Australian Government

Department of Health

# Application 1684

# Genetic testing for variants associated with haematological malignancies

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

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

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

Email: hta@health.gov.au
Website: www.msac.gov.au

# PART 1 – APPLICANT DETAILS

**1. Applicant details (primary and alternative contacts)**

| |
|---|
| Corporation / partnership details (where relevant): |
| Corporation name: The Royal College of Pathologists of Australasia |
| ABN: **REDACTED** |
| Business trading name: The Royal College of Pathologists of Australasia |

**Primary contact name: REDACTED**

| |
|---|
| Alternative contact numbers |
| Business: **REDACTED** |
| Mobile: **REDACTED** |
| Email: **REDACTED** |

**Alternative contact name: REDACTED**

| |
|---|
| Alternative contact numbers |
| Business: |
| Mobile: **REDACTED** |
| Email: **REDACTED** |

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

☐ Yes
☒ No

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

☐ Yes
☐ No

# PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

**3. Application title**

Genetic testing for variants associated with haematological malignancies.

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

The 2016 revision of the World Health Organization 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 4, Appendix A)

- mature B-cell lymphoid neoplasms;
- mature T-cell and natural killer cell (NK) neoplasms;
- Hodgkin lymphoma;
- post-transplant lymphoproliferative disorders (PTLD);
- histiocytic and dendritic cell neoplasms;[1] and

Myeloid neoplasms and acute leukaemia (see Table 5, Appendix A)

- myeloproliferative neoplasms (MPN);
- myeloid/lymphoid neoplasms with eosinophilia and rearrangement of PDGFRA, PDGFRB, or FGFR1, or with PCM1-JAK2;
- myelodysplastic/myeloproliferative neoplasms (MDS/MPN);
- myelodysplastic syndromes (MDS);
- acute myeloid leukaemia (AML) and related neoplasms;
- blastic plasmacytoid dendritic cell neoplasm;
- acute leukaemias of ambiguous lineage;
- B-lymphoblastic leukaemia/lymphoma;
- T-lymphoblastic leukaemia/lymphoma.[2]

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

Molecular characterisation of haematological malignancies as per diagnostic criteria within the World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues in order to establish a definitive diagnosis.

As stated by the Leukaemia Foundation's National Strategic Action Plan for Blood Cancer, commissioned by the Australian Government Department of Health "Early and accurate diagnosis is critical to not only the understanding of what type of blood cancer an individual has, but also to what treatment pathway will offer the best survival and quality of life outcomes".[3]

The most widely used technique for the molecular diagnosis of haematological malignancies is targeted next generation sequencing (NGS) panels (lymphoid or myeloid) focusing on specific genes as described by the WHO.

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

☒ Yes
☐ No

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

☐ Amendment to existing MBS item(s)
☒ New MBS item(s)

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

N/A

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

i. ☐ **An amendment to the way the service is clinically delivered under the existing item(s)**
ii. ☐ **An amendment to the patient population under the existing item(s)**
iii. ☐ **An amendment to the schedule fee of the existing item(s)**
iv. ☐ **An amendment to the time and complexity of an existing item(s)**
v. ☐ **Access to an existing item(s) by a different health practitioner group**
vi. ☐ **Minor amendments to the item descriptor that does not affect how the service is delivered**
vii. ☐ **An amendment to an existing specific single consultation item**
viii. ☐ **An amendment to an existing global consultation item(s)**
ix. ☐ **Other (please describe below):**

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

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

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

☐ Yes
☒ No

(g) If yes, please advise:

N/A

**7. What is the type of service:**

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

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

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

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

☐ Pharmaceutical / Biological
☐ Prosthesis or device
☒ No

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

N/A

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

N/A

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

N/A

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

N/A

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

N/A

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

N/A

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

N/A

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

N/A

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

N/A

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

Single use consumables: Laboratory consumables used for standard sequencing
Multi-use consumables: Nil

# PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

The National Association of Testing Authorities (NATA) and the Royal College of Pathologists Australasia (RCPA) oversee the regulation of genetic sequencing for clinical purposes. Laboratories require accreditation by a joint NATA/RCPA process to ISO 15189, with the accreditation process covering the technical aspects of the laboratory sequencing, analysis pipelines, curation (or interpretation) of results and production of the report to a clinical standard. This allows any accredited laboratory to provide equivalent genetic variant analysis services to a minimum standard. There are no requirements for use of specific manufacturers, reagents, equipment or analysis pipelines.

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

Type of therapeutic good: In-vitro diagnostic test
Manufacturer's name: N/A
Sponsor's name: Not applicable

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

☒ Class III
☐ AIMD
☐ N/A

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

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

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

☐ Yes (if yes, please provide details below)
☒ No

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

☐ Yes (please provide details below)
☒ No

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

☐ Yes (please provide details below)
☒ No

# PART 4 – SUMMARY OF EVIDENCE

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

| | Type of study design | Title of journal article or research project | Short description of research | Website link to journal article or research | Date of publication |
|---|---|---|---|---|---|
| 1. | Guideline | WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues | WHO Classification of Tumours, Revised 4th Edition, Volume 2, Edited by Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J<br>Also see<br>The 2016 revision of the World Health Organization classification of lymphoid neoplasms [1] and<br>The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia [2] | https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/WHO-Classification-Of-Tumours-Of-Haematopoietic-And-Lymphoid-Tissues-2017 | 2017 |
| 2. | Level III-2 diagnostic evidence<br>Clinical utility<br>NGS vs cytogenetics<br>Turkey | The Importance of Targeted Next-Generation Sequencing Usage in Cytogenetically Normal Myeloid Malignancies[4] | Cytogenetics, molecular cytogenetics, and NGS testing were conducted on 100 patients with myeloid malignancies. A 141 gene panel for cytogenetically normal patients was applied, which detected two or more pathogenic variations in 61 out of 100 patients (61%). NGS's pathogenic variation detection rate varies in disease groups: they were present in 85% of AML and 23% of MDS. 24 novel variations out of total pathogenic variations in myeloid malignancies were identified: 18 in AML, and 6 in MDS. | https://pubmed.ncbi.nlm.nih.gov/33489052/ | 2021 |

