## Myeloid NGS panel

With the publication of the summaries for the upcoming WHO HAEM5 and the IPSS-M prognostic model for MDS in June 2022 which incorporate molecular test outcomes into the diagnosis/classification and prognosis, respectively it is likely the following studies underestimate the change in diagnosis (alteration and refinement) and prognosis with NGS panel testing. Thus, the cost-effectiveness is likely to be greater with NGS panel testing for these domains and where they form part of a composite assessment of total benefit.

The economic evaluation presents results per study, using the MSAC supported fee of \$1,100 for DNA and RNA testing (upper estimate of cost-effectiveness).

[Patel et al 2021 Use of an NGS myeloid panel prior to cytogenetic/other genetic testing](#)

**Table 15 Cost-effectiveness of NGS testing with a myeloid panel in patients with a suspected haematological malignancy per outcomes reported in Patel et al (2021) at the MSAC supported fee of \$1,100 for DNA and RNA testing**

Patel et al (2021) NGS panel testing before cytogenetic/other genetic testing	37-gene NGS panel	Comparator (no NGS testing)	Increment	MSAC supported fee of \$1,100 for DNA and RNA testing
Cost of testing	\$1,100	\$0	\$1,100	-
Proportion of patients with NGS result that altered their diagnosis per 2016 WHO classification	0.017		0.017	\$62,883)
Proportion of patients with NGS result that subclassified their diagnosis per 2016 WHO classification	0.076		0.076	\$14,4512
Proportion of patients with NGS result that altered or subclassified their diagnosis per 2016 WHO classification	0.093		0.093	\$11,791
Proportion of patients where NGS results alter prognosis	0.615		0.615	\$1,788
Proportion of patients where initial treatment commenced then changed once NGS results available	0.350		0.350	\$3,145
Proportion of all patients where treatment offered changed by NGS result (initial or HSCT)	0.350		0.350	\$3,144



Patel et al (2021) NGS panel testing before cytogenetic/other genetic testing	37-gene NGS panel	Comparator (no NGS testing)	Increment	MSAC supported fee of \$1,100 for DNA and RNA testing
Number of treatment decisions altered by NGS result (initial or HSCT)/total population	0.423		0.423	\$2,602
Proportion of patients receiving a result that altered diagnosis incl subclassification, prognosis and/or treatment	0.711		0.711	\$1,546

Source DCAR calculations was updated based on MSAC's advice

\*An individual patient may have more than one informative variant, and a single variant may be informative across more than one domain so the total may exceed 100%

The small proportion (just under 2%) of patients who had a complete change in their diagnosis has resulted in a large ICER for this domain, although the ICER decreases when refinements of the diagnosis based on detection of gene variants are included. The ICER for the alteration/refinement in diagnosis in the studies by Patel and Carbonell et al (2019) below are similar which supports that this is a robust finding. This reflects that the absolute changes in diagnosis are uncommon as the clinical characteristics and morphological analysis in most cases can broadly categorise myeloid malignancies, but are insufficient to fully characterise the condition. Nonetheless, the context is important, and overturning a diagnosis of a haematological cancer is a critical benefit to the patient and potentially represents a significant benefit to the healthcare system. With the changes in WHO HAEM5, refinements in the diagnosis will be much more common as there are many new entities defined by genetic changes, particularly those associated with germline variants.

[Carbonell et al 2019 Use of a myeloid NGS panel after cytogenetic testing](#)

**Table 16 Cost effectiveness of NGS testing with a myeloid panel in patients with a suspected haematological malignancy per outcomes reported in Carbonell et al (2019) at the MSAC supported fee of \$1,100 for DNA and RNA testing**

Carbonell et al (2019) NGS panel testing of myeloid neoplasms after cytogenetic testing	54-gene NGS panel	Comparator (no NGS)	Increment	MSAC supported fee of \$1,100 for DNA and RNA testing
Cost of testing	\$1,100	\$0	\$1,100	-
<b>Effectiveness measures at initial diagnosis</b>				
Proportion of patients where NGS identified ≥1 clinically significant variants	0.843	0	0.843	\$1,305
Proportion of patients with NGS result that altered or refined/confirmed their diagnosis per 2016 WHO classification	0.058	0	0.058	\$19,014
Proportion of patients where NGS results reclassified prior classification of prognostic group differently using ELN system (AML) or PMF MIPSS	0.132	0	0.132	\$8,319

