Australian Government

Department of Health

MSAC Application 1684:

Genetic testing for variants associated with haematological malignancies

Ratified

PICO Confirmation

Summary of PICO/PPICO criteria to define question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

Table 1 PICO for genetic testing for variants associated with haematological malignancies in patients with lymphoid neoplasms (mature lymphoid, histiocytic, and dendritic neoplasms), myeloid neoplasms or acute leukaemia

Component	Description
Population	Patients/persons with clinically suspected myeloid or lymphoid neoplasm where accurate diagnosis sufficient for treatment planning is not achieved using conventional testing.
Prior tests	Clinical investigations including tests with primary health care providers (including full blood count and other basic laboratory investigations +/- limited single gene testing) and specialist haematologist physicians (i.e., further laboratory investigations, radiological investigations and/or diagnostic procedures)
Intervention	Genetic testing for variants associated with haematological malignancies using next generation sequencing (NGS) gene panel testing including at least 25 genes
Comparator/s	No NGS gene panel testing
Reference standard	Not required (diagnostic testing recommended by the World Health Organization (WHO) guidelines)
Clinical utility standard	Not required (diagnostic testing recommended by the WHO guidelines)
Outcomes	Safety Outcomes: • Test adverse events • Adverse events from treatment • Adverse events from change in patient management Clinical Effectiveness Outcomes: • Change in patient health outcomes: mortality, morbidity, quality of life (direct evidence) • Cumulative diagnostic yield (informative result) • Cumulative prognostic yield (from those with an informative result) • Change in management/treatment resulting in change in patient outcomes: mortality, morbidity, quality of life (indirect evidence) Health system resources: • Cost of gene panel test or variant-specific test • Reduced number of preliminary diagnostic tests • Cost of targeted therapies • Cost per quality-adjusted life year and/or cost-effectiveness [The economic evaluation is to be confirmed at the 28 January 2022 MSAC Executive meeting] • Total Australian Government healthcare costs
Assessment questions	What is the safety, effectiveness and cost-effectiveness of NGS gene panel testing for variants associated with haematological malignancies versus no NGS gene panel testing in people diagnosed with a likely haematological malignancy?

Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of genetic testing for variants associated with haematological malignancies to establish a definitive diagnosis was received from The Royal College of Pathologists of Australasia (RCPA) by the Department of Health.

The clinical claim is that gene testing for variants associated with haematological malignancies in patients diagnosed with haematological malignancies (classified as either lymphoid neoplasms or, myeloid neoplasms and acute leukaemia) results in superior health outcomes compared to no gene testing.

Background

Patients with haematological malignancies are clinically and genetically heterogeneous. The addition of genomic characterisation of lymphoid and myeloid neoplasms using the revised World Health Organization (WHO) criteria improves patient management by delivering a specific diagnosis that informs prognosis and, importantly, enables treatment to be tailored based on the identified tumour variants.

In addition, the Leukaemia Foundation's National Strategic Action Plan for Blood Cancer, commissioned by the Australian Government Department of Health, states that in order to deliver patients with a haematological malignancy a timely, accurate diagnosis, best practice should embrace the following action points:

- Action 2.2: Develop guidelines for diagnostics and review Australia's capacity to meet these guidelines; and
- Action 2.3: Make precision medicine the standard of care (Leukaemia Foundation, 2020).

MSAC applications 1526, 1527, and 1528

The applicant noted that at its August 2019 meeting, MSAC supported genetic tumour testing applications 1526, 1527 and 1528 (Medical Services Advisory Committee (MSAC), 2019a, 2019b, 2019c). The Public Summary Documents (PSDs) for these applications note that by virtue of their place in the WHO guidelines, the proposed genetic tests have documented clinical utility in these diseases. MSAC confirmed that it accepts the entry of each test into the WHO guidelines as sufficient demonstration of its diagnostic performance, clinical validity (prognostic value), and clinical utility (resulting in changes to subsequent clinical management), therefore the precedent has been established for MSAC accepting such claims based on WHO guidelines.

MSAC application 1532

At its November 2020 meeting, MSAC supported genetic testing (for both gene-specific and next generation sequencing (NGS), following *JAK2 V617F* triage) for myeloproliferative neoplasms (MSAC, 2020). MSAC considered that the identification of specific genetic variants underlying myeloproliferative neoplasms has diagnostic and prognostic and/or predictive clinical utility. This expansion of testing (MBS item 73325) is aligned with current WHO clinical guidelines, and reflects the WHO's diagnostic criteria for myeloproliferative neoplasms classification.

At the September 2021 MSAC Executive meeting, it was noted that following correspondence from MPN Alliance Australia and the Leukaemia Foundation (referred to as the Respondents), that the proposed expansion of NGS myeloid panel testing to include the secondary myeloproliferative neoplasms. The MSAC Executive recommended that the Department advise the Respondents to liaise with the RCPA in relation to amending the scope of this new application.

PICO criteria

Population

The testing population

The proposed testing population are patients diagnosed with a haematological malignancy post clinical investigations where genomic sub-categorisation is required. This typically occurs when diagnosis of a haematological malignancy is incomplete, and as such specific disease-causing variants cannot be identified and patients cannot receive targeted treatment. However, as the diagnosis at a molecular level can overturn or refine a phenotypic diagnosis, the test is not limited to those with an incomplete diagnosis.

The 2016 revision of the WHO classification of tumours of haematopoietic and lymphoid tissues describes the updated criteria, incorporating morphology, immunophenotyping, genomics, and clinical features, recommended to be used to characterise the diagnostic, prognostic, and therapeutic implications of haematological malignancies including:

Lymphoid neoplasms (see Table 9, Appendix A)

- mature B-cell lymphoid neoplasms;
- mature T-cell and natural killer cell neoplasms;
- Hodgkin lymphoma;
- post-transplant lymphoproliferative disorders;
- histiocytic and dendritic cell neoplasms (Swerdlow et al., 2016); and

Myeloid neoplasms and acute leukaemia (see Table 10Table 10, Appendix A)

- myeloproliferative neoplasms;
- myeloid/lymphoid neoplasms with eosinophilia and rearrangement of *PDGFRA, PDGFRB*, or *FGFR1*, or with *PCM1-JAK2*;
- myelodysplastic/myeloproliferative neoplasms;
- myelodysplastic syndromes;
- acute myeloid leukaemia and related neoplasms;
- blastic plasmacytoid dendritic cell neoplasm;
- acute leukaemias of ambiguous lineage;
- B-lymphoblastic leukaemia/lymphoma;
- T-lymphoblastic leukaemia/lymphoma (Arber et al., 2016).

PASC noted that the population of interest was initially described as patients/persons with a morphological diagnosis of haematological malignancy who require genomic sub-typing. PASC considered that the population should be revised to include patients with a suspicion of a haematological malignancy. This is in line with the applicant's pre-PASC response, which suggested changing 'morphological diagnosis' to a clinical diagnosis or suspected diagnosis. The applicant noted that morphological diagnosis would occur in some, but not all patients.

PASC noted the pre-PASC response which the applicant advised that the proposed population would encompass unclassified MPN or where the patient has already progressed to secondary (post PV/ET) myelofibrosis or perhaps even acute myeloid leukaemia.

Overview of haematological malignancies

The majority of human haematologic malignancies are caused by the clonal expansion of a single cell that has acquired a somatic variant in one allele of a gene responsible for cellular maturation and division. This variant, often referred to as an oncogene, stimulates inappropriate cellular proliferation, leading to the development of a haematologic malignancy (Schrijver & Zehnder, 2020). However, it should be noted that

it has been estimated that 8-15% of all haematological malignancies are familial, with the revised WHO classification criteria recognising a number of germline variants that result in an inherited predisposition to haematologic cancer (Brown & Hiwase, 2020).

Hematologic malignancies are a heterogeneous, genetically diverse group of disorders that originate from cells of the bone marrow and lymphatic system, and are categorised based on lineage as either myeloid or lymphoid neoplasms (Batista, Birmann, & Epstein, 2017). Myeloid neoplasms are a group of related disorders characterised by defective haematopoiesis originating from a haematopoietic stem/progenitor cell and showing myeloid differentiation. Myeloid neoplasms are derived from bone marrow progenitor cells that would normally develop into erythrocytes, granulocytes (neutrophils, basophils, and eosinophils), monocytes, or megakaryocytes (see Figure 7, Appendix B) (Docking & Karsan, 2019; Freedman, Friedberg, & Aster, 2020). The exceptions to this are chronic myeloid leukaemia, where the cell of origin is a pluripotent haematopoietic stem cell that is capable of giving rise to lymphoid cells as well (Freedman et al., 2020), and myeloid/lymphoid proliferations (e.g., those associated with rearrangements of *FGFR1*).

Myeloid neoplasms can be broadly classified into four groups (see Table 10, Appendix A):

- Acute myeloid leukaemia and related neoplasms. Acute myeloid leukaemia is characterised by an accumulation of leukaemic blasts (≥20%) or immature forms in the bone marrow and peripheral blood, with a reduction in the production of normal red blood cells, platelets, and mature granulocytes. The increased production of malignant cells, along with a reduction in mature elements, results in symptoms including anaemia, bleeding, and an increased risk of infection. Acute myeloid leukaemia is the most common acute leukaemia in adults (80% of cases), whereas acute myeloid leukaemia accounts for less than 10% of acute leukaemias in children (Schiffer & Gurbuxani, 2019);
- Myeloproliferative neoplasms, including chronic myeloid leukaemia, are often associated with variants that cause abnormal increases in activity of pro-growth signalling pathways, leading to the growth factor-independent proliferation of bone marrow progenitors. Unlike acute myeloid leukaemia, the percentage of blasts in the bone marrow may be normal or slightly increased, but is always <20% (Freedman et al., 2020);
- Myelodysplastic syndromes exhibit dysplasia, ineffective blood cell production leading to cytopenia, and a risk of transformation to acute leukaemia. Bone marrow cellularity can be increased, but may be normal or even low, and as with myeloproliferative neoplasms, the percentage of blasts in the bone marrow may be normal or increased, but <20% (Freedman et al., 2020); and
- Myelodysplastic/myeloproliferative neoplasms include disorders where both dysplastic and proliferative features co-exist (Freedman et al., 2020).

Some myeloid neoplasms show features that overlap between those of a myeloproliferative neoplasm and a myelodysplastic syndrome, and all myeloproliferative neoplasms and myelodysplastic syndromes have the potential to transform into acute myeloid leukaemia. Acute myeloid leukaemias are very aggressive, requiring immediate treatment, whereas myeloproliferative neoplasms and myelodysplastic syndromes are often indolent, and usually do not require immediate or aggressive treatment (Freedman et al., 2020).

