MSAC application 1813

Detection of measurable residual disease in patients with acute myeloid leukaemia

Application for MBS eligible service or health technology

HPP Application number:

HPP200343

Application title:

Detection of measurable residual disease in patients with acute myeloid leukaemia

Submitting organisation:

THE ROYAL COLLEGE OF PATHOLOGISTS OF AUSTRALASIA

Submitting organisation ABN:

52000173231

Application description

Succinct description of the medical condition/s:

Acute myeloid leukaemia (AML) is an aggressive blood cancer that starts in the bone marrow, where normal blood cells are made. It causes the uncontrolled growth of immature white blood cells called “blasts,” which crowd out healthy cells and lead to symptoms such as fatigue, infections, and bleeding. AML often relapses even after treatment, and is associated with poor 5-year survival.

Succinct description of the service or health technology:

Measurable residual disease (MRD) testing is a highly sensitive laboratory method used to detect tiny amounts of remaining leukaemia cells after treatment; levels too low to be seen under a microscope. It helps doctors understand how well the cancer has responded to treatments, estimate the risk of relapse, and decide whether more or less intensive treatment is needed.

Application contact details

Are you the applicant, or are you a consultant or lobbyist acting on behalf of the applicant?

Applicant

Are you applying on behalf of an organisation, or as an individual?

Organisation

Applicant organisation name:

THE ROYAL COLLEGE OF PATHOLOGISTS OF AUSTRALASIA

Application details

Does the implementation of your service or health technology rely on a new listing on the Pharmaceutical Benefits Scheme (PBS) and/or the Prescribed List?

No

Is the application for a new service or health technology, or an amendment to an existing listed service or health technology?

New

Relevant MBS items

What is the type of service or health technology?

Investigative

Please select the type of investigative health technology:

Molecular diagnostic tests

Please select the type of molecular diagnostics health technology:

Other genetic test

PICO sets

Application PICO sets:

Measurable residual disease (MRD) for acute myeloid leukaemia (AML)

Purpose category:

Monitoring

Purpose description:

To monitor a condition over time.

Population

Describe the population in which the proposed health technology is intended to be used:

The proposed service is intended for patients with acute myeloid leukaemia (AML) who have achieved morphological remission (less than 5% marrow blasts) after intensive induction therapy, and in selected cases after less-intensive therapy when further treatment decisions are required. AML is an aggressive and heterogeneous blood cancer that predominantly affects older adults in Australia (but can occur at any age) and has poor long-term survival, largely due to high relapse rates. Diagnosis relies on morphology, immunophenotyping, and genetic testing, with molecular profiling used to classify patients into favourable, intermediate, or adverse ELN 2022 risk groups that guide therapy. MRD testing is especially valuable in the large and clinically variable intermediate-risk group, where it refines prognosis and supports more personalised decisions about allogeneic stem cell transplantation (allo-HSCT). MRD-positive patients can be prioritised for transplant, while MRD-negative patients may avoid the risks and substantial costs of allo-HSCT, an intensive procedure with approximately 15% treatment-related mortality and an estimated cost of $246,855 per patient.

Select the most applicable Medical condition terminology (SNOMED CT):

Acute myeloid leukaemia

Intervention

Name of the proposed health technology:

MRD-AML testing using multiparametric flow cytometry (MFC), next generation sequencing (NGS) or polymerase chain reaction (PCR) assays.

Comparator

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). This includes identifying health care resources that are needed to be delivered at the same time as the comparator service:

Following induction therapy, patients who achieve complete remission are monitored for relapse risk. Without MRD testing, this surveillance relies on full blood examination and periodic bone marrow biopsy to detect morphological relapse (morphological assessment ± cytogenetic analysis), which becomes apparent once bone marrow blasts exceed 5%. Cytogenetic analysis is also frequently performed on bone marrow aspirates. This genetic technology will allow leukaemia cell burden to be measured to approximately 5 in 100 cells if a clonal cytogenetic marker is identified.