Proportion of patients in whom somatic test identified potential germline variant	0.174	0	0.174	\$6,338
Proportion of patients in whom germline pathogenic variant identified	0.176	0	0.176	\$6,233
Proportion of patients eligible for clinical trial based on NGS results	0.364	0	0.364	\$3,025
<b>Effectiveness measures at relapse (compared with initial diagnosis)</b>				\$0
Proportion of patients with change of variant expression (gain, loss, both)	0.600	0	0.600	\$1,822
Proportion of patients with change in treatment target at relapse likely to influence therapy	0.200	0	0.200	\$5,500

Source DCAR calculations was updated based on MSAC's advice

\*An individual patient may have more than one informative variant, and a single variant may be informative across more than one domain so the total may exceed 100%

#### Rosenthal et al (2021) Use of an NGS panel test with outcomes reported as standalone test

This study was carried out by a commercial service and the clinical information appears to be derived from the information supplied with request for testing. As such, it is likely to be very limited and the findings from NGS cannot be integrated into the clinicopathological context to provide information about the impact on either the diagnosis or prognosis nor the suitability of any therapies identified. It is unclear whether the test provider had any role beyond performing the NGS testing. This, however, is potentially how some services could be provided and reported, if the provider is not part of a multidisciplinary team delivering results that are discussed with the treating team.

The HTA group considers the findings of diagnostic variants and prognostic variants and any parameters where these are included should be interpreted with caution.

**Table 17 Cost-effectiveness of NGS testing with a myeloid panel in patients with a suspected haematological malignancy per outcomes reported in Rosenthal et al (2021) at the MSAC supported fee of \$1,100 for DNA and RNA testing**

Rosenthal et al (2021) NGS panel testing detection rates as part of work-up	47-gene NGS panel	Comparator (no NGS)	Increment	MSAC supported fee of \$1,100 for DNA and RNA testing
Cost of testing	\$1,100	0	\$1,100	-
<i>Effectiveness measures:</i>				
Proportion of patients receiving a result 'of diagnostic significance'	0.364		0.364	\$3,019
Proportion of patients receiving an NGS result of prognostic significance	0.346		0.346	\$3,176
Proportion of patients receiving a result that identified an approved therapeutic target or regimen	0.061		0.061	\$17,923
Proportion of patients receiving a result that identified an approved or off-label target	0.275		0.275	\$3,997

Rosenthal et al (2021) NGS panel testing detection rates as part of work-up	47-gene NGS panel	Comparator (no NGS)	Increment	MSAC supported fee of \$1,100 for DNA and RNA testing
Proportion of patients receiving a result that identified an experimental therapy/clinical trial option	0.401		0.401	\$2,744
#NGS variant detection that identified any potentially therapeutic target or regimen/total population	0.676		0.676	\$1,627
Proportion of patients receiving a result that altered diagnosis or prognosis, refined or confirmed diagnosis or identified a potentially therapeutic target or regimen	0.517		0.517	\$2,126

Source DCAR calculations was updated based on MSAC's advice

# Sum of patients with a result informing options for an approved targeted therapy, off-label targeted therapy or experimental therapy – a single patient may receive more than one informative result or change

\*Sum of patients with a change in diagnosis, prognosis, treatment with approved therapies – a single patient may receive more than one informative result or change, and a single variant may inform more than one domain

### **Summary and comments on cost-effectiveness of a myeloid panel**

The findings of a lower ICER where prognostic and predictive information are generated by NGS panel testing indicates the value of this testing is to alter/refine the diagnosis in a small proportion but contribute significantly to the risk stratification and management decisions for a significant proportion of the patients tested. The high ICER for the diagnostic informative results - likely be lower following early publications based on the WHO HAEM5 - should be interpreted in context as an alteration in the diagnosis absolutely fundamental to the correct management of the patient's condition. This demonstrates that NGS is a technology that should be integrated alongside other clinicopathological findings, not be viewed as a standalone test. The range of ICERs also indicate that the value of NGS panel testing should be considered across all domains as patient often have more than one clinically significant variant, and the variant may affect more than one domain. The findings from these studies underrepresent the value of detecting familial pathogenic variants which was only followed up and reported in one study (Carbonell et al, 2019). However, this is currently not proposed and there is no MBS item for further investigation of any potential germline variants, nor any cascade testing for families of probands (other than for *TP53*).