Lymphoid neoplasms arise from the malignant transformation of normal lymphoid cells at various stages of differentiation. Lymphoid neoplasms may derive from B cell progenitors (bone marrow derived), T cell progenitors (thymus-derived), mature T lymphocytes (cytotoxic T cells, helper T cells, or T regulatory cells) or mature B lymphocytes (B cells or plasma cells) (Freedman et al., 2020). As such, lymphoid neoplasms can be divided into three broad categories (see Table 9, Appendix A):

- Hodgkin lymphoma accounts for approximately 10% of all lymphomas (Shankland, Armitage, & Hancock, 2012). Hodgkin lymphoma is a neoplasm derived from B cells that spreads via the lymphatic system or the blood, and may affect a single lymph node, or a group of lymph nodes. Other commonly affected sites include the spleen, liver, lungs, and bone marrow. With the exception of the nodular lymphocyte-predominant Hodgkin lymphoma subtype (5-10% of all Hodgkin lymphomas), Hodgkin lymphoma is characterised by the presence of large malignant multinucleated Reed-Sternberg cells, which have lost their B-cell phenotype and demonstrate an unusual expression of many markers of other haematopoietic cell lineages (Ansell, 2015; Mathas, Hartmann, & Kuppers, 2016; Wang, Balakrishna, Pittaluga, & Jaffe, 2019).
- Mature B-cell neoplasms or non-Hodgkin lymphomas and multiple myeloma, encompassing at least 60 subtypes and representing one of the most common cancers. Most cases of non-Hodgkin lymphomas (85-90%) are B-cell lymphomas, with the remaining arising from T-cells or natural killer cells. Patients usually present with enlarged lymph nodes and either an excision or guided core biopsy is required to confirm the diagnosis, noting that a fine needle biopsy is usually insufficient for diagnosis (Bowzyk Al-Naeeb, Ajithkumar, Behan, & Hodson, 2018; Shankland et al., 2012); and
- Precursor lymphoid neoplasms are characterised by the proliferation of immature (blast) cells of B-cell or T-cell lineage. Acute lymphoblastic leukemias and lymphoblastic lymphomas can occur at any age; however, they are the most common type of childhood malignancy. Lymphoblastic lymphomas are defined as cases with tissue involvement with minimal or no involvement of the blood and bone marrow (less than 25% replacement of the marrow cellularity by lymphoid blasts). Most cases of lymphoblastic lymphomas are of T-cell origin, with B-lymphoblastic lymphoma accounting for only 10% of lymphoblastic lymphoma cases, with disease mainly involving lymph nodes or extra-nodal sites such as the central nervous system, bone, skin, and testis. Acute lymphoblastic leukemias are cases with greater than 25% marrow involvement. Acute lymphoblastic leukemia is a highly aggressive neoplasm that requires intensive chemotherapy (Choi, 2018; Nasr, Perry, & Skrabek, 2019).

Historically, lymphoid neoplasms that present with bone marrow and blood involvement have been categorised as leukaemia, whilst those presenting as a mass have been classified as a lymphoma. It is now recognised that this classification is not clear-cut, with the diagnosis of the various lymphoid neoplasms not dependent on the anatomic location of tumour cells, but instead on the cell of origin of the tumour, based on morphology, immunophenotyping and genetic testing (Freedman et al., 2020). In addition, lymphoid neoplasms can be difficult to distinguish from non-malignant reactive lymphocytosis in the absence of a clonal marker.

The current accepted world standard for diagnosing and subcategorising haematological malignancy recognises 15 different broad subgroups encompassing over 150 individual entities (Arber et al., 2016; Swerdlow et al., 2016). The clinical behaviour/natural history of haematological malignancies ranges from entities that behave relatively indolently (for example some forms of chronic lymphocytic leukaemia) which do not require intervention unless the patient is symptomatic, to other entities (for example Burkitt lymphoma or acute myeloid leukaemia) which are highly aggressive and uniformly result in death unless treated urgently.

Population characteristics

As a group haematologic malignancy is a relatively common group of disorders, constituting approximately 9% of all cancer cases diagnosed annually, as well as being a common cause of death in patients suffering from cancer (Prakash et al., 2016). In Australia, rates of the most common haematological cancers are consistently higher in males than females, as are rates of mortality (Table 2 and Table 3) (Australian

Institute of Health and Welfare (AIHW), 2019). It should be noted, however, that age at diagnosis varies considerably depending on individual subtype of haematological malignancy. In 2019, lymphoma was the most common diagnosed cancer in young adults aged 15–24 years, representing 19.5% of all cancers (n=1,002) in this age group. The most common cancer in children aged 0-14 years was leukaemia, representing 34% of all cancers in this age group (n=804). In this age group, lymphoma was the third most common cancer (9.3%) after brain cancer (AIHW, 2019).

Table 2 Incidence of haematological cancers in Australia, by sex, 2019

Cancer type (ICD-10 code)	Males		Females		Total	
	Cases	ASR (per 100,000)	Cases	ASR (per 100,000)	Cases	ASR (per 100,000)
Lymphoma (C81–C86)	3,647	25.9	2,776	18.1	6,423	21.8
Leukaemia (C91–C95)	2,609	18.5	1,642	10.7	4,251	14.4
Multiple myeloma (C90.0)	1,139	7.9	868	5.3	2,007	6.5
Myelodysplastic syndromes (D46)	986	6.9	631	3.6	1,618	5.1

Source: Australian Institute of Health and Welfare (AIHW) (2019)

ASR=age-standardised rate

Table 3 Rates of mortality associated with haematologic cancer in Australia, by sex, 2019

Cancer type (ICD-10 code)	Males		Females		Total	
	Deaths	ASR (per 100,000)	Deaths	ASR (per 100,000)	Deaths	ASR (per 100,000)
Lymphoma (C81–C86)	956	6.7	676	3.9	1,632	5.2
Leukaemia (C91–C95)	1,189	8.3	850	5.0	2,039	6.5
Multiple myeloma (C90.0)	615	4.3	446	2.6	1,062	3.3
Myelodysplastic syndromes (D46)	324	2.3	201	1.1	526	1.6

Source: Australian Institute of Health and Welfare (AIHW) (2019)

ASR=age-standardised rate

Most haematological malignancies, such as acute myeloid leukaemia, lymphoma and multiple myeloma occur in adults, with the incidence tending to increase with age. If all haematological malignancies are considered as a group, the incidence in Australia can be observed to steadily increase with age, reaching a predicted peak of 1,420 cases or 444 cases per 100,000 population in persons aged 85-89 years in 2021 (Figure 1).

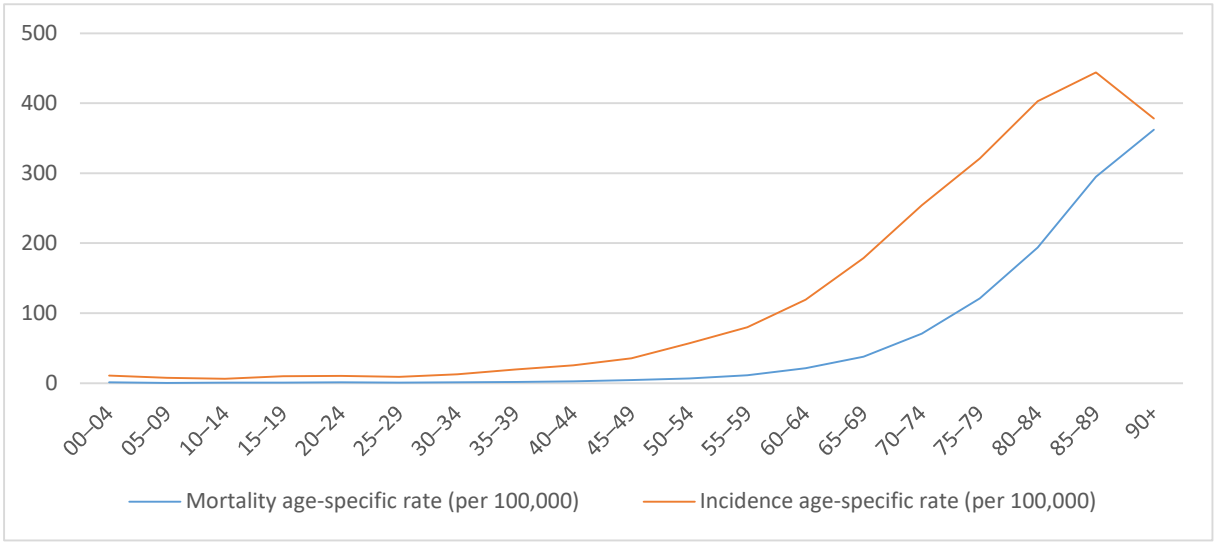

Figure 1 Estimated age-specific rates of all haematological malignancies in Australia, 2021

Source: Australian Institute of Health and Welfare (AIHW) (2021)

While the rate of mortality from combined haematological malignancies mirrors the incidence curve, the corresponding mortality rate remains relatively low and then steadily increases once patients reach 60-64 years of age (Figure 1). The mortality rate almost doubles from 170 deaths, or 11.1 deaths per 100,000 persons, in those aged 55-59 years, to 307 deaths, or 21.1 deaths per 100,000 persons in those aged 60-64 years (AIHW, 2021). When considered as a group, in 2012-2016 an average 66.7% (95% confidence interval (CI) 66.3-67.1%) of all patients with a haematological malignancy survived 5-years after diagnosis (AIHW, 2019).

Although the incidence of some haematological cancers such as Hodgkin lymphoma is highly variable across age groups (Figure 2), rates remain relatively low, reaching an estimated peak of 43 cases, or 7.9 cases per 100,000 persons in 2020 for those aged 80-84 (AIHW, 2021). The variability in incidence is not mirrored in the rate of mortality, which again is low, steadily increasing with age. On average, 87.4% of patients diagnosed with Hodgkin lymphoma in 2012-2016 survived 5 years after diagnosis (95% CI 86.1-88.7%) (AIHW, 2019).

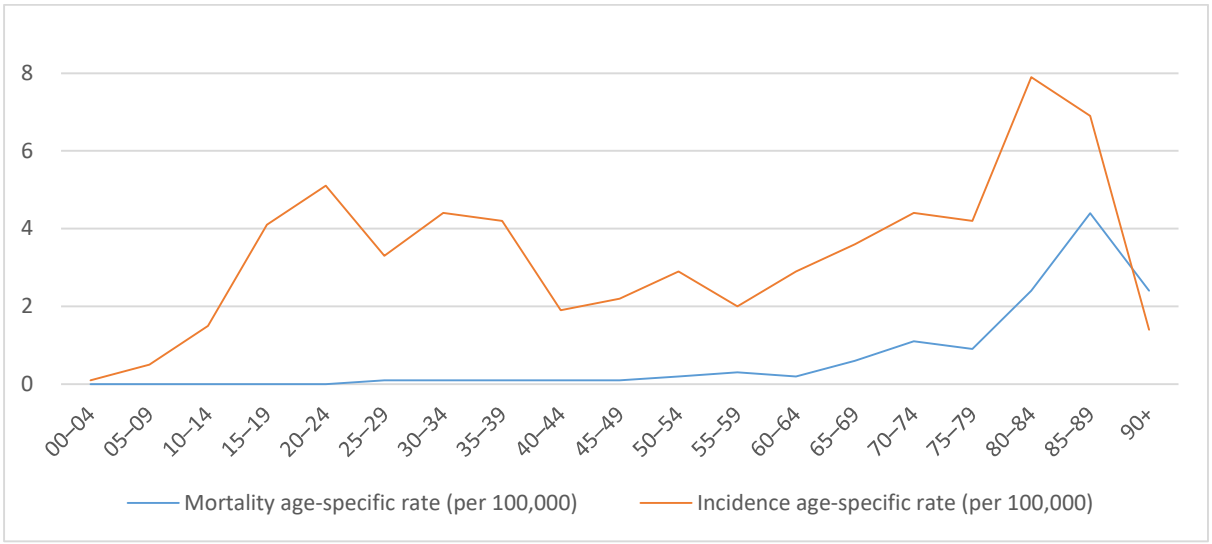

Figure 2 Estimated age-specific rates of Hodgkin lymphoma in Australia, 2021

Source: Australian Institute of Health and Welfare (AIHW) (2021)

The highest incidence of other cancers, such as acute lymphoblastic leukemias, occurs in very young patients, albeit at relatively low rates (a predicted 105 cases or 6.3 cases per 100,000 persons aged 0-4 years in 2021) as depicted in Figure 3 (AIHW, 2021). Mortality associated with acute lymphoblastic leukemias is also low, with a 5-year survival rate of 74.1% (AIHW, 2019).