| | Type of study design | Title of journal article or research project | Short description of research | Website link to journal article or research | Date of publication |
|---|---|---|---|---|---|
| 3. | Diagnostic accuracy<br>USA | Clinical performance and utility of a comprehensive next-generation sequencing DNA panel for the simultaneous analysis of variants, TMB and MSI for myeloid neoplasms [5] | Evaluation of the clinical performance and utility of a 523 gene NGS panel for screening for SNVs and indels/duplications in myeloid neoplasms. 61 previously well characterised samples were analysed. Clinical sensitivity (97%), specificity (100%), precision (100%) and accuracy (99%) compared to 100% for analytical sensitivity, specificity, precision, and accuracy for reference control results. A high intra- and inter-run reproducibility was reported. | https://pubmed.ncbi.nlm.nih.gov/33075099/ | 2020 |
| 4. | Diagnostic yield/accuracy<br>Canada | Clinical Validation of a Myeloid Next-Generation Sequencing Panel for Single-Nucleotide Variants, Insertions/Deletions, and Fusion Genes [6] | Clinical validation of the Oncomine Myeloid Research (OMR) NGS panel that interrogates for 40 genes and 29 fusion genes commonly seen in myeloid neoplasms. Validation set of 77 DNA samples included acute and chronic myeloid neoplasms, with 91 single-nucleotide variants and small insertions/deletions. 71 RNA samples from patients with AML included most of the AML-defining translocations. The panel achieved 91.3% and 100% concordance with reference DNA and RNA samples, respectively, with a clinical sensitivity and specificity of 96.7% and 100% for DNA and 99.8% and 100% for RNA, respectively. Precision and reproducibility were 100%, and the lower limit of detection was generally 5% variant allele fraction for DNA and 2-log reduction from initial value for RNA fusion genes. | https://pubmed.ncbi.nlm.nih.gov/31751678/ | 2020 |

| | Type of study design | Title of journal article or research project | Short description of research | Website link to journal article or research | Date of publication |
|---|---|---|---|---|---|
| 5. | Level III-2 diagnostic evidence<br>NGS vs karyotyping<br>Canada | The Value of Next-Generation Sequencing in the Screening and Evaluation of Hematologic Neoplasms in Clinical Practice [7] | Evaluation of the clinical value of NGS in the screening, diagnosis, and follow-up in haematologic neoplasms. A targeted NGS panel was used to assess a total of 178 patients for questionable or previously diagnosed myeloid neoplasms. Gene variants were identified in 53% of patients. Novel variants were identified in 29% of patients and variants of unknown significance in 34%. Bone marrow samples yielded a higher number of variants than in peripheral blood. NGS was more sensitive test than conventional cytogenetics. In several cases, NGS played a key role in the screening, diagnostics, prognostic stratification, and the clinical follow-up of a wide variety of myeloid neoplasms. | https://pubmed.ncbi.nlm.nih.gov/31875888/ | 2020 |
| 6. | Level III-2 diagnostic evidence<br>Clinical utility<br>NGS vs karyotyping<br>Spain | Next-Generation Sequencing Improves Diagnosis, Prognosis and Clinical Management of Myeloid Neoplasms [8] | Samples from 121 patients affected by myeloid neoplasms and ten relapse samples from a subset of acute myeloid leukemia patients were analysed using two enrichment-capture NGS gene panels. A total of 278 pathogenic variants were detected in 84% of patients. The detection of variants using NGS changed the diagnosis of seven patients and the prognosis of 15 patients. Six of the ten relapsed AML patients lost or gained variants, comparing with diagnostic samples. | https://pubmed.ncbi.nlm.nih.gov/31540291/ | 2019 |

| | Type of study design | Title of journal article or research project | Short description of research | Website link to journal article or research | Date of publication |
|---|---|---|---|---|---|
| 7 | Level III-2 diagnostic evidence<br>NGS vs Sanger sequencing<br>Spain | Clinical Utility of a Next-Generation Sequencing Panel for Acute Myeloid Leukemia Diagnostics [9] | A 19-gene acute myeloid leukaemia (AML) NGS panel was used to classify 162 patients. 339 variants were found (36% INDELs and 64% single nucleotide variants). Concordance between NGS and other conventional techniques was 100%, but the NGS approach was able to identify more clinically relevant mutations. All patients could be classified into one of the 2016 World Health Organization diagnostic categories. | https://pubmed.ncbi.nlm.nih.gov/30576870/ | 2019 |
| 8 | Diagnostic yield/clinical utility<br>Conference abstract<br>USA | Ordering patterns of NGS testing and impact of results on clinical management in patients with hematological disorders [10] | 250 patients with suspected or known haematological disorders underwent testing with NGS panel (PCR based, amplicon enrichment assay targeting mutational hot spots of 37 genes). At least one mutation was detected in 74% of samples. NGS results changed diagnosis 5% of the time and impacted therapy in 21% (53 pts). Of these 53 patients, 31 (58%) went on a clinical trial (10 pts on targeted and 21 non-targeted), and 22 (42%) received targeted therapy outside of a trial. NGS impacted future therapy in 76 pts (30%), the bulk of which were offered and received bone marrow transplant. Most common mutations were TET2(18%), DNMT3A(15%), ASXL1(13%), TP53(11%), SRSF2(10%), FLT3(10%), and RUNX1(9%). NGS results provided prognostic information considered additive to standard cytogenetic and clinical factors in 68% of patients based on current literature. NGS was reassuring for 26% of patients (i.e. no mutation detected). | | 2018 |

| | Type of study design | Title of journal article or research project | Short description of research | Website link to journal article or research | Date of publication |
|---|---|---|---|---|---|
| 9. | Diagnostic yield/clinical utility<br>Belgium | Targeted next-generation sequencing using a multigene panel in myeloid neoplasms: Implementation in clinical diagnostics [11] | 348 patients with myeloid neoplasm (n=287) or follow-up of a known MN (n=61) where sampling was performed as part of the regular follow-up or because of the suspicion of progressive disease. Testing was conducted using the TruSight Myeloid Sequencing NGS panel (54 genes) on either blood (n=49) or bone marrow (n=299).<br>155/287 (54%) patients had a final diagnosis of a MN, with 132 cases (46%) having insufficient evidence for a neoplastic myeloid condition. In 125/155 (81%) and 54/61 (89%) of the known MN cases had at least one mutation detected. Of the 28/173 lacking a conclusive MDS diagnosis, 10 (36%) were diagnosed as MDS based on the additional finding of a mutation. Similarly, 9 of 18 presumed but unconfirmed MPN cases could be confirmed in nine cases (50%) based on the presence of a mutation. | https://pubmed.ncbi.nlm.nih.gov/28722833/ | 2017 |