## Lymphoid NGS panel

[Bommier et al 2021 Cost-effectiveness of lymphoid NGS panel to resolve diagnostic uncertainty for suspected lymphoma after expert review, prior testing](#)

**Table 18 Cost-effectiveness analysis of an NGS lymphoid panel used to diagnose patients where there is uncertainty after expert review (as per outcomes reported in Bommier et al 2021) at the MSAC supported fee of \$1,100 for DNA and RNA testing**

Bommier et al (2021) NGS panel after other tests, expert review	46-gene NGS panel	Comparator (no NGS testing)	Increment	MSAC supported fee of \$1,100 for DNA and RNA testing
Cost of testing	\$1,100	\$0	\$1,100	-
<i>Effectiveness measures:</i>				
Proportion of patients with a change in diagnosis	0.105	0	0.105	\$10,496
Proportion of patients where NGS strengthened the suspected histological diagnosis	0.629	0	0.629	\$1,749
Proportion of patients with change or confirmation/strengthening of diagnosis	0.734		0.734	\$1,499
Proportion of patients where the management altered where change in diagnosis	0.083		0.083	\$13,258
Proportion of patients with confirmed exclusion of malignancy where residual uncertainty	0.079		0.079	\$13,994

Source DCAR calculations was updated based on MSAC's advice

[Jajosky et al 2021 Cost-effectiveness of routine NGS testing of patients with suspected low-grade lymphoproliferative disorders, including 16 patients where other tests likely to be inconclusive](#)

**Table 19 Cost-effectiveness analysis of an NGS lymphoid panel used routinely to diagnose patients with a low-grade lymphoproliferative disorder including those unlikely to be diagnosed with conventional testing (as per outcomes reported in Jajosky et al 2021) at the MSAC supported fee of \$1,100 for DNA and RNA testing**

Jajosky et al (2021) NGS Routine panel testing as part of initial work-up	31-gene NGS panel	Comparator (no NGS)	Increment	MSAC supported fee of \$1,100 for DNA and RNA testing
Cost of testing	\$1,100	\$0	\$1,100	-
<i>Effectiveness measures:</i>				
Proportion of patients with $\geq 1$ clinically significant variant	0.626		0.626	\$1,758
* Proportion of patients receiving a diagnosis where not previously possible	0.625		0.625	\$1,760
Proportion of patients where diagnosis assisted (new or increased certainty)	0.252		0.252	\$4,370
Proportion of patients receiving prognostic information	0.340		0.340	\$3,234
Proportion of patients receiving result identifying an approved therapy	0.184		0.184	\$5,989

Proportion of patients receiving result identifying an off-label or investigational therapy	0.177		0.177	\$6,219
Proportion of patients receiving a result and management altered where change in diagnosis	0.517		0.517	\$2,128

Source DCAR calculations was updated based on MSAC's advice  
 \* 10/16 patients were given a diagnosis where this was not previously possible

[Jajosky et al 2021 Routine NGS panel testing of samples where suspected chronic lymphocytic leukaemia](#)

**Table 20 Cost-effectiveness analysis of an NGS lymphoid panel used routinely in patients with chronic lymphocytic leukaemia (as per outcomes reported in Jajosky et al 2021) at the MSAC supported fee of \$1,100 for DNA and RNA testing**

<b>Jajosky et al 2021 NGS panel testing Chronic lymphocytic leukaemia</b>	<b>31-gene NGS panel</b>	<b>Comparator (no NGS)</b>	<b>Increment</b>	<b>MSAC supported fee of \$1,100 for DNA and RNA testing</b>
Cost of testing	\$1,100	\$0	\$1,100	-
Proportion of patients with ≥1 clinically significant variant	0.651		0.651	\$1,899
Proportion of patients receiving a change in diagnosis	0.000		0.000	N/A
Proportion of patients receiving prognostic information	0.628		0.628	\$1,752
Proportion of patients receiving result directing therapy	0.140		0.140	\$7,883
Proportion of patients receiving result identified an investigational therapy	0.326		0.326	\$3,379

Source DCAR calculations was updated based on MSAC's advice

[Vicente-Garces et al 2022 NGS testing in children, adolescents and young adults with acute leukaemia](#)

In this analysis, the testing was performed after other testing and it is likely that the reported detection of variants may have been greater if the testing had been done during the diagnostic work-up (and may have reduced use of other genetic tests).