Outcomes

Outcome description – please include information about whether a change in patient management, or prognosis, occurs as a result of the test information:

MRD detection in patients achieving complete remission (CR or CRi) has clear prognostic value across both intensive and less-intensive treatment settings. Numerous studies and meta-analyses confirm its association with relapse risk and overall survival. Detectable MRD before allo-HSCT predicts poorer post-transplant outcomes, but additional chemotherapy before transplant has not been shown to improve prognosis; such patients may instead benefit from more intensive myeloablative treatment conditioning or early immunosuppression tapering.
The strong prognostic information provided by MRD can be used to inform treatment decisions, particularly the avoidance of allo-HSCT in lower risk patients. Using an epidemiological approach, MRD-guided disease management is estimated to avoid allo-HSCT in 26 MRD-negative patients per year in Australia. These patients will avoid the high risk of severe adverse events associated with allo-HSCT, as well as the significant costs associated with allo-HSCT shared between hospital budgets and out-of-pocket co-payments (mean $246,855 per patient or ~$6.67m total; unpublished data available upon request).

Proposed MBS items

Proposed item:

AAAAA

MBS item number (where used as a template for the proposed item):

NA

Category number:

PATHOLOGY SERVICES

Category description:

P7 - Genetics

Proposed item descriptor:

Measurable residual disease (MRD) testing by next-generation sequencing, performed on bone marrow (or a peripheral blood sample if bone marrow cannot be collected) from a patient diagnosed with acute myeloid leukaemia, requested by a specialist or consultant physician practising as a haematologist or oncologist

Proposed MBS fee:

$950.00

Indicate the overall cost per patient of providing the proposed health technology:

$950.00

Please specify any anticipated out of pocket expenses:

$0.00

Provide any further details and explain:

PN.0.35 applies : The number of measurable residual disease (MRD) tests per patient, per episode of disease or per relapse is not expected to exceed 12, inclusive of a baseline assessment.

Proposed item:

BBBBB

MBS item number (where used as a template for the proposed item):

73316

Category number:

PATHOLOGY SERVICES

Category description:

GENETICS

Proposed item descriptor:

Measurable residual disease (MRD) testing by a quantitative molecular assay performed on bone marrow or peripheral blood collected from a patient diagnosed with acute myeloid leukaemia, requested by a specialist or consultant physician practising as a haematologist or oncologist

Proposed MBS fee:

$430.00

Indicate the overall cost per patient of providing the proposed health technology:

$430.00

Please specify any anticipated out of pocket expenses:

$0.00

Provide any further details and explain:

PN.0.35 Applies: The number of measurable residual disease (MRD) tests per patient, per episode of disease or per relapse is not expected to exceed 12, inclusive of a baseline assessment.

Proposed item:

CCCCC

MBS item number (where used as a template for the proposed item):

NA

Category number:

PATHOLOGY SERVICES

Category description:

P4 - Immunology

Proposed item descriptor:

Measurable residual disease (MRD) testing by flow cytometry using a panel containing a minimum of 20 antibodies, performed on bone marrow from a patient diagnosed with acute myeloid leukaemia, requested by a specialist or consultant physician practising as a haematologist or oncologist

Proposed MBS fee:

$857.00

Indicate the overall cost per patient of providing the proposed health technology:

$857.00

Please specify any anticipated out of pocket expenses:

$0.00

Provide any further details and explain:

PN.0.35 applies: The number of measurable residual disease (MRD) tests per patient, per episode of disease or per relapse is not expected to exceed 12, inclusive of a baseline assessment.

How is the technology / service funded at present? (For example: research funding; State-based funding; self-funded by patients; no funding or payments):

Despite being routinely performed, funding for MRD services is highly inconsistent across service providers. Hospitals rely on a mix of internal budgets (run at-cost or at a loss) and charitable support, with some centres asking patients for co-payments. Some patients access MRD-AML through clinical trials (e.g. AMLM26 Intercept).

Claims

In terms of health outcomes (comparative benefits and harms), is the proposed technology claimed to be superior, non-inferior or inferior to the comparator(s)?