| | Type of study design | Title of journal article or research project | Short description of research | Website link to journal article or research | Date of publication |
|---|---|---|---|---|---|
| 10 | QAP<br>Australia | Laboratory quality assessment of candidate gene panel testing for acute myeloid leukaemia: a joint ALLG / RCPAQAP initiative [12] | Accurate classification of acute myeloid leukaemia (AML) has become increasingly reliant on molecular characterisation of this blood cancer. Throughout Australia and New Zealand massively parallel sequencing (MPS) is being adopted by diagnostic laboratories for the routine evaluation of patients with AML. This technology enables the surveying of many genes simultaneously, with many technical advantages over single gene testing approaches. However, there are many variations in wet and dry lab MPS procedures, which raises the prospect of discordant results between laboratories. This study compared the results obtained from MPS testing of ten diagnostic AML bone marrow aspirate samples sent to eight participating laboratories across Australasia. A reassuringly high concordance of 94% was observed with regard to variant detection and characterisation of pathogenicity. | https://pubmed.ncbi.nlm.nih.gov/33272691/ | 2020 |

| | Type of study design | Title of journal article or research project | Short description of research | Website link to journal article or research | Date of publication |
|---|---|---|---|---|---|
| 11. | Review<br>Australia | Design, implementation and clinical utility of next generation sequencing in myeloid malignancies: acute myeloid leukaemia and myelodysplastic syndrome [13] | Assessment of clinically important mutations by NGS is a powerful tool to define diagnosis, determine prognostic risk, monitor measurable residual disease and uncover predictive mutational markers/therapeutic targets, and is now a routine component in the workup and monitoring of haematological disorders. There are many technical challenges in the design, implementation, analysis and reporting of NGS based results, and expert interpretation is essential. It is vital to distinguish relevant somatic disease associated mutations from those that are known polymorphisms, rare germline variants and clonal haematopoiesis of indeterminate potential (CHIP) associated variants. This review highlights and addresses the technical and biological challenges that should be considered before the implementation of NGS based testing in diagnostic laboratories and seeks to outline the essential and expanding role NGS plays in myeloid malignancies. Broad aspects of NGS panel design and reporting including inherent technological, biological and economic considerations are covered, following which the utility of NGS based testing in AML and MDS are discussed. | https://pubmed.ncbi.nlm.nih.gov/33676768/ | 2021 |

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

| | Type of study design | Title of research | Short description of research | Date |
|---|---|---|---|---|
| 1. | Case series<br>2,000 patients<br>France | Bergonie Institut Profiling : Fighting Cancer by Matching Molecular Alterations and Drugs in Early Phase Trials<br>NCT02534649 | A comprehensive assessment of the biological characteristics of solid malignant tumour or haematological malignancy from each individual using validated biomarkers to identify subgroups of patients who are most likely to benefit from a given therapy. | Estimated Study Completion Date : December 2025 |
| 2. | Observational<br>3,960 patients<br>France | Economic Evaluation of Innovative Molecular Analyses in Onco-haematology<br>NCT03750994 | To evaluate the impact of innovative molecular diagnostics on the clinical management of patients with haematological malignancies via updated Appropriate-Prescribing-Guides including Next-Generation Sequencing (NGS) panels, facilitated therapeutic orientation, and optimised use of costly novel therapeutics and risk-adapted treatment. A micro-costing approach will be used to develop flat fee tariffs for NGS analyses | Estimated Primary Completion Date : October 2020 |
| 3. | Observational cohort<br>1,000 patients<br>Italy | Molecular Disease Profile of Hematological Malignancies (RELab1)<br>NCT02459743 | Prospective multicentric study, will analyse gene mutations in haematological malignancies using NGS techniques. Patients with a conclusive diagnosis of haematological malignancies will be enrolled. Patient DNA samples will be analysed at diagnosis and sequentially at specific timepoints. | Estimated Study Completion Date : December 2018 |
| 4. | Observational<br>200 patients<br>USA | Genomic Profiling in Cancer Patients<br>NCT01775072 | Molecular profiling of haematological malignancies | Estimated Study Completion Date : January 2021 |

# PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

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

    Royal College of Pathologists of Australasia

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

    Australasian Leukaemia & Lymphoma Group (ALLG)

    Human Genetics Society of Australasia (HGSA) and Australasian Society of Diagnostic Genomics (ASDG)

    Haematology Society of Australia & New Zealand (HSANZ)

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

    Leukaemia Foundation and the Blood Cancer Taskforce

    Myeloma Australia

    Lymphoma Australia

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

    N/A

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

    **REDACTED**

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

***PART 6a – INFORMATION ABOUT THE PROPOSED POPULATION***

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

Haematological malignancies are the result of the clonal expansion of cells throughout the blood forming organs. The current accepted world standard for diagnosing and subcategorising haematological malignancy recognises 15 different broad subgroups encompassing over 150 individual entities.[1, 2] The clinical behaviour/natural history of haematological malignancy 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.

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.

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.[14] However, it should be noted that it has been estimated that 8-15 per cent of all haematological malignancies are familial, with the revised World Health Organization classification criteria recognising a number of germline variants that result in an inherited predisposition to haematologic cancer.[15]

Haematologic 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.[16]

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).[17, 18] The exceptions to this are chronic myeloid leukaemia (CML), where the cell of origin is a pluripotent haematopoietic stem cell that is capable of giving rise to lymphoid cells as well,[18] and myeloid/lymphoid proliferations (e.g. those associated with rearrangements of FGFR1).