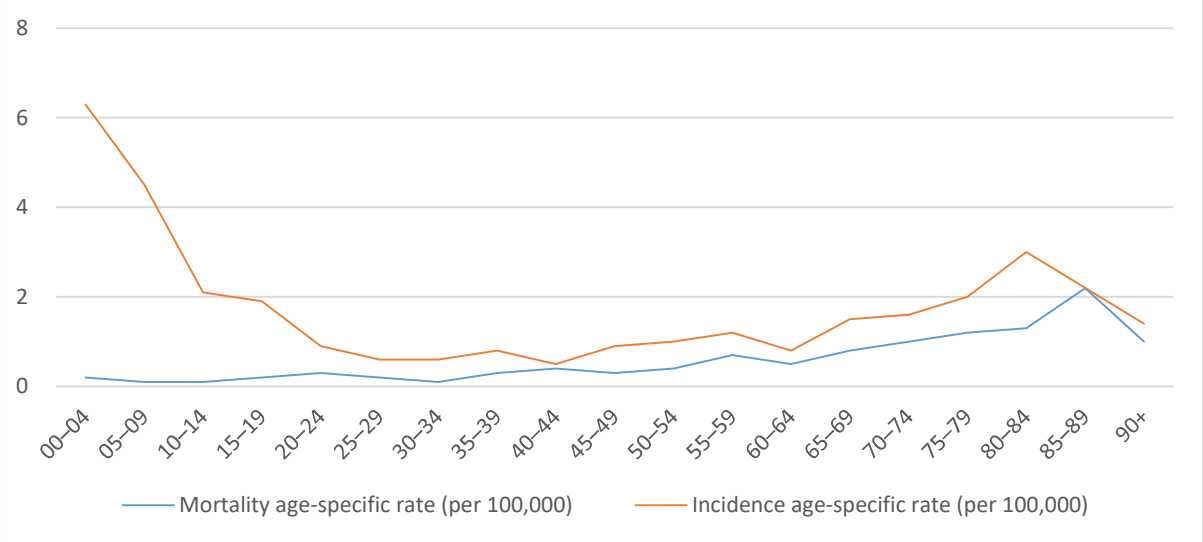

Figure 3 Estimated age-specific rates of acute lymphoblastic leukaemia in Australia, 2021

Source: Australian Institute of Health and Welfare (AIHW) (2021)

Of all the haematological cancers, lymphoma is associated with the highest incidence, estimated to peak at 467 cases, or 146.1 cases per 100,000 in 2021 (AIHW, 2021). Lymphoma is associated with relatively good outcomes, with a reported 5-year survival rate after diagnosis of 76.7%. This is contrasted by acute myeloid leukaemia, which has one of the highest rates of mortality and the poorest 5-year survival rate (27.7%, 95% CI 26.4-29.1% in 2012-2016) of all haematological malignancies (AIHW, 2019).

The AIHW estimates that the number of haematological malignancies in 2021 will increase by approximately 3.1% from 2020 numbers, from 17,321 to 17,858 patients. It would be expected that this rate would remain constant over the next three years. Expected numbers of patients with individual haematological cancers are summarised in Table 4 (AIHW, 2019). Approximately 50% of these patients may be required to undergo genomic sub-characterisation.

Table 4 Expected number of patients with a haematological malignancy in Australia

Malignancy (average increase*)	2020	Expected 2021	Expected 2022	Expected 2023
All haematological cancers (3.1%)	17,321	17,858	18,412	18,983
Acute lymphoblastic leukaemia (3%)	445	458	472	486
Acute myeloid leukaemia (1.97%)	1,122	1,144	1,166	1,189
Chronic lymphocytic leukaemia (3.33%)	1,875	1,937	2,001	2,068
Chronic myeloid leukaemia (1.47%)	378	384	390	396
Hodgkin lymphoma (3.07%)	784	808	833	859

Malignancy (average increase*)	2020	Expected 2021	Expected 2022	Expected 2023
Multiple myeloma (4.43%)	2,339	2,443	2,551	2,664
Myelodysplastic syndromes (1%)	1,496	1,511	1,526	1,541
Non-Hodgkin lymphoma (3.29%)	6,148	6,350	6,559	6,775

Source: Australian Institute of Health and Welfare (AIHW) (2019)

* Average increase calculated from the increase of cases each year from 2017-2020

PASC noted the assumption that the estimated testing population would represent about 50% of people with haematological malignancies was based on clinical judgement. PASC considered that this estimate did not include those 'suspected' of malignancy (rather utilisation estimates based on incidence of diagnosed haematological malignancy), which should be accounted for in the assessment report. For example, a sub-population of patients with a clinical presentation of a presumed haematological malignancy that would be confirmed to be non-malignant after the proposed test. In addition, PASC considered that the estimated population size may increase over time as more diagnostic and/or prognostic markers are identified in different malignancies. The applicant agreed that this was likely and noted that the 50% utilisation estimate was framed using a diagnostic utility framework, rather than a clinical relevance framework.

Current investigations for haematological malignancies

Patients presenting with clinical features suspicious for haematological malignancy typically undergo investigations by their primary health care provider including full blood count and other basic laboratory investigations. If the results of these investigations are consistent with a haematological malignancy, patients are typically referred to a specialist haematologist physician for further investigations, which may include further laboratory investigations (immunophenotyping of peripheral blood, cytological/histopathological examination of bone marrow biopsy/lymph nodes), radiological investigations and/or diagnostic procedures (bone marrow biopsy, biopsy of lymph nodes/affected organs). The aim of these investigations is to establish a definitive diagnosis (including sub-categorisation) of haematological malignancy as per the current WHO diagnostic criteria (Swerdlow et al., 2016). In some cases, this categorisation cannot be achieved without additional genetic profiling including cytogenetic and molecular analysis.

If the diagnosis can be made based using the investigations described above, then diagnostic testing would cease, and the patient would commence treatment specific for the individual subtype of haematological malignancy diagnosed (see Figure 5).

The treatment of haematological malignancy depends on the precise sub-categorisation but may include (i) cytotoxic chemotherapy (ii) targeted agents (iii) immunotherapy (iv) autologous/allogeneic stem cell transplantation and/or (v) observation alone/supportive care.

PASC agreed with the applicant that although NGS gene panel testing is used for both diagnosis and sub-classification, people who undertake these tests often have a suspicion of a malignancy, and initially undergo diagnostic testing with existing MBS reimbursed tests prior to subclassification.

Cascade testing

The applicant has noted that approximately 8-15% of all haematological malignancies are familial (Brown & Hiwase, 2020). However, the application does not request cascade testing of family members, and the primary intention of the test is to investigate somatic genes.

PASC discussed the issue of germline variants that result in an inherited predisposition to haematological cancer which represent around 8-15% of haematological malignancies. PASC noted the pre-PASC response, which the applicant stated that familial variant diagnosis may be relevant for future donor selection for transplantation. The applicant advised that the need for a cascade test in patients with unselected myeloid malignancies is in the range of just 1-2%. As there are existing numbers for germline testing and inherited conditions which can cover some of the germline gene variants, PASC confirmed that cascade testing for germline variants is out of scope for this application.

Equity of access

Currently, genetic testing for private patients is either (i) being performed at cost to the referring pathology provider/patient or (ii) not being performed; the former leading to inequity in access and the latter leading to inaccurate diagnosis and treatment. Public funding of these genetic tests would provide equity of access for all Australian patients and would align Australian clinical practice with the established clinical practice guidelines and diagnostic standard of care as stipulated by the revision of the WHO classification of haematological malignancy.

Intervention

The proposed genetic test is an investigative medical service (*in-vitro* diagnostic test) that uses precision medicine to molecularly analyse and definitively diagnose haematological malignancies by identifying their sub-classification. It is a new item that is proposing a way of clinically delivering a service that is new to the MBS in terms of new technology. The primary purpose of performing the service is to assist in establishing a diagnosis in newly diagnosed patients or those at disease relapse. The test results may subsequently provide information about prognosis and/or identify a patient's suitability for therapy.

PASC noted that the proposed intervention is genetic testing for variants associated with haematological malignancies using next generation sequencing (NGS) gene panel testing.

The investigative test, using NGS gene panel testing, should be restricted to once per diagnostic episode (new diagnosis or relapse), conducted in addition to other investigative procedures.

As stipulated by the applicant, testing would be requested by the treating clinician and provided by approved practising pathologists in line with other tests on the MBS Pathology Services Table. Patients should be referred by a specialist haematologist/oncologist or consultant physician. Testing would occur in a National Association of Testing Authorities (NATA) accredited diagnostic laboratory in accordance with the National Pathology Accreditation Advisory Council (NPAAC) guidelines.

Investigations are intended to be entirely rendered in Australia and would be delivered only by approved practising pathologists with appropriate scope of practice in NATA-accredited pathology laboratories (as defined in MBS Pathology Services Table) by referral only by registered medical practitioners (non-pathologists) in line with other tests in the MBS Pathology Services Table.

The investigative process of the proposed health technology involves the extraction of nucleic acid from the tissue of interest with haematological malignancy (typically blood, bone marrow aspirate or lymph node biopsy), and then undergoes target enrichment using either hybridisation-based target enrichment or amplicon-based target enrichment. The most widely used molecular characterisation technique for clinical applications is targeted panels (Lymphoid, Myeloid) that focus on a certain number of genes or gene regions according to the cancer phenotype. The sequence data is processed by a bioinformatics pipeline which includes sequence read alignment and variant calling and annotation. Genomic variants are then curated by scientists/pathologists and a clinical report generated.

Patients with a suspected haematological malignancy would still be required to undergo initial diagnostic tests, such as full blood counts, immunohistochemistry, cytogenetic testing and fluorescence in situ hybridisation (FISH). Once diagnosed, a proportion of patients will need to undergo assessment of genomic variation in order to make a specific, definitive diagnosis, or refine, or change the presumptive diagnosis, that will enable the selection of the most appropriate therapy and guide prognostication (see Figure 6). The number of genes and diversity of variants that need to be assessed practically necessitates the use of massively parallel sequencing technologies.

The results of these genomic tests are interpreted by the clinician with the rest of the pathological data to categorise the patient as per WHO 2017 diagnostic criteria and to guide the patient treatment approach (Swerdlow et al., 2016). The applicant lists 105 possible exemplar and 130 facilitated genes (Appendix C). The panel would consist of approximately 25-40 genes, some of them "core" and some supplemental depending on the cancer subtype.

The diagnostic utility of gene panel analysis in haematological malignancy is broad and covers a wide range of clinical settings. In some settings, the detection of somatic variants in general (requiring the survey of a wide array of genes) can aid in the diagnosis of a malignant rather than non-malignant haematological condition (e.g., T-cell lymphoma versus autoimmune conditions) through the demonstration of the presence of clonal haematopoiesis, directing subsequent investigations and therapy choices. In other settings, variants in specific genes can distinguish between differential diagnoses (e.g., hairy cell leukaemia vs hairy cell leukaemia-variant/splenic marginal zone lymphoma) or determine the genomic subtype of a disease (e.g., *RUNX1*-variant in acute myeloid leukaemia), which in turn provides important prognostic information and directs therapy decisions (ranging from chemotherapy to targeted therapies to bone marrow transplant). Additionally, the identification of germline variants in some diseases define WHO-based entities (e.g., myeloid neoplasms with germline *GATA2* variants) as well as have additional implications for the patient's health (where some inherited syndromes have clinical manifestations outside of the haematological compartment), fertility management and donor selection for transplant if required, as well as for family members who may also be at risk.