**Table 21 Cost-effectiveness analysis of an NGS lymphoid panel used after other testing in paediatric and young adults with acute leukaemia (as per outcomes reported in Vicente-Garces 2022) at the MSAC supported fee of \$1,100 for DNA and RNA testing**

Vicente-Garces 2022 NGS panel testing after other testing in acute leukaemia	52-gene NGS panel	Comparator (no NGS)	Increment	MSAC supported fee of \$1,100 for DNA and RNA testing
Cost of testing	\$1,100	\$0	\$1,100	-
Proportion of patients with $\geq 1$ clinically significant variant	0.684		0.684	\$1,608
Proportion of patients receiving a change/refinement in diagnosis	0.408		0.408	\$2,697
Proportion of patients receiving prognostic information	0.697		0.697	\$1,577
Proportion of patients where germline variant identified	0.066		0.066	\$16,720
Proportion of patients receiving result directing therapy	0.408		0.408	\$2,697

Source DCAR calculations was updated based on MSAC's advice

### **Summary and comments on cost-effectiveness of a myeloid panel**

NGS testing critically supports pathologists to establish the correct diagnosis, whether used initially (Jajosky et al, 2021) or if uncertainty remains after all other tests and reviews (Bommier et al, 2021). The invaluable role of the prognostic and predictive impact for the management of CLL is clearly demonstrated by Jajosky et al (2021) and patients cannot be managed appropriately without knowing the variant status of genes such as *TP53*. The potential to identify therapeutic options is clearly demonstrated in all three studies, as is the overall contribution across all the domains. Patients may receive informative results across multiple domains, and Vicente-Garces (2022) identified the potential to detect familial predisposition affecting cancer risk and the safe use of medicines.

## **14. Financial/budgetary impacts**

An epidemiological approach was used to estimate the uptake of the proposed technology, and the proportion of testing known in terms of myeloid:lymphoid panel testing ratio plus the out-of-hospital testing rate are known as this is already established as the standard of care for some Australian patients.

The data presented in the following tables for 'Number of people who receive NGS panel test (includes incident and prevalent population)' represents an estimate of the sum of patients to be tested with either the myeloid panel test or the lymphoid panel test. The Peter MacCallum Cancer Centre advised the HTA group that it tests 5,000-6,000 samples a year of which the breakdown is probably 70% myeloid/30% lymphoid. Given the earlier estimate that 5000 tests were performed at the Peter MacCallum Cancer Centre in 2021, and that this is the only reported site to offer a lymphoid panel, this suggests that these figures are from that centre. This clearly indicates that the myeloid panel is used more frequently (although myeloid malignancies account for only 25% of all haematological cancers), especially as this was the only testing offered at other sites. This percentage breakdown can be used to inform the likely utilisation of the two new MBS items, AAAA for NGS testing with a myeloid panel and BBBB for NGS testing with a lymphoid panel.

The financial implications to the MBS resulting from the proposed listing of NGS panel testing for the characterisation of haematological malignancies are summarised below.

All of the following tables are based on the 85% benefit incorporating the Greatest Permissible Gap (GPG). However, the GPG is indexed annually on 1 November in line with the Consumer Price Index (CPI) (June quarter), resulting in a reduction of the 85% benefit each year. For example, the 85% benefit used in Table 22 will become \$834.70 from 1 November 2022 and will reduce again by a currently unknown amount, the following year.

The financial estimates were also calculated based on the MSAC-supported 85% benefit (\$1,006.80) incorporating the GPG of \$93.20 from 1 November 2022 (Table 22).

**Table 22 Net financial implications - MSAC supported 85% benefit for DNA and RNA panel testing (\$1,006.80)**

	2023	2024	2025	2026	2027	2028
<b>Estimated use and cost of the proposed health technology at MSAC supported 85% benefit (\$1,000)</b>						
Number of people with suspected condition or past diagnosis	75,595	76,763	77,955	79,171	80,413	81,682
Number of people eligible for NGS panel test	59,131	60,071	61,030	62,011	63,011	64,034
Number of people who receive NGS panel test (includes incident and prevalent population)	10,545	10,828	11,118	11,417	11,725	12,041
Cost to the MBS (with appropriate copayments excluded)	\$10,616,706	\$10,901,630	\$11,139,602	\$11,494,636	\$11,804,730	\$12,122,879
<b>Change in use and cost of other health technologies</b>						
Change in costs to MBS of change in other genetic tests* with NGS	-\$3,794,414	-\$4,268,716	-\$4,802,305	-\$5,402,594	-\$6,077,918	-\$6,837,658
<b>Net financial impact to the MBS</b>	<b>\$6,822,292</b>	<b>\$6,632,914</b>	<b>\$6,391,297</b>	<b>\$6,092,042</b>	<b>\$5,726,812</b>	<b>\$5,285,221</b>