Myeloid neoplasms can be broadly classified into four groups (see Table 5):

- Acute myeloid leukaemia (AML) and related neoplasms. AML 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. AML is the most common acute leukaemia in adults (80% of cases), whereas AML accounts for less than 10 per cent of acute leukaemias in children.[19]
- Myeloproliferative neoplasms (MPN), including chronic myeloid leukaemia, are often associated with mutations that cause abnormal increases in activity of pro-growth signalling pathways, leading to the growth factor-independent proliferation of bone marrow progenitors. Unlike AML, the percentage of blasts in the bone marrow may be normal or slightly increased, but is always <20 per cent;[18]
- Myelodysplastic syndromes (MDS) 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 MPN, the percentage of blasts in the bone marrow may be normal or increased, but <20 per cent.[18] and

- Myeloproliferative/myelodysplastic syndromes include disorders where both dysplastic and proliferative features co-exist.[18]

Some myeloid neoplasms show features that overlap between those of an MPN and an MDS, and all MPNs and MDS have the potential to transform into AML. AMLs are very aggressive, requiring immediate treatment, whereas MPNs and MDS are often indolent, and usually do not require immediate or aggressive treatment.[18]

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) (see *Figure 7*, Appendix B).[18] As such, lymphoid neoplasms can be divided into three broad categories (see Table 4):

- Hodgkin lymphoma (HL) accounts for approximately 10 per cent of all lymphomas.[20] HL 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 HL), HL 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.[21-23]
- Mature B-cell neoplasms or non-Hodgkin lymphomas (NHL) and multiple myeloma, encompassing at least 60 subtypes and represents one of the most common cancers. Most cases of NHL (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.[20, 24]; and
- Precursor lymphoid neoplasms are characterised by the proliferation of immature (blast) cells of B-cell or T-cell lineage. Acute lymphoblastic leukemias (ALL) and lymphoblastic lymphomas (LBL) can occur at any age; however, they are the most common type of childhood malignancy. LBLs 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 LBL are of T-cell origin, with B-lymphoblastic lymphoma accounting for only 10 per cent of LBL cases, with disease mainly involving lymph nodes or extra-nodal sites such as the central nervous system, bone, skin, and testis. ALLs are cases with greater than 25 per cent marrow involvement. ALL is a highly aggressive neoplasm that requires intensive chemotherapy.[25, 26]

Historically, lymphoid neoplasms that present with bone marrow and blood involvement have been categorised as leukaemia, whilst those presenting as a mass as 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.[18] In addition, lymphoid neoplasms can be difficult to distinguish from non-malignant reactive lymphocytosis in the absence of a clonal marker.

As a group haematologic malignancy is a relatively common group of disorders, constituting approximately nine per cent of all cancer cases diagnosed annually, as well as being a common cause of death in patients suffering from cancer.[27] In Australia, rates of the most common haematological cancers are consistently higher in males than females, as are rates of mortality (

*Table 1* and *Table 2*).[28] 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 per cent of all cancers (n=1,002) in this age group. The most common cancer in children aged 0-14 years was leukaemia, representing 34 per cent 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.[28]

*Table 1 Incidence of haematologic cancers in Australia, by sex, 2019* [28]

| Cancer type (ICD-10 code) | Males | | Females | | Total | |
|---|---|---|---|---|---|---|
| | Cases | ASR | Cases | ASR | Cases | ASR |
| 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 |

ASR = age standardised rate

*Table 2 Rates of mortality associated with haematologic cancers in Australia, by sex, 2019* [28]

| Cancer type (ICD-10 code) | Males | | Females | | Total | |
|---|---|---|---|---|---|---|
| | Deaths | ASR | Deaths | ASR | Deaths | ASR |
| 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 | | | | |

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 1,308 cases or 418 cases per 100,000 population in persons aged 85-89 years (*Figure 1*) in 2020.[29]

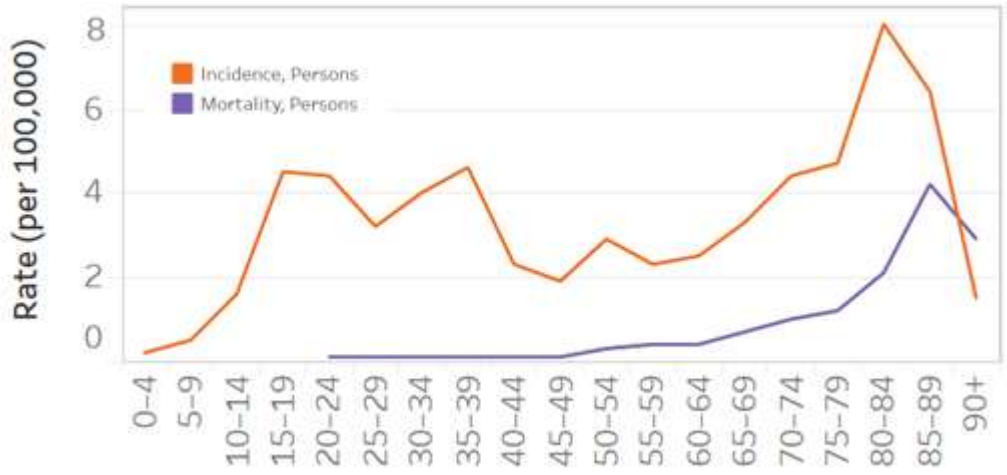


*Figure 1 Estimated age-specific rates of all haematological malignancies in Australia, 2020* [29]

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. The mortality rate almost doubles from 185 deaths, or 12 deaths per 100,000 persons, in those aged 55-59 years, to 318 deaths, or 22.4 deaths per 100,000 persons in those aged 60-64 years. When considered as a group, in 2012-2016 an average 66.7 per cent (95% CI 66.3-67.1%) of all patients with a haematological malignancy survived 5-years after diagnosis .[29]

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 42 cases, or 8 cases per 100,000 persons in 2020. The variability in incidence is not mirrored in the rate of mortality, which again is low, steadily increasing with age. On average, 87.4 per cent of patients diagnosed with Hodgkin lymphoma in 2012-2016 survived 5-years after diagnosis (95% CI 86.1-88.7%).[29]