PASC acknowledged that a minimum gene panel is required for quality assurance. The applicant stated that an attempt was made to list genes in the appendix (exemplar and facilitated). Additionally, the applicant suggested that the gene panel list should not be too prescriptive as this is subject to gene identification and laboratory preferences. PASC agreed with the applicant that this is appropriate, however, minimum requirements should be set for clarity.

PASC ultimately recommended that explanatory notes be included in the PICO to specify minimum gene panel requirements, acknowledging these panels will change over time with advances in technology. The Department also raised the possibility of listing the minimum gene panel requirements on an online forum.

Comparator(s)

The nominated comparator is no genetic testing.

Several diagnostic tests, such as full blood counts with morphology review, bone marrow examination and tissue biopsy are utilised. These are supplemented by flow cytometry, immunohistochemistry, cytogenetic testing including FISH and individual molecular genetic tests. These provide a working diagnosis of a haematological malignancy. Genetic characterisation is required for many patients to provide additional diagnostic information that enables the selection of the most appropriate therapy, provides prognostic information and may assist in monitoring the response to treatment.

PASC confirmed that the proposed comparator is no NGS-based gene panel testing. Although PASC acknowledged that currently FISH testing is included on the MBS for single gene testing and for gene rearrangements, which currently cannot be identified by an NGS DNA panel. Therefore, the proposed NGS panel would not replace the FISH testing, at least not in the near future. PASC agreed with the applicant that although FISH testing tends to overlap with other NGS testing for multi-gene panels, it occupies a different role compared to NGS gene panel testing.

The applicant also advised that within the next few years gene rearrangements may be able to be tested by NGS, however, the focus of FISH is currently on DNA single gene variant (particularly rearrangement) testing (see "Outcomes" below).

The expansion of MBS item number 73325 has recently been approved by the MSAC for genetic testing for myeloproliferative neoplasms, for both gene-specific and NGS gene panel testing, following initial *JAK2 V617F* triage testing (MSAC, 2020). In addition, there are several MBS items that test for gene rearrangements and/or fusions using FISH (that are not typically detectable using NGS), and patients would need to undergo multiple testing for diagnosis using MBS items detailed in Table 5.

Table 5 Existing MBS items for gene rearrangements and/or fusions using fluorescence in situ hybridisation

Item number	Gene rearrangement/fusion
73326	Characterisation of the gene rearrangement *FIP1L1-PDGFRA* in the diagnostic work-up and management of a patient with laboratory evidence of mast cell disease, idiopathic hypereosinophilic syndrome, or chronic eosinophilic leukaemia.
73314	Characterisation of gene rearrangement or the identification of mutations within a known gene rearrangement, in the diagnosis and monitoring of patients with laboratory evidence of acute myeloid leukaemia, acute promyelocytic leukaemia, acute lymphoid leukaemia, or chronic myeloid leukaemia.
73369	Characterisation of (i) *TCL1A* gene rearrangement; and/or (ii) *MTCP1* gene rearrangement.
73364	Characterisation of *MYC* gene rearrangement. If positive, then the characterisation of either or both of *BCL2* and *BCL6* gene rearrangements for patients with evidence of diffuse large B-cell lymphoma or high-grade B-cell lymphoma.
73365	Characterisation of *MYC* gene rearrangement in patients with clinical or laboratory evidence of Burkitt lymphoma.
73366	Characterisation of *CCND1*and/or *CCND2* gene rearrangement(s) in patients with clinical or laboratory evidence of mantle cell lymphoma.
73368	Characterisation of *DUSP22* and/or *TP63* gene rearrangement(s) in patients with clinical or laboratory evidence of ALK negative anaplastic large cell lymphoma

Note: Most genetic testing of patients with a haematological malignancy is conducted either by state-funded services, or through private laboratories as an out-of-pocket expense for patients.

Genetic testing for variants in patients with acute myeloid leukaemia, myelodysplastic syndromes and many of the myeloproliferative neoplasm variants requires NGS, which is not covered by existing MBS items. Therefore, beside the specific items described above that use FISH, for the majority of patients with a haematological malignancy, the nominated comparator is no gene panel testing.

The introduction of genetic testing for variants associated with haematological malignancies using NGS gene panel testing would therefore be additional to the currently listed MBS items, where patients have a malignant diagnosis. These MBS items for diagnostic tests are often performed to provide initial characterisation of a haematological malignancy (Table 6).

Table 6 Existing MBS items for diagnostic test to characterise haematological malignancies

Investigative technology	Item number	Description and fee
Full blood count to rule in/out leukaemia	65070 (Group P1 – Haematology)	Erythrocyte count, haematocrit, haemoglobin, calculation or measurement of red cell index or indices, platelet count, leucocyte count and manual or instrument generated differential count - not being a service where haemoglobin only is requested - one or more instrument generated sets of results from a single sample; and (if performed) (a) a morphological assessment of a blood film; (b) any service in item 65060 or 65072 Fee: $16.95 Benefit: 75% = $12.75 85% = $14.45
Biopsy/cytology.	73049 (Group P6 – Cytology)	Cytology of material obtained directly from a patient by fine needle aspiration of solid tissue or tissues - 1 identified site Fee: $68.15 Benefit: 75% = $51.15 85% = $57.95 (Although an excision lymph node biopsy is best, especially in the case of lymphomas, bone marrow biopsy is sometimes performed for staging but is rarely the diagnostic investigation. A normal bone marrow biopsy does not exclude lymphoma.(Bowzyk Al-Naeeb et al., 2018))
	30075 (Group T8 - Surgical Operations, Subgroup 1 – General)	DIAGNOSTIC BIOPSY OF LYMPH NODE, MUSCLE OR OTHER DEEP TISSUE OR ORGAN, as an independent procedure, if the biopsy specimen is sent for pathological examination Fee: $154.45 Benefit: 75% = $115.85 85% = $131.30
	30078 (Group T8 - Surgical Operations, Subgroup 1 – General)	DIAGNOSTIC DRILL BIOPSY OF LYMPH NODE, DEEP TISSUE OR ORGAN, as an independent procedure, where the biopsy specimen is sent for pathological examination Fee: $50.00 Benefit: 75% = $37.50 85% = $42.50
	65084 (Group P1 – Haematology)	Bone marrow trephine biopsy - histopathological examination of sections of bone marrow and examination of aspirated material (including clot sections where necessary), including (if performed): any test described in item 65060, 65066 or 65070 Fee: $165.85 Benefit: 75% = $124.40 85% = $141.00
Cytogenetic testing for risk stratification in myeloid malignancies	73290 (Group P7 – Genetics)	The study of the whole of each chromosome by cytogenetic or other techniques, performed on blood or bone marrow, in the diagnosis and monitoring of haematological malignancy (including a service in items 73287 or 73289, if performed). - 1 or more tests. Fee: $394.55 Benefit: 75% = $295.95 85% = $335.40
Immunohistochemistry/ immunofluorescence	71139 (Group P4 – Immunology)	Characterisation of 3 or more leucocyte surface antigens by immunofluorescence or immunoenzyme techniques to assess lymphoid or myeloid cell populations, including a total lymphocyte count or total leucocyte count by any method, on 1 or more specimens of blood, CSF or serous fluid Fee: $104.05 Benefit: 75% = $78.05 85% = $88.45
	73364 (Group P7 – Genetics)	Analysis of tumour tissue, requested by a specialist or consultant physician, that: (a) is for: (i) the characterisation of *MYC* gene rearrangement; and (ii) if the results of the characterisation mentioned in subparagraph (i) are positive—the characterisation of either or both of *BCL2* gene rearrangement and *BCL6* gene rearrangement; and (b) is for a patient: (i) for whom *MYC* immunohistochemistry is non-negative; and (ii) with clinical or laboratory evidence, including morphological features, of diffuse large B-cell lymphoma or high-grade B-cell lymphoma; and (c) is not performed in conjunction with item 73365. Applicable only once per lifetime Fee: $400.00 Benefit: 75% = $300.00 85% = $340.00

Investigative technology	Item number	Description and fee
Immunohistochemistry/ immunofluorescence (cont.)	73365 (Group P7 – Genetics)	Analysis of tumour tissue, requested by a specialist or consultant physician, that: (a) is for the characterisation of *MYC* gene rearrangement; and(b) is for a patient with clinical or laboratory evidence, including morphological features, of Burkitt lymphoma; and (c) is not performed in conjunction with item 73364. Applicable only once per lifetime Fee: $340.00 Benefit: 75% = $255.00 85% = $289.00

Reference standard

On the basis that the diagnostic testing is recommended by the WHO guidelines, a reference standard or clinical utility standard are not required in this instance.

PASC confirmed that a reference standard or clinical utility standard are not required for this application by virtue of the recommendations for diagnostic testing in WHO guidelines.

Outcomes

Patient-relevant health outcomes

Safety Outcomes:

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

Clinical Effectiveness Outcomes:

Direct evidence

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

Indirect evidence

- Cumulative diagnostic yield (informative result)
- Cumulative prognostic yield (from those with an informative result)
- Change in management/treatment resulting in change in patient outcomes: mortality, morbidity, quality of life (indirect evidence)

Health system resources

- Cost of gene panel test or variant-specific test
- Reduced number of preliminary diagnostic tests
- Cost of targeted therapies
- Cost per quality-adjusted life year and/or cost-effectiveness [The economic evaluation TBC at the 28 January 2022 MSAC Executive meeting]
- Total Australian Government healthcare costs

PASC confirmed that the outcomes listed in the PICO are appropriate, with the potential addition of the outcome of 'reduced number of preliminary diagnostic tests' under health system resources.

The applicant advised that while existing MBS items to assess gene rearrangements in select haematological malignancies are currently performed via FISH, it may be able to be tested via NGS in future. PASC considered that the extent to which other genetic testing that would be required to be performed as a preliminary test was unclear. PASC advised that any cost offsets relating to the replacement of existing FISH testing items, and any projections concerning the rate in which NGS may replace FISH, should be considered as part of the assessment report.

Assessment framework (for investigative technologies)

The proposed assessment framework is depicted in Figure 4

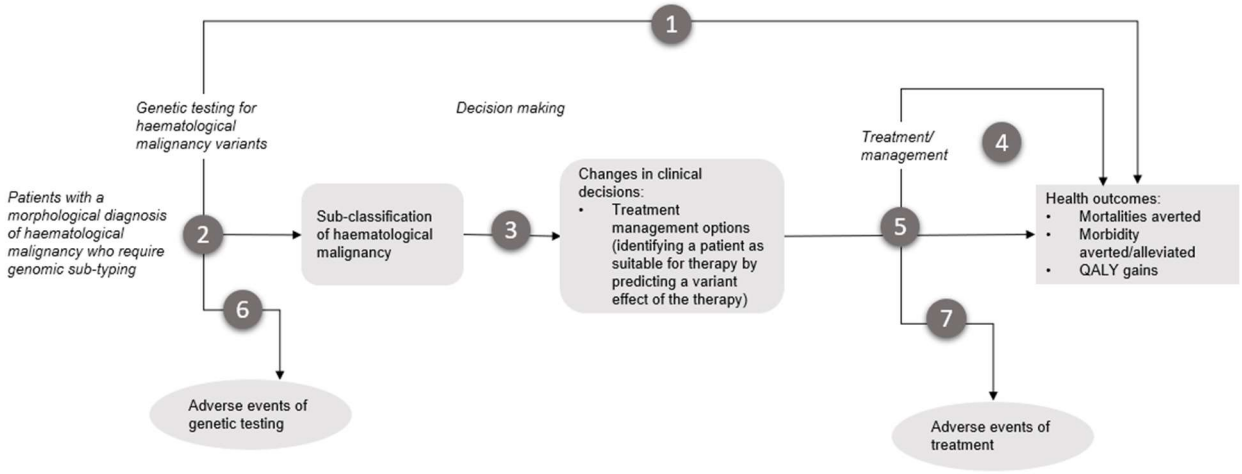

Figure 4 Assessment framework

Figure notes: 1: direct from test to health outcomes evidence; 2: test accuracy; 3: change in diagnosis/treatment/management; 4: influence of the change in management on health outcomes; 5: influence of the change in management on intermediate outcomes; 6: adverse events due to testing; 7: adverse events due to treatment

QALY=quality-adjusted life-years

PASC confirmed that the proposed assessment framework is appropriate for genetic testing for haematological malignancies.