Source DCAR calculations was updated based on MSAC's advice

Out-of-hospital testing rate 70% for myeloid malignancies, 90% for lymphoid malignancies

\*MBS Items 73290, 73326, 73314, 73343, 73364, 73365, 73366, 73367, 73368, 73369 and 77370

\*\*Estimated testing rate at 50% testing rate for incident population and 5% per annum for prevalent population and all where malignancy excluded

## 15. Other relevant information

Nil.

## 16. Key issues from ESC to MSAC

<p><b>Main issues for MSAC consideration</b></p> <p><b>Clinical issues:</b></p> <p>Clinical effectiveness and safety – The evidence from several case series studies predominantly at moderate risk of bias demonstrated that NGS panel testing has superior effectiveness and non-inferior safety compared with no NGS panel testing in suspected haematological malignancies of myeloid, lymphoid or uncertain lineage results. Molecular testing in addition to other haematological testing is now a standard requirement to accurately diagnose and comprehensively characterise many haematological malignancies, and to exclude some other differential diagnoses.</p> <p>Germline variants and test outcomes – The main safety and effectiveness issue is the unintended identification of germline variants. The Applicant has acknowledged the need for an additional</p>
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application to evaluate germline testing. Although outside the intent of this application for somatic NGS panel testing, MSAC may wish to consider whether a generic MBS items for cascade testing for blood relatives, and identification of somatic versus germline variants be created to allow predictive testing given the rate of expansion of clinically relevant pathogenic/likely pathogenic variants being identified across all malignancies.

MBS item panel size and test methodology – The optimal panel size or composition is not described given the changing evidence base. The panel size and composition will need to be sufficient for testing of common and rare forms of haematological malignancy. However, the panel size is almost certain to increase in the future, and will likely require RNA analysis as well as DNA.

- It was reiterated that the WHO Classification includes genes which have been confirmed to have diagnostic and/or prognostic, and/or predictive utility. This Classification is proposed by the Applicant as the reference for determining the panel composition.
- Genes with established clinical utility, but not included in the WHO Classification, have been identified by the Assessment Group
- Currently, identifying a maximal panel composition is not critical, although there should be a minimum requirement for genes with established clinical utility to be included. This may vary by clinical setting (e.g. children and young adults vs. adult). There are currently no local guidelines or Australian data to inform these key genes, but MSAC may wish to align them with WHO diagnostic guidelines and other recognised expert guidance about prognosis and management options, noting the WHO guideline was updated 6 years after the previous version.

Implementation – MSAC may wish to consider a test directory to define the minimum gene list and as a reference for updating the panel as new variants are identified.

MBS item fee justification – the fee for a next-generation sequencing (NGS) panel of genes with established clinical utility will depend on the size of the panel and the complexity of the tests (depending on the clinical context). MSAC may wish to review the proposed fee (\$927.90) to ensure it is futureproofed.

Equity in access to NGS panel testing – is currently limited and predominantly only funded by philanthropy.

**Economic issues:**

- The ICERs presented are consistent with the approach taken in other somatic gene panel applications considered by MSAC, which reflect the multiplicity of test purpose. However, the ICERs are not likely to be overly informative for MSAC decision-making due to the heterogenous and potentially overlapping populations, the lack of synthesised evidence, and the lack of direct comparative evidence for the use of single gene tests and gene panels.

**Financial issues:**

- The proposed utilisation (50% of patients with suspected haematological malignancy) may be underestimated, thus underestimating the financial impact. There may be cost offsets due to this testing replacing other types of tests, and more appropriate use of therapeutics. However, the estimated cost offsets are highly uncertain, as they are based on data from a single centre in Victoria.
- The net total cost of NGS-based gene panel testing for approximately 10,000 individuals in Year 1 is estimated to be \$5.1m, which reduces to \$3.3m at Year 6 (estimate of 12,000 patients) due to the reduction in the prevalent pool of patients who may require testing, and assumption regarding the extent of cost offsets being similar to current Victorian utilisation data, which is currently philanthropically funded.