Superior

Please state what the overall claim is, and provide a rationale:

Relative to disease surveillance with morphological examination ± cytogenetic testing, MRD testing is claimed to result in superior health outcomes, principally by enabling timely, risk-adapted interventions that improve relapse-free survival (with growing evidence for overall survival in defined subgroups). MRD positivity is the strongest prognostic indicator in AML. Relative to morphology ± cytogenetic testing without MRD testing, MRD testing enables treating clinicians to better determine which patients will benefit from allo-HSCT and which can safely avoid allo-HSCT (i.e. lower risk patients). Further, MRD monitoring of patients in remission informs sub-morphological relapse, enabling earlier intervention with fewer associated complications.

Estimated utilisation

Estimate the prevalence and/or incidence of the proposed population:
According to the Australian Institute of Health and Welfare (AIHW), the age-standardised incidence rate of AML in Australia between 2018 and 2021 was approximately 4 cases per 100,000 persons, corresponding to between 1,180-1,280 new diagnoses annually. AML represents a small but clinically significant proportion of new leukaemia cases (~7%), with incidence increasing markedly with age; most diagnoses occur in individuals aged over 60 years.
Guidelines recommend MRD assessment in patients who achieve complete remission (i.e. to monitor disease burden below morphological cut-offs), to guide management

decisions. Of the ~1,280 patients newly diagnosed with AML in Australia each year, approximately 65% (n=832) that are candidates for induction therapy will achieve remission, with rates varying by age and other prognostic factors. This is an optimistic estimate (upper estimate), as not all patients will be candidates for, or elect to undergo, induction chemotherapy.
The prevalence of AML is substantially lower than other blood cancers, owing to its relatively poor 5-year survival (27%). The AIHW reports 100,764 Australians were living with a leukaemia diagnosis up to the end of 2021; of these, 3,695 were living with AML. This low prevalence relative to the incidence rate reflects the poor prognosis of AML.

Provide the percentage uptake of the proposed health technology by the proposed population:

Year 1 estimated uptake (%):
MFC 50 / qPCR 22 / NGS 15

Year 2 estimated uptake (%):
MFC 55 / qPCR 27 / NGS 20

Year 3 estimated uptake (%):
MFC 60 / qPCR 32 / NGS 25

Year 4 estimated uptake (%):
MFC 65 / qPCR 37 / NGS 30

Estimate the number of patients who will utilise the proposed technology for the first full year:
MRD-MFC is recommended in 100% of AML cases, MRD-NGS in 30% (i.e. FLT3), and qPCR in 37-49 % (CBF-AML and NPM1). However, not all eligible patients will receive MRD testing due to access, clinical decisions, delays, patient preferences, or death. An audit of MRD testing from Western Australia suggests adherence to ELN MRD recommendations varies substantially based on a range of factors. Based on real-world uptake, it can be conservatively assumed that 50% of eligible patients will undergo MRD testing at the optimal timepoints in practice. Uptake estimates (above) were calculated by applying these assumptions to the proportion of the 843 eligible cases (i.e. new AML cases expected to achieve remission following induction therapy). Uptake is expected to improve over time, as the availability of an MBS item will remove a substantial barrier to testing for many patients.
Based on the above assumptions (i.e. estimated uptake % multiplied by the eligible population n=832), the number of patients estimated to uptake each service in the

first full year is:

- MRD-MFC: 416
- MRD-NGS: 125
- MRD-PCR: 183

Will the technology be needed more than once per patient?
Yes, multiple times

Over what duration will the health technology or service be provided for a patient? (preferably a number of years):
3 years

Optionally, provide details:
Monitoring of MRD is recommended by current clinical practice guidelines as part of the standard management of AML for up to 3 years per disease episode. Specifically, the ELN guideline recommends MRD testing during treatment, and for up to 2 years post-treatment. Noting that ninety percent of patients who relapse after an allo-HSCT do so within 2 years, and further treatments may be initiated, we propose that the frequency of testing not be limited per patient. Ultimately, the duration of testing will be naturally limited by the relatively poor 5-year survival of the disease.