Clinical management algorithms

The clinical management algorithm for the comparator is depicted in Figure 5. Patients with an incomplete diagnosis of a malignant condition in the absence of NGS-based subtyping are required to commence generalised anti-cancer treatment. However, for the majority of patients with haematological malignancies (patients with acute myeloid leukaemia, myelodysplastic syndromes and many of the myeloproliferative neoplasm variants), genetic testing for variants using NGS is required.

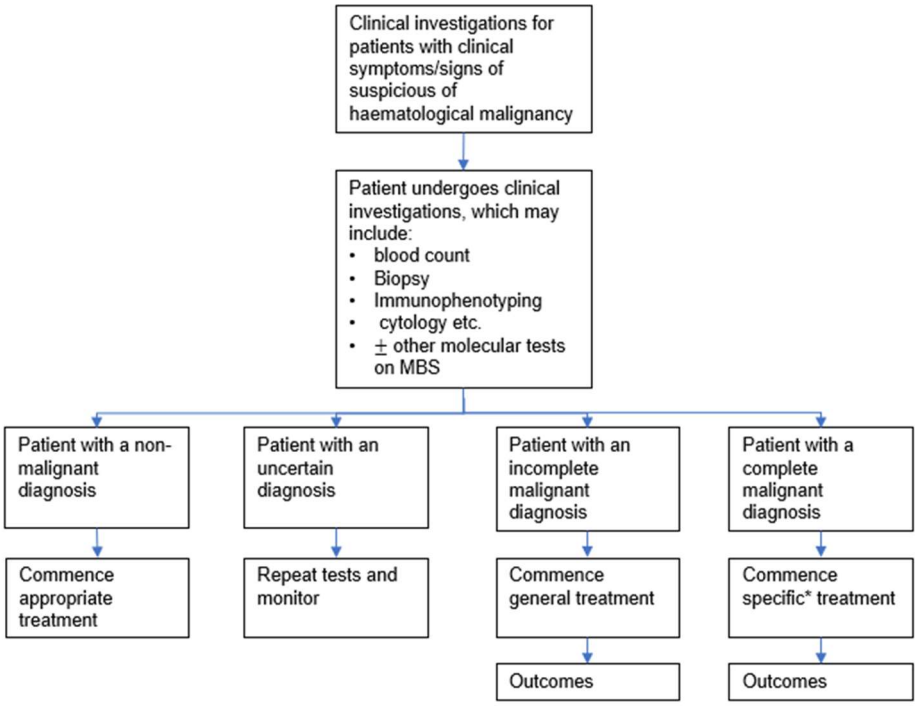

Figure 5 Current management algorithm for investigations associated with haematological malignancies

*Treatment delivered will depend on the variant(s) identified. The number and types of treatment are too numerous to list.

Note: Genetic testing for variants in patients with acute myeloid leukaemia, myelodysplastic syndromes and many of the myeloproliferative neoplasm variants requires NGS, which is not covered by existing MBS item numbers. Patients would need to undergo multiple testing for diagnosis using a range of MBS items for genomic subtyping using FISH and individual molecular genetic tests investigating gene rearrangements.

The proposed clinical management algorithm is depicted in Figure 6. Patients who receive a malignant diagnosis from clinical investigations can undergo genomic subtyping using NGS gene panel testing for diagnostic purposes and to potentially identify specific treatment pathways and prognosis information.

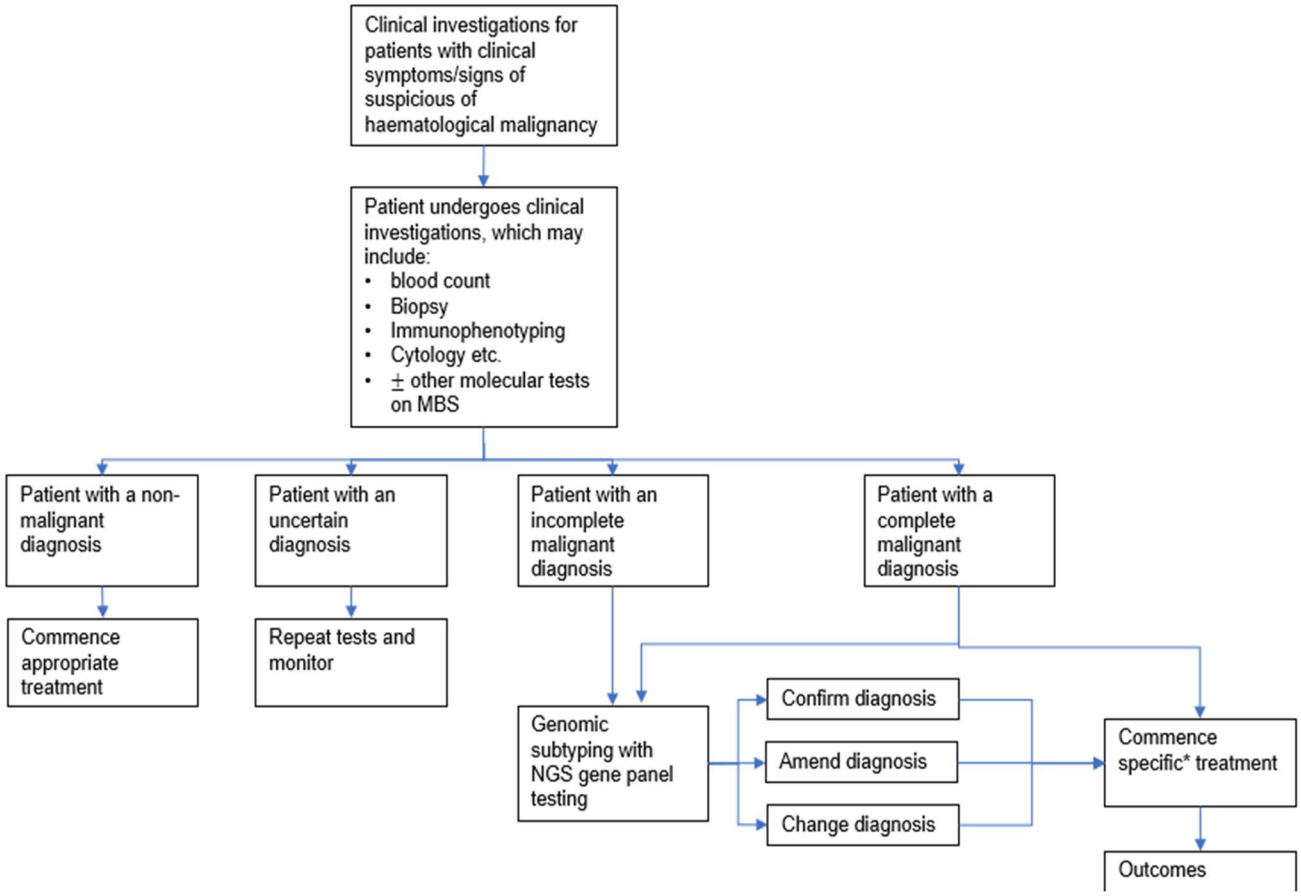

Figure 6 Proposed management algorithm for investigations associated with haematological malignancies

*Treatment delivered will depend on the variant(s) identified. The number and types of treatment are too numerous to list.

Genomic subtyping is an additional service provided to patients with a malignant diagnosis post clinical investigations. Patients with a malignant diagnosis are currently directed to receive generalised treatment, whereas the proposed management algorithm suggests the introduction of genomic subtyping and thereafter specific treatment. The introduction of genomic subtyping for these patients can increase the success of treatment and improve health outcomes by delivering a specific diagnosis that informs prognosis and allows use of precision medicine through the identification of tumour variants.

The proposed test will primarily be considered for diagnostic purposes at initial diagnosis and at disease relapse(s) only, with prognosis as a secondary outcome. Whilst the applicant discussed the use of monitoring, other currently available methods and technologies will be used to monitor patients' response to the treatment.

PASC confirmed that the clinical management algorithms are appropriate. Although, PASC advised that the other molecular tests on the MBS should be captured in the algorithms.

During the pre-PASC response, the applicant confirmed that NGS gene testing is not intended for the monitoring (e.g. minimal residual disease analysis) of a patient's response to treatment. Instead, this application is intended to provide genomic subtyping to those patients with an incomplete diagnosis to confirm, amend or change the initial diagnosis, and at disease relapse. Patients are monitored clinically and through the use of other non-NGS-based tests. PASC acknowledged that repeat testing may be required if patient results are inconclusive.

Proposed economic evaluation

Based on the clinical claim of superiority in clinical effectiveness, a cost-effectiveness or cost-utility analysis would be appropriate (Table 7Table 7). Further, a cost-effectiveness and/or cost-utility analysis will accurately represent the incremental health outcomes to be considered (i.e., QALYs, mortality and morbidity). As the comparator is no gene panel testing, the economic evaluation should capture the incremental value of current testing procedures for all conditions in the absence of gene panel testing.

Table 7 Classification of comparative effectiveness and safety of the proposed intervention, compared with its main comparator, and guide to the suitable type of economic evaluation

Comparative safety	Comparative effectiveness			
	Inferior	**Uncertain[a]**	**Noninferior[b]**	**Superior**
Inferior	Health forgone: need other supportive factors	Health forgone possible: need other supportive factors	Health forgone: need other supportive factors	? Likely CUA
Uncertain[a]	Health forgone possible: need other supportive factors	?	?	? Likely CEA/CUA
Noninferior[b]	Health forgone: need other supportive factors	?	CMA	CEA/CUA
Superior	? Likely CUA	? Likely CEA/CUA	CEA/CUA	CEA/CUA

CEA=cost-effectiveness analysis; CMA=cost-minimisation analysis; CUA=cost-utility analysis

? = reflect uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis

[a] 'Uncertainty' covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or the comparative safety considerations

[b] An adequate assessment of 'noninferiority' is the preferred basis for demonstrating equivalence

In the pre-PASC response, the applicant noted that the clinical claim of genetic testing for haematological malignancies is non-inferior in terms of safety and superior in terms of clinical effectiveness, compared with no genetic testing. Therefore, a cost-utility analysis would be the most appropriate. PASC confirmed the clinical claim is appropriate.

PASC discussed whether a full economic evaluation was required, in addition to an assessment of budget impact, based on the precedence of MSAC not requiring the full economic evaluation for applications 1526, 1537, 1538 and 1532. PASC concluded a full economic evaluation was required regardless of the testing being recommended by the WHO guidelines.