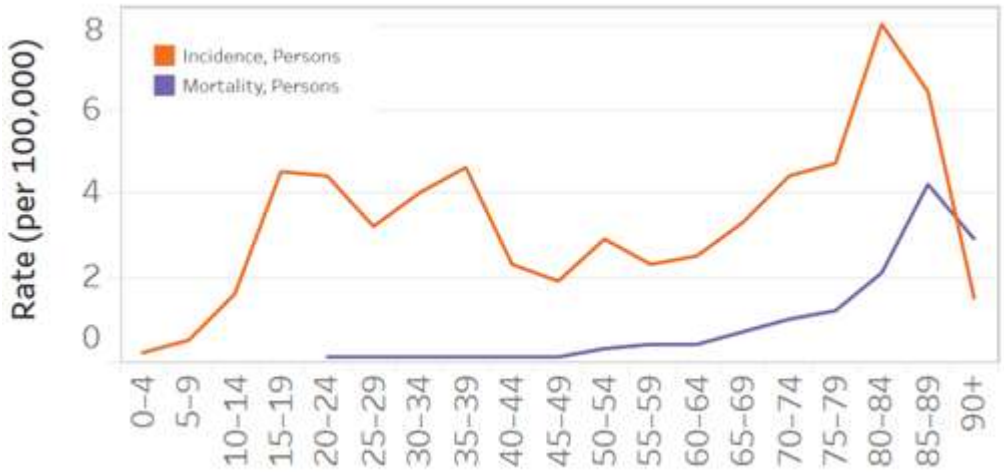


*Figure 2 Estimated age-specific rates of Hodgkin lymphoma in Australia, 2020 [29]*

The highest incidence of other cancers, such as acute lymphoblastic leukaemia, occurs in very young patients, albeit at relatively low rates (a predicted 100 cases or 6.1 cases per 100,000 persons in 2020, *Figure 3*). Mortality associated with ALL is also low, with a 5-year survival rate of 74.1 per cent.[29]

Of all the haematological cancers, lymphoma is associated with the highest incidence, estimated to peak at 448 cases, or 143.2 cases per 100,000 in 2020. Lymphoma is associated with relatively good outcomes, with a reported 5-year survival rate after diagnosis of 76.7 per cent. 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.[29]

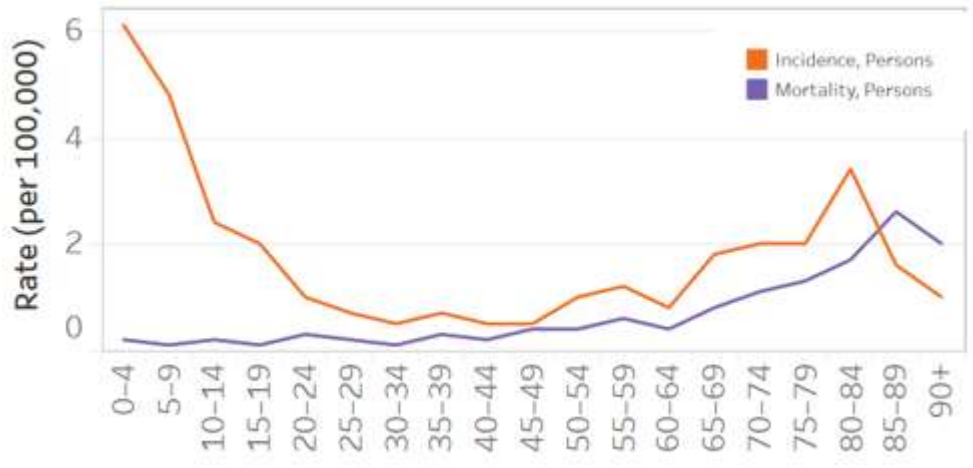


*Figure 3 Estimated age-specific rates of acute lymphoblastic leukaemia in Australia, 2020 [29]*

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

Patients 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 (2017) diagnostic criteria. In some cases, this categorisation cannot be achieved without additional genetic profiling including cytogenetic and molecular analysis.

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

If the diagnosis can be made based using the investigations described in Q25, then diagnostic testing would cease, and the patient would commence treatment specific for the individual subtype of haematological malignancy diagnosed (*Figure 4*).

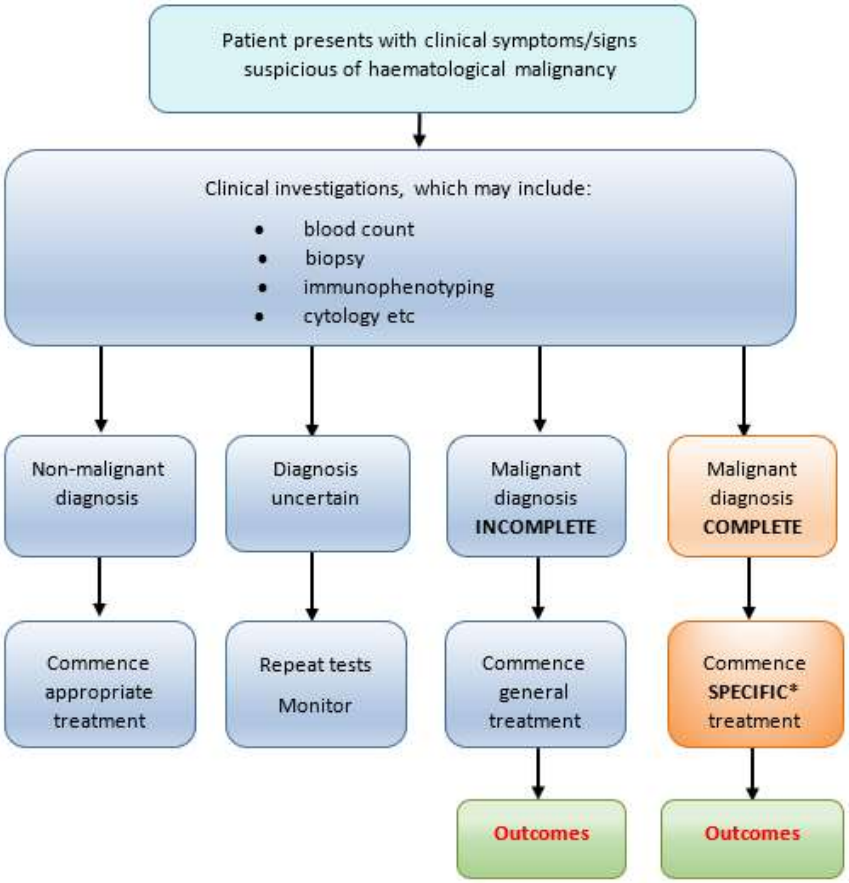


*Figure 4 Current clinical algorithm for the diagnosis of haematological malignancies*