## ESC discussion

ESC noted that this application from the Royal College of Pathologists of Australasia (RCPA) was for Medicare Benefits Schedule (MBS) listing of next-generation sequencing (NGS) gene panel testing for variants associated with haematological malignancies to establish a definitive diagnosis that cannot be established by conventional testing alone.

ESC noted that haematological malignancies are a broad group of cancers, and the numerous subtypes, that include myelodysplastic syndromes, myeloproliferative neoplasms, myelofibrosis, acute/chronic leukaemias, myelomas and Hodgkin/non-Hodgkin lymphomas. ESC noted that the Ratified PICO simplified the testing for the eligible conditions to cancers of myeloid or lymphoid origin, but that nearly all haematological malignancies are encompassed by the application, including some myeloproliferative disorders for which there are other existing MBS items, for example: MBS item 73399 characterisation of variants in at least 20 genes including Janus kinase 2 (*JAK2*), calreticulin (*CALR*) and myeloproliferative leukaemia (*MPL*) testing in primary myelofibrosis; [PSD 1532](#)).

ESC noted that the categorisation of the broad range of diseases is making it increasingly difficult to define, diagnose and treat haematological malignancies without molecular testing, and that the fifth edition of the World Health Organization (WHO) Classification of Haematolymphoid Tumours 2022 recommends molecular testing for establishing a comprehensive diagnosis. ESC noted that, in August 2019, MSAC supported genetic testing for diagnosing a limited number of lymphoid neoplasms, and for prognostic testing in patients with myeloma ([PSD 1526](#)).

ESC noted that from the targeted consultation several organisations supported the application. Respondents stated that genetic testing for these types of malignancies is now standard of care. As a result, respondents claimed that there would be equity and access issues if this testing is not publicly funded. Consultation feedback also considered that the proposed fee (\$800) was too low (but did not propose an alternative). However, the Departmental-contracted assessment report (DCAR) proposed a revised fee of \$927.90 based on expert opinion which was confirmed by the applicant in the pre-ESC response. ESC noted that this fee was calculated as \$840 plus the Greatest Permissible Gap (GPG) and is broadly consistent with the fee proposed for the glioblastoma 25-gene panel ([PSD 1709](#)). However, ESC noted that the Department is currently establishing a genetic test fee matrix to guide future decisions on fees for proposed MBS items. MSAC may wish to consider the fee to ensure it is appropriate based on the proposed panel composition.

ESC discussed consumer issues such as whether testing may identify variants that may occur at varying frequencies across different groups of patients according to their demographic origin. ESC queried whether data on this were available from the current testing done in Peter MacCallum Cancer Centre in Victoria.

ESC noted the clinical management algorithms include other MBS-funded clinical investigations such as blood counts, biopsy and bone marrow aspirate, and some single gene testing. The NGS panel would be used as clinically necessary, depending on the suspected malignancy and clinical context. Although the genetic testing would provide a definite comprehensive diagnosis (i.e. confirmation of suspected diagnosis, refinement of a diagnosis or refute the diagnosis of a malignant condition), it will, if based on the WHO Classification additionally provide prognostic value and identify targeted treatment or management change. The proposed test is not to be used for measurable residual disease monitoring.

ESC noted that, consistent with PASC, that the comparator is no NGS panel testing.

Other diagnostic options include morphology, flow cytometry, cytogenetics, individual molecular tests and fluorescence in situ hybridisation (FISH). These tests provide a working diagnosis of a haematological malignancy. ESC noted the sequential nature of this testing delays diagnosis and therapy, contributing to patient anxiety. ESC noted that there may be some cost offsets related to the replacement of existing MBS items for these tests, and that these were considered by the DCAR in the modelled budget impact.

ESC noted that the proposed MBS item descriptor is for either a myeloid or lymphoid somatic NGS panel of at least 25 genes, with a separate minimum gene composition for each. ESC noted that the number of genes is certain to increase as more relevant genes are identified, and that the descriptor and fee may need to be reconsidered in the future. ESC advised that a test directory and mechanism for updating the genes included on the panel would be necessary. ESC noted that the DCAR added genes with established clinical utility, but not included in the WHO Classification. ESC considered that it was not critical to identify an exact and universal myeloid or lymphoid gene panel as the clinical context may differ (e.g. infant/paediatric- versus adult-onset conditions), although a minimum requirement for key variants should be included. ESC noted that there are no local guidelines or Australian data to inform such a list of key variants, but that the WHO diagnostic criteria and other expert guidance (e.g. European LeukemiaNet, National Comprehensive Cancer Network, NHS England) could be used to ascertain the minimum panel genes for prognosis and treatment selection. ESC noted that future variants would likely require RNA analysis in addition to DNA analysis.