What frequency will the health technology or service be required by the patient over the duration? (range, preferably on an annual basis):
Different tests will be required at different frequencies depending on the subtype of AML. Figure 1 in the PICO Set outlines the recommended frequency of MRD assessments for different subtypes of AML per the ELN guidelines. To summarise:
- NPM1 patients are recommended to undergo MRD-PCR testing at diagnosis, after 2 cycles, at the end of treatment, and every 3 months post-treatment for up to 2 years.
- FLT3 patients are not included in the current ELN guideline, but will be included in a coming update. Local guidelines from ALLG (not publicly available) recommend testing every 2-3 months post-treatment for up to 2 years. Note: over half of FLT3-ITD patients also have NPM1, and both tests are only needed at certain time points (after induction and before transplant). Otherwise typically just NPM1 is performed.
- CBF-AML patients are recommended to undergo MRD-PCR testing at diagnosis, after 2 cycles, at the end of treatment, and every 4-6 weeks post-treatment for up to 2 years.
- All AML patients are recommended to undergo MRD-MFC testing at diagnosis, after 2 cycles, the end of treatment, and every 3 months post-treatment for up to 2 years.

Consultation

List all entities that are relevant to the proposed service / health technology. The list can include professional bodies / organisations who provide, request, may be impacted by the service/health technology; sponsor(s) and / or manufacturer(s) who produce similar products; patient and consumer advocacy organisations or individuals relevant to the proposed service/health technology.

Entities who provide the health technology/service:

HAEMATOLOGY SOCIETY OF AUSTRALIA AND NEW ZEALAND

PATHOLOGY AUSTRALIA LIMITED

THE ROYAL COLLEGE OF PATHOLOGISTS OF AUSTRALASIA

PUBLIC PATHOLOGY AUSTRALIA

Entities who request the health technology/service:

HAEMATOLOGY SOCIETY OF AUSTRALIA AND NEW ZEALAND

AUSTRALIAN AND NEW ZEALAND CHILDREN'S HAEMATOLOGY/ONCOLOGY GROUP

AUSTRALASIAN LEUKAEMIA & LYMPHOMA GROUP

THE LEUKAEMIA FOUNDATION OF AUSTRALIA LIMITED

Entities who may be impacted by the health technology/service:

THE ROYAL AUSTRALASIAN COLLEGE OF PHYSICIANS

Patient and consumer advocacy organisations relevant to the proposed service/health technology:

CONSUMERS HEALTH FORUM OF AUSTRALIA LTD

THE LEUKAEMIA FOUNDATION OF AUSTRALIA LIMITED

RARE CANCERS AUSTRALIA LTD

RARE VOICES AUSTRALIA LTD

Regulatory information

Would the proposed health technology involve the use of a medical device, in-vitro diagnostic test, radioactive tracer or any other type of therapeutic good?
Yes

Has it been listed or registered or included in the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)?
No

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

Is the therapeutic good to be used in the service exempt from the regulatory requirements of the Therapeutic Goods Act 1989?
No

Is the therapeutic good classified by the TGA as for Research Use Only (RUO)?
No

Is the therapeutic good in the process of being considered by the TGA?
No

Please provide details of when you intend to lodge an ARTG inclusion application, or provide a rationale if you do not intend to lodge an ARTG inclusion application:

Each method related to the proposed services (MFC, qPCR, NGS) are currently conducted as in-house IVDs in laboratories that are NATA accredited within the scope of the application. For example, the Alfred Pathology Service has NATA accreditation for FLT3-ITD (NGS) and NPM1 (PCR) mutation testing. The Sydney Children's Hospitals Network (Randwick and Westmead), NSW Health Pathology, and Pathology Queensland Central Laboratory have NATA accreditation for MFC AML-MRD. These are searchable via the NATA website, and are examples of existing services but do not constitute an exhaustive list.