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

- A 62 year old man with a diagnosis of T-cell lymphoma after histological analysis with immunohistochemistry of an excised lymph node. Cytotoxic chemotherapy (CHOP) was commenced. NGS was performed on the tumour specimen. Mutations typical of diffuse large B-cell lymphoma (including mutations in *SOCS1*, *SGK1*, *ID3* and translocations involving *IGH*) were identified. Treatment was changed to chemoimmunotherapy incorporating rituximab (a B-cell specific treatment). The change of diagnosis allowed patient access to the PBS subsidised therapy shown to improve survival in DLBCL as well as giving access to correct therapies should a relapse in the future.
- A 45 year old woman presented with a high white blood cell count and fever. Histological and immunophenotypic analysis of a bone marrow biopsy resulted in a diagnosis of acute myeloid leukaemia. Cytogenetic analysis revealed a normal karyotype. NGS panel testing on the bone marrow aspirate identified mutations in *NPM1*, *WT1* and *IDH2*, resulting in disease re-classification according to WHO criteria as AML with mutated *NPM1*. The patient received induction/consolidation chemotherapy followed by minimal residual disease monitoring of her *NPM1* mutation without the need for stem cell transplantation (due to her *NPM1*-mutation and favourable molecular prognosis).
- A 55 year old man presented with an enlarged spleen and pancytopenia. Examination of his bone marrow biopsy showed increased numbers of lymphocytes with villous projections. A differential diagnosis between splenic marginal zone lymphoma, hairy cell leukaemia-variant and hairy cell leukaemia was made with the pathologist unable to be definitive about the exact subtype. After molecular testing a *BRAF* mutation was detected, resulting in an amended, definitive diagnosis of hairy cell leukaemia and specific treatment, cladribine, not typically used for the other suspected disease subtypes, was commenced.
- Younger AML/MPN patients may be triaged to allogeneic bone marrow transplantation rather than consolidation chemotherapy if an ASXL1 somatic variant is identified.
- The identification of the BCR-ABL1 T315I mutation in CML patients allows access to ponatinib, which results in better outcomes compared to standard therapy.

***PART 6b – INFORMATION ABOUT THE INTERVENTION***

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

Nucleic acid is extracted 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 that focus on a certain number of genes or gene regions. 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.

Testing occurs in a NATA accredited diagnostic laboratory in accordance with NPAAC guidelines - Requirements for human medical genome testing utilising massively parallel sequencing technologies.

The results of these genomic tests are then interpreted with the rest of the pathological data of the patient to categorise the patient as per WHO 2017 diagnostic criteria.

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

N/A

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

N/A

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

Once off diagnostic test; however, proviso should be made for some patients who may experience a second, unrelated disease.

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

Nil

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

Testing would be requested by the treating clinician and provided by Approved Practising Pathologists in line with other tests on the MBS Pathology Table.

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

N/A

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

Patients should be referred by a specialist haematologist/oncologist or consultant physician.

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

Testing would be delivered only by Approved Practising Pathologists with appropriate scope of practice in NATA Accredited Pathology Laboratories (as defined in MBS Pathology table) by referral only by registered Medical Practitioners (non-pathologists) in line with other tests in the MBS Pathology Table.

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

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

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

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

- ☒ Yes
- ☐ No – please specify below

***PART 6c – INFORMATION ABOUT THE COMPARATOR(S)***

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

The nominated comparator is no gene panel 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 fluorescence in situ hybridisation 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.

The expansion of MBS item number 73325 has recently been approved by the MSAC for genetic testing for myeloproliferative neoplasms (MPNs), for both gene-specific and next generation sequencing (NGS) gene panel testing, following initial JAK2 V617F triage testing. In addition, there are a number of MBS item numbers that test for gene rearrangements and/or fusions using fluorescence in situ hybridisation (not NGS), and patients would need to undergo multiple testing for diagnosis using:

- Item 73326 for the 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.
- Item 73314 for the 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.
- Item 73369 for the characterisation of (i) TCL1A gene rearrangement; and/or (ii) MTCP1 gene rearrangement.
- Item 73364 for the 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.
- Item 73365 the characterisation of MYC gene rearrangement in patients with clinical or laboratory evidence of Burkitt lymphoma.
- Item 73366 for the characterisation of CCND1and/or CCND2 gene rearrangement(s) in patients with clinical or laboratory evidence of mantle cell lymphoma.
- Item 73368 for the characterisation of DUSP22 and/or TP63 gene rearrangement(s) in patients with clinical or laboratory evidence of ALK negative anaplastic large cell lymphoma.

However, most genetic testing of haematological malignancy patients 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 AML, MDS and many of the MPN variants requires NGS, which is not covered by existing MBS item numbers. Therefore, beside the specific item numbers as described above that use FISH, for the **majority** of patients with a haematological malignancy, the nominated comparator is no gene panel testing.

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

☐ Yes (please list all relevant MBS item numbers below)
☒ No

The true comparator is no genetic testing; however, there are several MBS item numbers for diagnostic tests that are often performed to provide initial characterisation of a haematological malignancy.

1. Full blood count to rule in/out leukaemia

   **MBS item number 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

2. Biopsy/cytology. 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.24

   **MBS item number 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

   **MBS item number 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

   **MBS item number 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

   **MBS item number 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

3. Cytogenetic testing for risk stratification in myeloid malignancies

   **MBS item number 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

4. Immunohistochemistry/ immunofluorescence

   **MBS item number 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

   **MBS item number 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

**MBS item number 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

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

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. Once diagnosed, a proportion of patients will need to undergo assessment of genomic variation in order to make a specific, definitive diagnosis that will enable the selection of the most appropriate therapy, guide prognostication and assist in monitoring the response to treatment (*Figure 5*). The number of genes and diversity of mutations that need to be assessed practically necessitates the use of massive parallel sequencing technologies.