ESC considered that an NGS virtual panel was more suitable than whole genome sequencing (WGS) for this type of testing, as WGS would yield much unnecessary data and prolong the turnaround time for the test (already 3–4 weeks), thus delaying patient diagnosis, prognostication or management change.

ESC discussed including the phrase “clinically suspected” and queried whether it could lead to leakage to a broader population, noting that the proposed test would not be used in patients where the diagnosis can be categorically determined by other tests. Although ESC considered the scope of testing to be uncertain, it concluded that haematologists are unlikely to order the testing unnecessarily when there are other prior tests that are more suitable for diagnosing the conditions not covered by this testing.

ESC suggested the following amendments (in italics and strikethrough) to the proposed revised MBS descriptor in the pre-ESC response:

Characterisation of ~~gene~~ variant(s), *in a panel of at least 25 genes*, requested by a specialist or consultant physician, *to determine the diagnosis, prognosis and/or management of* ~~in~~ a patient presenting with a *clinically suspected* haematological malignancy of: myeloid origin (Item number AAAA); lymphoid origin (Item number BBBB) ~~that includes at least 25 genes from the exemplar list.~~

Applicable once per diagnostic episode at ~~initial~~ *diagnosis, disease progression or at disease-relapse*

ESC noted that a small number of patients covered by MBS item 73399 may develop secondary myelofibrosis and may need genetic testing which would be in the scope of the proposed MBS items.

ESC noted that the DCAR’s clinical effectiveness and safety data came from three studies comprising prospective and retrospective case series for the myeloid panel, and three studies comprising retrospective case series for the lymphoid panel. ESC acknowledged the DCAR’s concerns of limited generalisability of the study by Pillionel et al (2020) in lymphoid malignancies (due to the larger panel size of 68 genes than the proposed minimum panel size of at least 25 genes in MBS item BBBB) but considered, on balance, this study was also relevant for MSAC’s consideration (see Table 6). Overall, ESC noted most of the case series had moderate risk of bias.

ESC considered the main safety and effectiveness issue to be the identification of incidental germline variants that may impact family members; with increased somatic testing, potential germline variants will be identified, and these have implications for the safety and efficacy of medicines, transplant donor screening, familial risk identification and management. ESC noted that where heritable variants are identified, cascade testing was out of scope for this application, and suggested that MSAC may wish to consider whether a generic MBS item for cascade testing for blood relatives be created to allow predictive testing given the rate of expansion of clinically relevant pathogenic/likely pathogenic variants being identified across all malignancies, but to date

no evidence has been assessed to support these tests. Any identified germline variants may also adversely impact bone marrow donor status. ESC agreed with consultation feedback that systems that include genetic counselling and informed consent should be in place for such testing. ESC considered that a too-small panel may miss some very rare diagnoses which may also be a safety issue. However, ESC considered the benefits to likely outweigh any safety issues.

ESC agreed with the clinical claim of superior effectiveness compared with no NGS panel testing, as the NGS panel testing demonstrated it provides diagnostic, prognostic and treatment decision-making information. In particular, the study by Pillonel et al (2020) supported genetic testing for lymphoid diagnosis but used a much larger gene panel size of 68 genes. However, ESC considered that this demonstrated the resolution of diagnostic challenges, as there are several subtypes of some malignancies. For example, in lymphoid malignancies there are no core set of genes that can be identified/readily defined as these are diverse, heterogeneous conditions and a large panel is required to differentiate between the conditions efficiently.

ESC noted that the economic evaluation was a simple cost-effectiveness analysis (see Table 14). ESC noted the resulting incremental cost-effectiveness ratios (ICERs) ranged from about \$700 to about \$53,000 per change in diagnosis (see Tables 15–21), noting that the genes in the WHO Classification do not just have diagnostic utility. The ICERs presented reflect the multiplicity of the proposed testing, which estimates for other utilities (i.e. prognostic value and/or predictive value, beyond diagnostic utility) being lower than that described for diagnosis alone. ESC also noted that the results were more favourable when considered across multiple domains (diagnosis, prognosis, treatment and management) with ICERs ranging from \$526–\$849 per informative result. Despite the approach of the economics being consistent with other somatic gene panel applications considered by MSAC, ESC advised that, in this case, the ICERs were of limited value for decision-making due to the very heterogeneous and potentially overlapping populations and the lack of synthesised evidence. ESC also considered other limitations were: the lack of direct comparative evidence for cumulative yield from other existing genetic tests (e.g. single gene tests and gene panels), although these may also be performed as prior tests both in the intervention and comparator arm; and the estimation of the cost of the comparator to be zero. ESC considered the cost of the comparator would depend on the clinical context which is complicated due to the heterogeneous patient population; however, a pragmatic approach would suggest the costs of any comparative profiling would be considerable.