PASC agreed with the Department that the question of the required economic evaluation could be raised to the MSAC Executive.

Proposal for public funding

Public funding is requested for an investigative medical service that uses genetic testing to identify variants associated with haematological malignancies (most widely used technique for molecular diagnosis of haematological malignancies is targeted NGS panel (lymphoid or myeloid) focusing on specific genes as described by the WHO). The applicant is proposing a new MBS item that will clinically deliver this service that is new to the MBS. The applicant has stated that there are no other associated applications related to the proposed health technology in progress.

The investigative tests mentioned below will take 2-4 weeks in total to perform. An approximation of costs has been provided by the applicant and is detailed below.

Costings will vary from laboratory to laboratory; however, approximate costs include:

- DNA extraction/sample processing $35
- Target enrichment consumables $200
- Sequencing consumables per sample $50
- Technician labour for sample set up $300
- Genomic analysis/interpretation/report generation $150

The proposed MBS item descriptor is presented in Table 8.

Table 8 Proposed MBS item descriptor

Category (6) – Pathology services – Group P7 Genetics
MBS item *XXXX 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. Applicable once per diagnostic episode at initial diagnosis or at disease relapse
Fee: $800 Benefit: 75% = $600 85% = $680

Most genetic testing of haematological malignancy patients is currently conducted either by state-funded services, or through private laboratories as an out-of-pocket expense for patients.

PASC noted the proposed item descriptor.

PASC confirmed the coverage of item descriptor in terms of the primary purpose of testing being initial diagnosis, or testing at disease relapse, and the secondary purposes of identification of potential therapeutic targets or prognostication. PASC also noted that utilisation projections for this testing should be identified so that the budget impact can be realised into the future.

PASC noted the proposed fee of $800 and that there are several benchmark fees for characterisation of multiple genes through gene panels on the MBS ($700 to $1,200). PASC noted that consultation feedback stated the proposed fee was too low which could have flow-on impacts to the consumer (see "Summary of public consultation input"), and as such advised that the assessment report include a fee justification based on actual costs with an appropriate benchmark and sensitivity test for panel sizes and fee. This is in line with comments from public pathology and the private facility advocacy bodies, which proposed that the costing was conservative or manifestly inadequate.

Summary of public consultation input

Consultation input was received from five (5) organisations:

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

All were supportive of the application. LF also consulted consumers and the Blood Cancer Taskforce and advised that they were also supportive of the application.

Benefits

All responses considered that the proposed service would provide clarity of diagnosis as well as selection of the most appropriate treatment options, which would lead to better health outcomes. PPA and AG noted that the testing will ensure patients have access to the standard of care in accordance with the World Health Organisation (WHO) guidelines.

PA considered that precision cancer care is emerging as standard of care, and avoids the need for expensive therapies associated with treatment related side effects.

Public funding of the proposed test would improve equity of access for consumers with a diagnosis or potential diagnosis of cancer, noting that barriers to accessing this testing would likely affect clinical outcomes. The MPNAA considered that public funding would increase the knowledge base for myeloproliferative neoplasms, and could inform clinical practice and best treatment pathways.

PPA stated that genetic testing is normally performed as part of a suite of other pathology testing such as blood counts, morphology, immunophenotyping, and cytogenetics. Current WHO guidelines already outline how genetic testing should be used in conjunction with these other pathology test, but genetic testing does not have absolute dependencies on these other tests and can provide standalone information on diagnosis, prognosis, and treatment. PPA also stated that broader genetic testing carries with it the requirement of up-to-date education to explain the purpose and results to the patient.

PA considers that the proposed MBS fee does not adequately reimburse the cost of the test.

Disadvantages

Testing in some genes for tumour associated variants may also discover inherited variants associated with blood cancer predisposition, and 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. However, this would allow for early intervention for some consumers.

PASC noted that many organisations provided detailed consultation feedback

In terms of the issues raised, PASC acknowledged that:

- *the issue of minimum residual disease analysis would not be covered by this item.*
- *the impact of genetic counselling should be considered where germline variants are identified. The issue of familial variants is also important for donor selection for bone marrow transplant.*
- *the proposed fee is too low and as such this could have flow on impacts on consumers*

Next steps

PASC noted that the applicant would like to proceed to a department-contracted assessment report (DCAR) after the PICO is ratified by PASC.

Applicant Comments on the PICO Confirmation

Population

The College agrees that the inclusion of "*patients with a suspicion of a haematological malignancy*" may lead to leakage of the item number and an increase in numbers of patients being tested. Perhaps this should be worded along the lines of "*in patients with clinicopathological features consistent with a haematological malignancy*", that is, patients whose preliminary diagnosis with established testing modalities is suggestive of a haematological malignancy.

Assessment framework

The initial patient population should be amended in line with text describing the population i.e. change from "*Patients with a morphological diagnosis*…." to "*patients with a suspicion of a haematological malignancy*". However, in light of the College's comments above, this should be amended to "P*atients with clinicopathological features consistent with a haematological malignancy*", that is, patients whose preliminary diagnosis with established testing modalities is suggestive of a haematological malignancy.

Proposal for public funding

The College agrees with PASC that the proposed fee is slightly too low. This may have resulted from a miscommunication between the College and the expert Working Party in that the proposed $800 actually represents the 85% fee. This fee was arrived at by surveying labs that are currently conducting this panel testing. The amended fee structure would then be:

Fee: $940 Benefit: 75% = $705 85% = $799

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Appendix A

Table 9 2016 WHO classification of mature lymphoid, histiocytic, and dendritic neoplasms (Swerdlow et al., 2016)

Mature B-cell neoplasms
Chronic lymphocytic leukemia/small lymphocytic lymphoma
Monoclonal B-cell lymphocytosis*
B-cell prolymphocytic leukemia
Splenic marginal zone lymphoma
Hairy cell leukemia
Splenic B-cell lymphoma/leukemia, unclassifiable
Splenic diffuse red pulp small B-cell lymphoma
Hairy cell leukemia-variant
Lymphoplasmacytic lymphoma
Waldenström macroglobulinemia
Monoclonal gammopathy of undetermined significance (MGUS), IgM*
μ heavy-chain disease
γ heavy-chain disease
α heavy-chain disease
Monoclonal gammopathy of undetermined significance (MGUS), IgG/A*
Plasma cell myeloma
Solitary plasmacytoma of bone
Extraosseous plasmacytoma
Monoclonal immunoglobulin deposition diseases*
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Nodal marginal zone lymphoma
Paediatric nodal marginal zone lymphoma
Follicular lymphoma
In situ follicular neoplasia*
Duodenal-type follicular lymphoma*
Paediatric-type follicular lymphoma*
Large B-cell lymphoma with IRF4 rearrangement*
Primary cutaneous follicle centre lymphoma
Mantle cell lymphoma
In situ mantle cell neoplasia*
Diffuse large B-cell lymphoma (DLBCL), NOS
Germinal centre B-cell type*
Activated B-cell type*
T-cell/histiocyte-rich large B-cell lymphoma
Primary DLBCL of the central nervous system (CNS)
Primary cutaneous DLBCL, leg type
EBV^+ DLBCL, NOS*
EBV^+ mucocutaneous ulcer*
DLBCL associated with chronic inflammation
Lymphomatoid granulomatosis
Primary mediastinal (thymic) large B-cell lymphoma

Intravascular large B-cell lymphoma
ALK+ large B-cell lymphoma
Plasmablastic lymphoma
Primary effusion lymphoma
HHV8+ DLBCL, NOS*
Burkitt lymphoma
Burkitt-like lymphoma with 11q aberration*
High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements*
High-grade B-cell lymphoma, NOS*
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma
Mature T and NK neoplasms
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK cells
Aggressive NK-cell leukemia
Systemic EBV1 T-cell lymphoma of childhood*
Hydroa vacciniforme–like lymphoproliferative disorder*
Adult T-cell leukemia/lymphoma
Extranodal NK-/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Monomorphic epitheliotropic intestinal T-cell lymphoma*
Indolent T-cell lymphoproliferative disorder of the GI tract*
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30+ T-cell lymphoproliferative disorders
Lymphomatoid papulosis
Primary cutaneous anaplastic large cell lymphoma
Primary cutaneous γδ T-cell lymphoma
Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma
Primary cutaneous acral CD8+ T-cell lymphoma*
Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder*
Peripheral T-cell lymphoma, NOS
Angioimmunoblastic T-cell lymphoma
Follicular T-cell lymphoma*
Nodal peripheral T-cell lymphoma with TFH phenotype*
Anaplastic large-cell lymphoma, ALK+
Anaplastic large-cell lymphoma, ALK-*
Breast implant–associated anaplastic large-cell lymphoma*
Hodgkin lymphoma
Nodular lymphocyte predominant Hodgkin lymphoma
Classical Hodgkin lymphoma
Nodular sclerosis classical Hodgkin lymphoma
Lymphocyte-rich classical Hodgkin lymphoma
Mixed cellularity classical Hodgkin lymphoma

Lymphocyte-depleted classical Hodgkin lymphoma
Post-transplant lymphoproliferative disorders (PTLD)
Plasmacytic hyperplasia PTLD
Infectious mononucleosis PTLD
Florid follicular hyperplasia PTLD*
Polymorphic PTLD
Monomorphic PTLD (B- and T-/NK-cell types)
Classical Hodgkin lymphoma PTLD
Histiocytic and dendritic cell neoplasms
Histiocytic sarcoma
Langerhans cell histiocytosis
Langerhans cell sarcoma
Indeterminate dendritic cell tumour
Interdigitating dendritic cell sarcoma
Follicular dendritic cell sarcoma
Fibroblastic reticular cell tumour
Disseminated juvenile xanthogranuloma
Erdheim-Chester disease*

Provisional entities are listed in italics, *Changes from the 2008 classification.