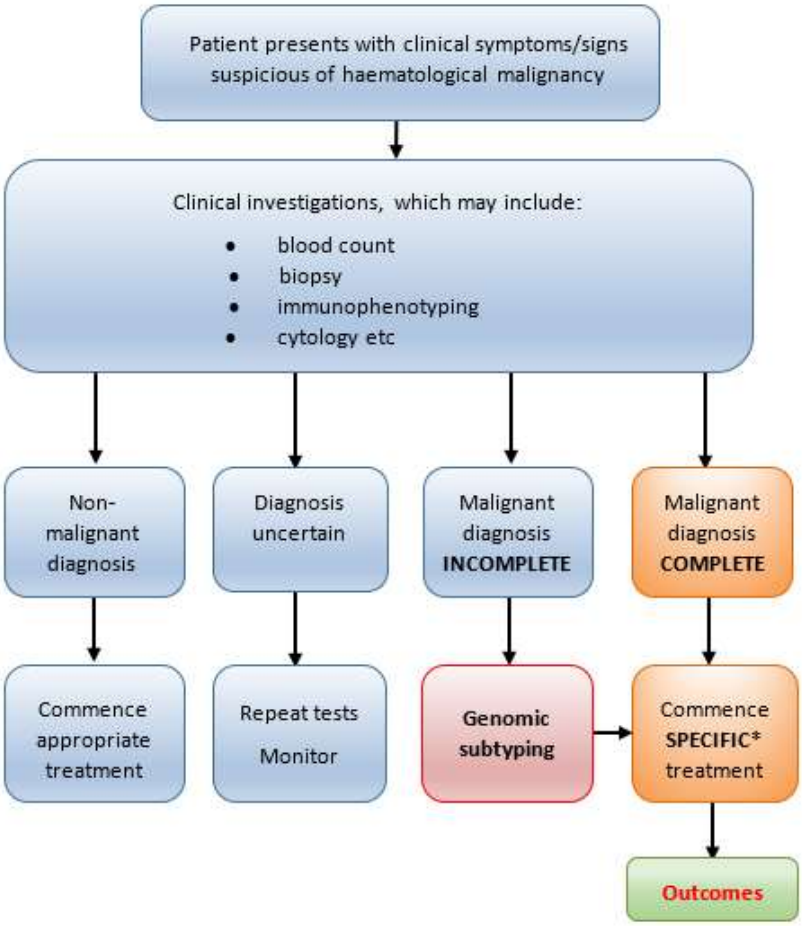


*Figure 5* *Clinical algorithm for the diagnosis of haematological malignancies using genomic subtyping*

* For details of specific treatments see examples in Q26 on page 21

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

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

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

N/A

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

Patients with haematological malignancies are clinically and genetically heterogeneous. The addition of genomic characterisation of lymphoid and myeloid neoplasms using the revised 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.

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 mutations 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, mutations 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*-mutated AML), 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 mutations in some diseases define WHO-based entities (*e.g.* myeloid neoplasms with germline *GATA2* mutations) 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.

***PART 6d – INFORMATION ABOUT THE CLINICAL OUTCOME***

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

Given that there is no current MBS item number that covers this testing, this testing is either (i) currently 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. Access to genetic testing will allow more patients to have a definitive diagnosis, resulting in better patient management and improved outcomes.

At its August 2019 meeting, MSAC supported genetic tumour testing applications 1526, 1527 and 1528. The 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.

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.[3]

**43. Please advise if the overall clinical claim is for:**

☒ Superiority
☐ Non-inferiority

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

Safety Outcomes:

Test adverse events

Adverse events from treatment

Adverse events from change in patient management

Clinical Effectiveness Outcomes:

Direct evidence:

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

Indirect evidence

Assessment of diagnostic/test accuracy: sensitivity, specificity, number of false positives, number of false negatives, number of inconclusive results

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

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

Total Australian Government healthcare costs

# PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

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

Data from the AIHW indicate that the incidence of all haematological malignancies combined has increased only marginally over time (*Figure 6*). In Australia there were an estimated 15,780 patients, or 56.0 cases per 100,000 persons, diagnosed with a haematological malignancy in 2017. In 2018, this number increased by 3.2 per cent to 16,288 patients, equivalent to an age standardised rate of 56.3 per 100,000 persons. The number of patients increased by a similar rate (3.3%) in 2019, and in 2020 (2.94%). It would be expected that this rate would remain constant over the next three years (average increase of 3.1%).[29] Expected numbers of patients with individual haematological cancers are summarised in Table 3.

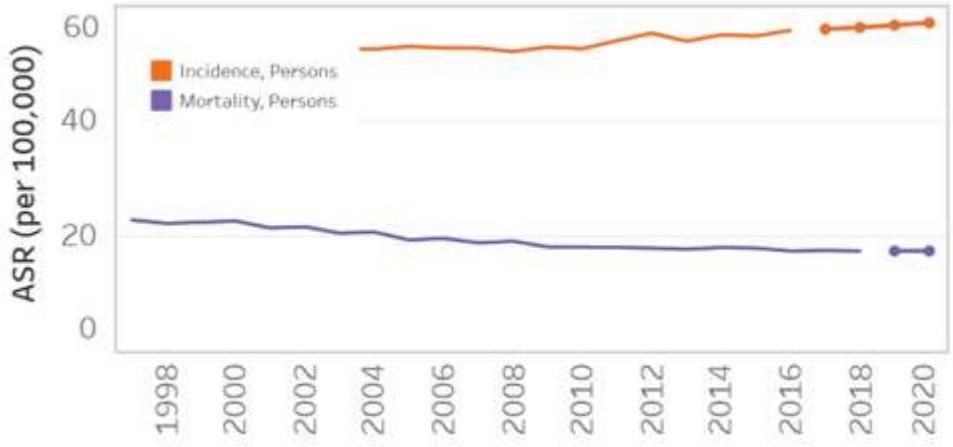


*Figure 6 Incidence of all haematological malignancies combined, Australia 1997-2020[29]*

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

Once per disease episode.

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

Once per disease episode.

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

It is estimated that the number of haematological malignancies in 2021 will increase by approximately 3.1 per cent from 2020 numbers, from 17,321 to 17,858 patients. Approximately 50 per cent of these patients may be required to undergo genomic sub-characterisation.

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

As stated above, data from the AIHW indicate that the incidence of all haematological malignancies combined has increased only marginally over time at an average rate of 3.1 per cent. 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 3.[29] Approximately 50 per cent of these patients may be required to undergo genomic sub-characterisation.

*Table 3 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 |
| 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 |

* Average increase calculated from the increase of cases each year from 2017-2020[29]

# PART 8 – COST INFORMATION

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

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 |

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

2-4 weeks

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

| **Category 6 – PATHOLOGY SERVICES –Group P7 Genetics** |
|---|
| 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 haematological malignancy.<br><br>Applicable once per diagnostic episode<br><br>**MBS Fee**: $800 Benefit: 75% = $600 85% = $680 |

See Appendix C for a full list of exemplar and facilitated genes.