ESC noted that an epidemiological approach (incidence and prevalence of blood cancer data from the Australian Institute for Health and Welfare) was used to estimate utilisation. This included proportions of myeloid (20%) and lymphoid (70%) lineage and “other” (10%), but ESC noted that these are likely to require different testing rates.) ESC noted a key source of uncertainty in the estimation of the budget impact was the assumption that 50% of people with haematological malignancies would be eligible for testing and access NGS panel testing based on the applicant’s clinical judgment. ESC queried whether this assumption was based on data from the Peter MacCallum Cancer Centre (Victoria), where genetic panel testing has been philanthropically reimbursed. Although data were collected from a large cohort of approximately 5,000 patients, ESC noted that there could be state-by-state variation in utilisation, making the 50% estimate uncertain. ESC agreed that using a 3.1% growth in incidence population and 1% growth in prevalence population, as done in the DCAR, was appropriate. ESC agreed with the DCAR that 5% repeat testing in the prevalent population is reasonable. However, ESC questioned whether the 5% of the prevalent population and 1.65% of those who were ruled out having a malignancy by expert opinion were included in the original 50% utilisation estimate but advised that this is not of great concern if the 50% estimate is already uncertain. The lymphoma registry was established in 2016 and, since then, only 10% of patients have been reported to have received molecular testing; ESC queried if there was underreporting in this data analysis. Overall, ESC considered the applicant’s assumption of a 50% testing population to be highly uncertain and likely an underestimate. These uncertainties may result in demand that is nearly double the current utilisation estimates, although there may be capacity constraints in performing NGS testing more broadly. ESC noted the pre-ESC response that the prevalent population will decrease over time as testing becomes more accessible.

ESC noted the estimated financial impact (85% rebate=\$840 accounting for the GPG), including cost offsets, was \$5.2 million in Year 1 to \$3.3 million in Year 6 (see Table 22). ESC noted the cost offsets were due to the replacement of some existing MBS-reimbursed tests (e.g. single gene tests), including those described in MSAC PSDs for applications 1526 and 1532. However, ESC considered the extent of cost offsets were highly uncertain as the DCAR assumed that all utilisation is related to current testing patterns in Victoria, and it was shown that there are inconsistent state-by-state usage trends.

ESC noted that laboratory workload, reporting, and quality assurance may become an issue if listed, especially for the lymphoid cancers. However, ESC considered that laboratories would likely expand to include the necessary testing given the accepted place of genetic testing in informing a comprehensive diagnosis. Associated services such as genetic counselling may also be affected by the introduction of the test, particularly once expanded to include germline variants.

ESC also noted that there is a need for a diagnostic test registry in Australia; work on this is currently underway.

## **17. Applicant comments on MSAC's Public Summary Document**

The College's Working Party would like to express their delight in MSAC approving public funding genetic testing for variants associated with haematological malignancies, and would like to take this opportunity to thank the Department for its assistance throughout the assessment process. The College and Fellows have only minor comments to make on the PSD for Application 1684.

Firstly, the College would like to reiterate that an optimal panel size or composition was not described in the application given the changing evidence base, with the proposed minimum of 25 genes being intended to be agnostic to a specific list of genes in order to future-proof the item given that relevant genes change over time. Selection of genes will depend on clinical presentation and clinician/pathologist judgement. The application referenced the WHO classification of haematological malignancies used by clinicians and pathologists to classify and manage patients; however, the Department may wish to reference NHS England's National Genomic Test Directory for Cancer, which specifies genomic tests by the technology by which they are available, and the patients who will be eligible to access to a test.

In closing, whilst germline testing did not form part of this current application due to the complexity of including somatic and germline variant testing, the College would be largely supportive of an application for cascade testing for heritable variants.

## **18. Further information on MSAC**

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