Table 10 2016 WHO classification of myeloid neoplasms and acute leukaemia (Arber et al., 2016)

Myeloproliferative neoplasms (MPN)
Chronic myeloid leukaemia (CML), *BCR-ABL1*$^{+}$
Chronic neutrophilic leukaemia (CNL)
Polycythaemia vera (PV)
Primary myelofibrosis (PMF)
PMF, pre-fibrotic/early stage
PMF, overt fibrotic stage
Essential thrombocythaemia (ET)
Chronic eosinophilic leukaemia, NOS
MPN, unclassifiable
Mastocytosis
Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of *PDGFRA*, *PDGFRB*, or *FGFR1*, or with *PCM1-JAK2*
Myeloid/lymphoid neoplasms with *PDGFRA* rearrangement
Myeloid/lymphoid neoplasms with *PDGFRB* rearrangement
Myeloid/lymphoid neoplasms with *FGFR1* rearrangement
Myeloid/lymphoid neoplasms with PCM1-JAK2
Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)
Chronic myelomonocytic leukaemia (CMML)
Atypical chronic myeloid leukaemia (aCML), *BCR-ABL1*$^{-}$
Juvenile myelomonocytic leukemia (JMML)
MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)
MDS/MPN, unclassifiable
Myelodysplastic syndromes (MDS)
MDS with single lineage dysplasia
MDS with ring sideroblasts (MDS-RS)

MDS-RS and single lineage dysplasia
MDS-RS and multilineage dysplasia
MDS with multilineage dysplasia
MDS with excess blasts
MDS with isolated del(5q)
MDS, unclassifiable
Refractory cytopenia of childhood
Acute myeloid leukaemia (AML) and related neoplasms
AML with recurrent genetic abnormalities
AML with t(8;21)(q22;q22.1);*RUNX1-RUNX1T1*
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);*CBFB-MYH11*
AML with *PML-RARA*
AML with t(9;11)(p21.3;q23.3);*MLLT3-KMT2A*
AML with t(6;9)(p23;q34.1);*DEK-NUP214*
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM*
AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);*RBM15-MKL1*
AML with BCR-ABL1
AML with mutated NPM1
AML with biallelic mutations of *CEBPA*
AML with mutated RUNX1
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
AML, NOS
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukaemia
Acute monoblastic/monocytic leukaemia
Pure erythroid leukaemia
Acute megakaryoblastic leukaemia
Acute basophilic leukaemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
Transient abnormal myelopoiesis (TAM)
Myeloid leukemia associated with Down syndrome
Blastic plasmacytoid dendritic cell neoplasm
Acute leukaemias of ambiguous lineage
Acute undifferentiated leukaemia
Mixed phenotype acute leukaemia (MPAL) with t(9;22)(q34.1;q11.2); *BCR-ABL1*
MPAL with t(v;11q23.3); *KMT2A* rearranged
MPAL, B/myeloid, NOS
MPAL, T/myeloid, NOS
B-lymphoblastic leukaemia/lymphoma
B-lymphoblastic leukaemia/lymphoma, NOS
B-lymphoblastic leukaemia/lymphoma with recurrent genetic abnormalities

B-lymphoblastic leukaemia/lymphoma with t(9;22)(q34.1;q11.2);*BCR-ABL1*
B-lymphoblastic leukaemia/lymphoma with t(v;11q23.3);*KMT2A* rearranged
B-lymphoblastic leukaemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*
B-lymphoblastic leukaemia/lymphoma with hyperdiploidy
B-lymphoblastic leukaemia/lymphoma with hypodiploidy
B-lymphoblastic leukaemia/lymphoma with t(5;14)(q31.1;q32.3) *IL3-IGH*
B-lymphoblastic leukaemia/lymphoma with t(1;19)(q23;p13.3);*TCF3-PBX1*
B-lymphoblastic leukaemia/lymphoma, BCR-ABL1–like
B-lymphoblastic leukaemia/lymphoma with iAMP21
T-lymphoblastic leukaemia/lymphoma
Early T-cell precursor lymphoblastic leukaemia
Natural killer (NK) cell lymphoblastic leukaemia/lymphoma

Provisional entities are listed in italics, NOS = not otherwise specified

Appendix B

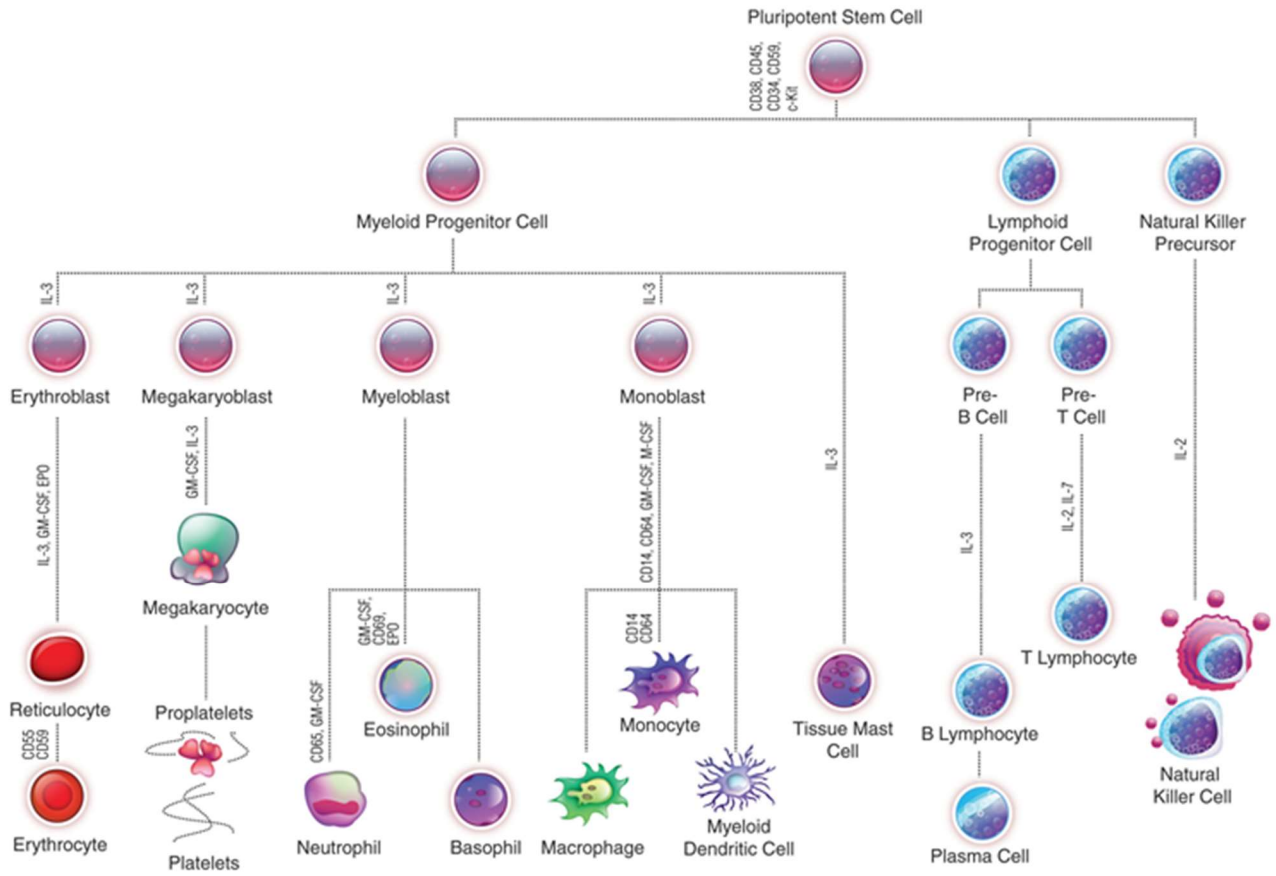

Figure 7 Haematopoiesis (Northrup, Maybank, Carson, & Rahmeh, 2020)

Appendix C

Exemplar and facilitated genes are presented as a list and tabulated (Table 11), indicating the source where genes are currently recommended for use (clinical advice, Peter MacCallum Cancer Centre).

Exemplar genes (n=105) – *ALK, ANKRD26, ASXL1, BCR-ABL1, BCR-JAK2, BIRC3-MALT1 (t(11;18)), BRAF, BRCA2, BRIP1, CALR, CBFB-MYH11, CBL, CD274, CEBPA, CSF3R, CTC1, DDX41, DEK-NUP214, DKC1, DNMT3A, ELANE, ETNK1, ETV6, ETV6-JAK2, ETV6-RUNX1, EZH2, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FGFR1, FLT3, G6PC3, GATA1, GATA2, GATA2-MECOM, GFI1, HAVCR2, HAX1, IDH1, IDH2, IGH-BCL10 (t(1;14)), IGH-BCL2 (t(14;18)), IGH-BCL6 (t(3;14)), IGH-CCND1 (t(11;14)), IGH-MYC (t(8;14)), IKZF1, JAK1, JAK2, JAK3, KIT, KMT2A, KMT2A-MLLT3, KRAS, MPL, MYD88, NF1, NHP2, NOP10, NOTCH1, NPM1, NRAS, PALB2, PCM1-JAK2, PDCD1LG2, PDGFRA, PDGFRA, PDGFRB, PML-RARA, PTPN11, RAD51C, RBM15-MKL1, RPL11, RPL35A, RPL5, RPS10, RPS17, RPS19, RPS24, RPS26, RPS7, RTEL1, RUNX1, RUNX1-RUNX1T1, SBDS, SETBP1, SF3B1, SLX4, SRSF2, STAT3, STAT5B, STAT6, TCF3-PBX1, TERC, TERT, TET2, TINF2, WAS, WRAP53*

Facilitated genes (n=130) – *ABL1, ACD, ADA2, ARAF, ARID1A, ATM, ATR, ATRX, B2M, BCL2, BCL6, BCOR, BCORL1, BIRC3, BTK, CARD11, CBLB, CBLC, CCND1, CCND2, CCND3, CD58, CD79A, CD79B, CDC25C, CDKN2A, CDKN2B, CHD2, CIITA, CRBN, CREBBP, CUX1, CXCR4, DCK, DDX3X, DHX15, DIS3, DNAJC21, EFL1 , EGFR, EGR2, EP300, ERBB2, ERCC6L2, ETV6, FAM46C, FBXW7, FGFR2, FGFR3, FOXO1, FUS, FYN, GNA13, GNAS, HIST1H1E, HMGA2, HRAS, ID3, IRF4, IRF8, JAGN1, KDM6A, KLF2, KMT2D, LUC7L2, MAL, MAP2K1, MECOM, MEF2B, MET, MLL, MLLT10, MLLT3, MTOR, MYBL1, MYC, MYH11, NFKBIE, NOTCH2, NTRK3, NUP214, PARN, PAX5, PHF6, PIGA, PIM1, PLCG1, PLCG2, POT1, PPM1D, PRDM1, PRPF8, PTEN, RAD21, RARA, RB1, RBBP6, RBM15, REL, RHOA, RPL15, RPL26, RPS14, RPS15, RPS29, RRAGC, SAMD9, SAMD9L, SH2B3, SLC29A1, SMARCD2, SMC1A, SMC3, SOCS1, SRP54, SRP72, STAG2, TCF3, TFE3, TNFAIP3, TNFRSF14, TP53, TRAF2, TRAF3, U2AF1, U2AF2, VPS45, WT1, XPO1, ZRSR2*

Table 11 Exemplar and facilitated genes associated with haematological malignancies

Gene	WHO*-	WHO**	ARCHER †	Oncomine ‡	Oncomine #	PeterMac $	PeterMac §	SOPHiA ¶	SOPHiA ¥	TruSight † †	TruSight § §	Category
ALK		Y			Y							Exemplar
ANKRD26	Y		Y			Y	Y					Exemplar
ASXL1	Y		Y		Y		Y		Y		Y	Exemplar
BCR-ABL1		Y										Exemplar
BCR-JAK2		Y										Exemplar
BIRC3-MALT1 (t(11;18))		Y										Exemplar
BRAF	Y		Y	Y	Y		Y	Y	Y	Y	Y	Exemplar
BRCA2	Y											Exemplar
BRIP1	Y											Exemplar
CALR	Y		Y		Y		Y		Y		Y	Exemplar
CBFB-MYH11		Y										Exemplar
CBL	Y		Y		Y		Y		Y		Y	Exemplar
CD274	Y						Y					Exemplar
CEBPA	Y		Y		Y		Y		Y		Y	Exemplar