# Appendix A

*Table 4 2016 WHO classification of mature lymphoid, histiocytic, and dendritic neoplasms[1]*

| 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 5 2016 WHO classification of myeloid neoplasms and acute leukaemia[2]*

| |
|---|
| 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

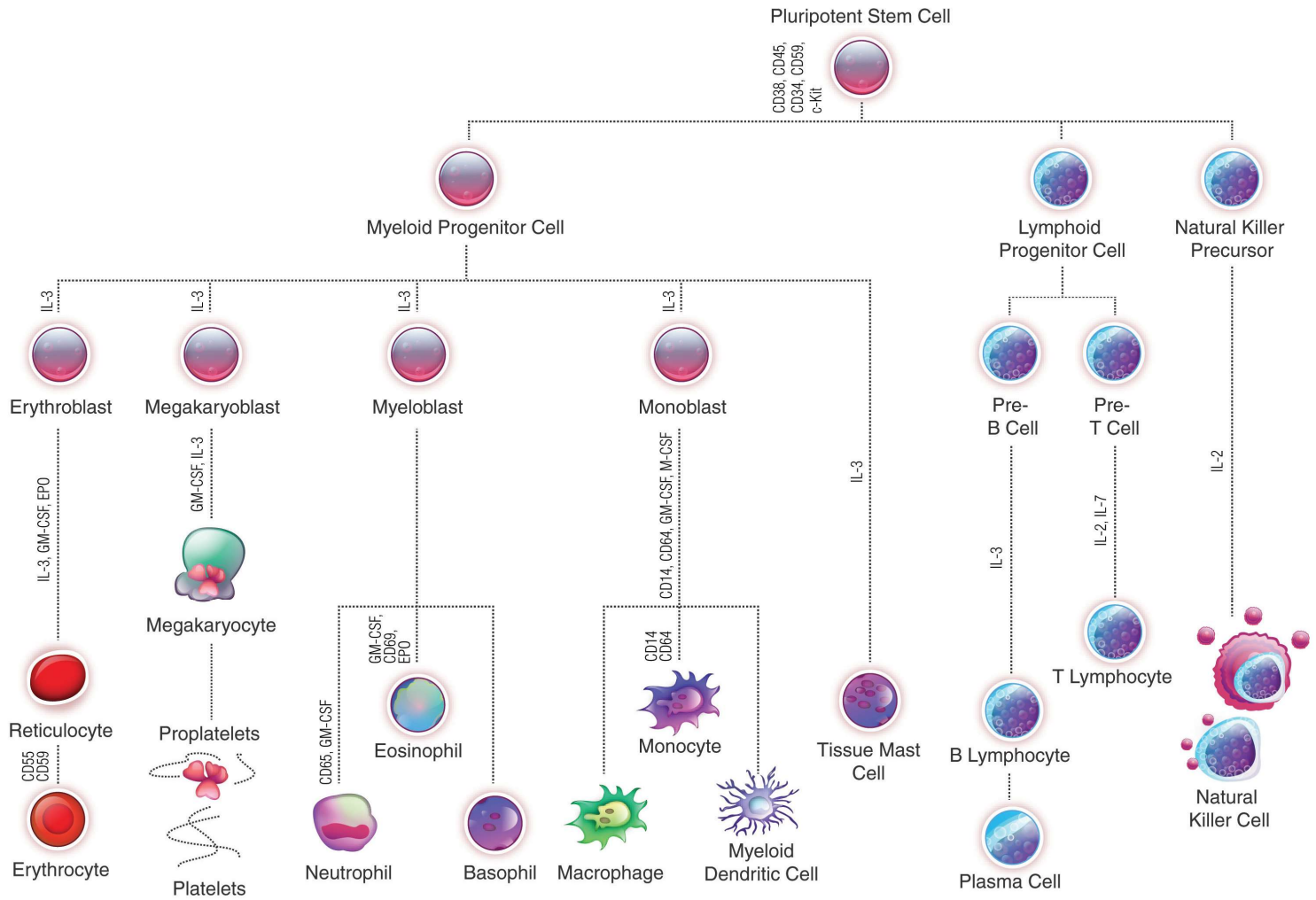


*Figure 7* *Haematopoiesis*[30]

# Appendix C

Exemplar and facilitated genes are presented as a list and tabulated, 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*

| | 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 |
| *CSF3R* | Y | | Y | | Y | Y | Y | | Y | | Y | Exemplar |
| *CTC1* | Y | | | | | Y | | | | | | Exemplar |
| *DDX41* | Y | | Y | | | Y | Y | | | | | Exemplar |

| | WHO*- | WHO** | ARCHER † | Oncomine ‡ | Oncomine # | PeterMac $ | PeterMac § | SOPHiA ¶ | SOPHiA ¥ | TruSight † † | TruSight § § | Category |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *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 |

| | 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 |

| | WHO*- | WHO** | ARCHER † | Oncomine ‡ | Oncomine # | PeterMac $ | PeterMac § | SOPHiA ¶ | SOPHiA ¥ | TruSight † † | TruSight § § | Category |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *SF3B1* | Y | | Y | Y | Y | | Y | Y | Y | Y | Y | Exemplar |
| *SLX4* | Y | | | | | | | | | | | Exemplar |
| *SRSF2* | Y | | Y | | Y | | Y | | Y | | Y | Exemplar |
| *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 |

| | WHO*- | WHO** | ARCHER † | Oncomine ‡ | Oncomine # | PeterMac $ | PeterMac § | SOPHiA ¶ | SOPHiA ¥ | TruSight † † | TruSight § § | Category |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *CDC25C* | | | Y | | | | | | | | | Facilitated |
| *CDKN2A* | | | Y | Y | | | | Y | | | Y | Facilitated |
| *CDKN2B* | | | | | | | | Y | | | | Facilitated |
| *CHD2* | | | | | | | | Y | | | | Facilitated |
| *CIITA* | | | | | | | | Y | | Y | | Facilitated |
| *CRBN* | | | | | | | Y | | | | | Facilitated |
| *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 |

| | WHO*- | WHO** | ARCHER † | Oncomine ‡ | Oncomine # | PeterMac $ | PeterMac § | SOPHiA ¶ | SOPHiA ¥ | TruSight † † | TruSight § § | Category |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *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 |
| *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 |

| | WHO*- | WHO** | ARCHER † | Oncomine ‡ | Oncomine # | PeterMac $ | PeterMac § | SOPHiA ¶ | SOPHiA ¥ | TruSight † † | TruSight § § | Category |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *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 |
| *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

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