Gene	WHO*-	WHO**	ARCHER †	Oncomine ‡	Oncomine #	PeterMac $	PeterMac §	SOPHiA ¶	SOPHiA ¥	TruSight † †	TruSight § §	Category
CSF3R	Y		Y		Y	Y	Y		Y		Y	Exemplar
CTC1	Y					Y						Exemplar
DDX41	Y		Y			Y	Y					Exemplar
DEK-NUP214		Y										Exemplar
DKC1	Y					Y						Exemplar
DNMT3A	Y		Y		Y		Y		Y		Y	Exemplar
ELANE	Y					Y						Exemplar
ETNK1	Y		Y									Exemplar
ETV6	Y		Y		Y	Y			Y			Exemplar
ETV6-JAK2		Y										Exemplar
ETV6-RUNX1		Y										Exemplar
EZH2	Y		Y	Y	Y		Y	Y	Y	Y	Y	Exemplar
FANCA	Y					Y						Exemplar
FANCB	Y											Exemplar
FANCC	Y					Y						Exemplar
FANCD2	Y											Exemplar
FANCE	Y											Exemplar
FANCF	Y											Exemplar
FANCG	Y					Y						Exemplar
FANCI	Y											Exemplar
FANCL	Y											Exemplar
FANCM	Y					Y						Exemplar
FGFR1		Y			Y							Exemplar
FLT3	Y		Y		Y		Y		Y		Y	Exemplar
G6PC3	Y					Y						Exemplar
GATA1	Y		Y			Y					Y	Exemplar
GATA2	Y		Y		Y	Y	Y				Y	Exemplar
GATA2-MECOM		Y										Exemplar
GFI1	Y											Exemplar
HAVCR2*	Y											Exemplar
HAX1	Y					Y						Exemplar
IDH1	Y		Y		Y		Y		Y		Y	Exemplar
IDH2	Y		Y		Y		Y		Y	Y	Y	Exemplar
IGH-BCL10 (t(1;14))		Y										Exemplar
IGH-BCL2 (t(14;18))		Y										Exemplar
IGH-BCL6 (t(3;14))		Y										Exemplar
IGH-CCND1 (t(11;14))		Y										Exemplar
IGH-MYC (t(8;14))		Y										Exemplar
IKZF1	Y		Y		Y		Y				Y	Exemplar
JAK1	Y						Y					Exemplar

Gene	WHO*-	WHO**	ARCHER †	Oncomine ‡	Oncomine #	PeterMac $	PeterMac §	SOPHiA ¶	SOPHiA ¥	TruSight † †	TruSight § §	Category
JAK2	Y		Y		Y		Y		Y		Y	Exemplar
JAK3	Y		Y				Y			Y	Y	Exemplar
KIT	Y		Y		Y		Y		Y		Y	Exemplar
KMT2A		Y	Y		Y			Y				Exemplar
KMT2A-MLLT3		Y										Exemplar
KRAS	Y		Y		Y		Y	Y	Y		Y	Exemplar
MPL	Y		Y		Y	Y	Y		Y		Y	Exemplar
MYD88	Y		Y	Y	Y		Y	Y		Y	Y	Exemplar
NF1	Y		Y		Y							Exemplar
NHP2	Y					Y						Exemplar
NOP10	Y											Exemplar
NOTCH1	Y		Y				Y	Y		Y	Y	Exemplar
NPM1	Y		Y		Y		Y		Y		Y	Exemplar
NRAS	Y		Y		Y		Y	Y	Y		Y	Exemplar
PALB2	Y											Exemplar
PCM1-JAK2		Y										Exemplar
PDCD1LG2	Y						Y					Exemplar
PDGFRA	Y	Y	Y		Y						Y	Exemplar
PDGFRB		Y			Y							Exemplar
PML-RARA		Y										Exemplar
PTPN11	Y		Y		Y		Y	Y	Y		Y	Exemplar
RAD51C	Y											Exemplar
RBM15-MKL1		Y										Exemplar
RPL11	Y					Y						Exemplar
RPL35A	Y					Y						Exemplar
RPL5	Y					Y						Exemplar
RPS10	Y					Y						Exemplar
RPS17	Y											Exemplar
RPS19	Y					Y						Exemplar
RPS24	Y					Y						Exemplar
RPS26	Y					Y						Exemplar
RPS7	Y					Y						Exemplar
RTEL1	Y					Y						Exemplar
RUNX1	Y		Y		Y	Y	Y		Y		Y	Exemplar
RUNX1-RUNX1T1		Y										Exemplar
SBDS	Y					Y						Exemplar
SETBP1	Y		Y		Y		Y		Y		Y	Exemplar
SF3B1	Y		Y	Y	Y		Y	Y	Y	Y	Y	Exemplar
SLX4	Y											Exemplar
SRSF2	Y		Y		Y		Y		Y		Y	Exemplar

Gene	WHO*-	WHO**	ARCHER †	Oncomine ‡	Oncomine #	PeterMac $	PeterMac §	SOPHiA ¶	SOPHiA ¥	TruSight † †	TruSight § §	Category
STAT3	Y		Y				Y			Y		Exemplar
STAT5B	Y						Y			Y		Exemplar
STAT6	Y						Y	Y				Exemplar
TCF3-PBX1		Y										Exemplar
TERC	Y					Y						Exemplar
TERT	Y					Y						Exemplar
TET2	Y		Y		Y		Y		Y	Y	Y	Exemplar
TINF2	Y					Y						Exemplar
WAS	Y					Y						Exemplar
WRAP53	Y											Exemplar
ABL1			Y		Y		Y		Y		Y	Facilitated
ACD						Y						Facilitated
ADA2						Y						Facilitated
ARAF							Y					Facilitated
ARID1A				Y				Y				Facilitated
ATM				Y			Y	Y		Y		Facilitated
ATR							Y					Facilitated
ATRX			Y								Y	Facilitated
B2M				Y				Y		Y		Facilitated
BCL2				Y	Y		Y	Y				Facilitated
BCL6				Y				Y				Facilitated
BCOR			Y		Y		Y				Y	Facilitated
BCORL1			Y				Y				Y	Facilitated
BIRC3							Y	Y		Y		Facilitated
BTK			Y	Y			Y	Y		Y		Facilitated
CARD11				Y			Y	Y		Y		Facilitated
CBLB			Y								Y	Facilitated
CBLC			Y								Y	Facilitated
CCND1					Y		Y	Y				Facilitated
CCND2			Y									Facilitated
CCND3								Y				Facilitated
CD58								Y				Facilitated
CD79A								Y		Y		Facilitated
CD79B				Y			Y	Y		Y		Facilitated
CDC25C			Y									Facilitated
CDKN2A			Y	Y				Y			Y	Facilitated
CDKN2B								Y				Facilitated
CHD2								Y				Facilitated
CIITA								Y		Y		Facilitated
CRBN							Y					Facilitated

Gene	WHO*-	WHO**	ARCHER †	Oncomine ‡	Oncomine #	PeterMac $	PeterMac §	SOPHiA ¶	SOPHiA ¥	TruSight † †	TruSight § §	Category
CREBBP				Y	Y		Y	Y		Y		Facilitated
CUX1			Y								Y	Facilitated
CXCR4			Y				Y	Y		Y		Facilitated
DCK			Y									Facilitated
DDX3X							Y					Facilitated
DHX15			Y									Facilitated
DIS3							Y					Facilitated
DNAJC21						Y						Facilitated
EFL1						Y						Facilitated
EGFR					Y							Facilitated
EGR2										Y		Facilitated
EP300							Y	Y				Facilitated
ERBB2							Y					Facilitated
ERCC6L2						Y						Facilitated
ETV6											Y	Facilitated
FAM46C							Y					Facilitated
FBXW7			Y				Y	Y			Y	Facilitated
FGFR2					Y							Facilitated
FGFR3							Y					Facilitated
FOXO1							Y	Y				Facilitated
FUS					Y							Facilitated
FYN							Y					Facilitated
GNA13				Y				Y		Y		Facilitated
GNAS			Y								Y	Facilitated
HIST1H1E				Y								Facilitated
HMGA2					Y							Facilitated
HRAS			Y		Y				Y		Y	Facilitated
ID3							Y	Y		Y		Facilitated
IRF4								Y				Facilitated
IRF8							Y					Facilitated
JAGN1						Y						Facilitated
KDM6A			Y								Y	Facilitated
KLF2										Y		Facilitated
KMT2D				Y				Y				Facilitated
LUC7L2			Y									Facilitated
MAL								Y				Facilitated
MAP2K1			Y				Y			Y		Facilitated
MECOM					Y	Y						Facilitated
MEF2B								Y				Facilitated
MET					Y							Facilitated

Gene	WHO*-	WHO**	ARCHER †	Oncomine ‡	Oncomine #	PeterMac $	PeterMac §	SOPHiA ¶	SOPHiA ≠	TruSight † †	TruSight § §	Category
MLL											Y	Facilitated
MLLT10					Y							Facilitated
MLLT3					Y							Facilitated
MTOR				Y								Facilitated
MYBL1					Y							Facilitated
MYC			Y	Y				Y				Facilitated
MYH11					Y							Facilitated
NFKBIE							Y	Y		Y		Facilitated
NOTCH2							Y	Y		Y		Facilitated
NTRK3					Y							Facilitated
NUP214					Y							Facilitated
PARN						Y						Facilitated
PAX5								Y				Facilitated
PHF6			Y		Y		Y				Y	Facilitated
PIGA							Y					Facilitated
PIM1				Y				Y				Facilitated
PLCG1							Y			Y		Facilitated
PLCG2							Y	Y		Y		Facilitated
POT1								Y		Y		Facilitated
PPM1D			Y									Facilitated
PRDM1							Y	Y				Facilitated
PRPF8					Y							Facilitated
PTEN			Y					Y			Y	Facilitated
RAD21			Y								Y	Facilitated
RARA					Y							Facilitated
RB1					Y							Facilitated
RBBP6			Y									Facilitated
RBM15					Y							Facilitated
REL								Y				Facilitated
RHOA							Y			Y		Facilitated
RPL15						Y						Facilitated
RPL26						Y						Facilitated
RPS14			Y									Facilitated
RPS15										Y		Facilitated
RPS29						Y						Facilitated
RRAGC							Y			Y		Facilitated
SAMD9						Y						Facilitated
SAMD9L						Y						Facilitated
SH2B3			Y		Y							Facilitated
SLC29A1			Y									Facilitated

Gene	WHO*-	WHO**	ARCHER †	Oncomine ‡	Oncomine #	PeterMac $	PeterMac §	SOPHiA ¶	SOPHiA ¥	TruSight † †	TruSight § §	Category
SMARCD2						Y						Facilitated
SMC1A			Y								Y	Facilitated
SMC3			Y								Y	Facilitated
SOCS1				Y			Y	Y		Y		Facilitated
SRP54						Y						Facilitated
SRP72						Y						Facilitated
STAG2			Y		Y						Y	Facilitated
TCF3					Y		Y	Y		Y		Facilitated
TFE3					Y							Facilitated
TNFAIP3				Y			Y	Y		Y		Facilitated
TNFRSF14				Y				Y		Y		Facilitated
TP53			Y	Y	Y		Y	Y	Y	Y	Y	Facilitated
TRAF2							Y					Facilitated
TRAF3										Y		Facilitated
U2AF1			Y		Y		Y		Y		Y	Facilitated
U2AF2			Y									Facilitated
VPS45						Y						Facilitated
WT1			Y		Y		Y		Y		Y	Facilitated
XPO1			Y	Y			Y	Y		Y		Facilitated
ZRSR2					Y		Y		Y		Y	Facilitated
Total	**81**	**24**	**74**	**25**	**64**	**49**	**81**	**54**	**30**	**40**	**54**	

* WHO mutated genes, ** WHO fusion genes, † ARCHER VariantPlex Myeloid, ‡ Oncomine Lymphoma Panel, # Oncomine Myeloid Assay GX, $ PeterMac inherited bone marrow disorders panel, § PeterMac tumour (somatic analysis) panels, ¶ SOPHiA Genetics Lymphoma Solution, ¥ SOPHiA Genetics Myeloid Solution; †† TruSight Lymphoma 40 Gene List; §§ TruSight Myeloid Sequencing Panel