Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1703 – Detection of measurable residual disease in patients with acute lymphoblastic leukaemia

Applicant: **Royal College of Pathologists of Australasia**

Date of MSAC consideration: **30-31 March 2023**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of tests to detect measurable residual disease (MRD) in patients with acute lymphoblastic leukaemia (ALL) was received from the Royal College of Pathologists of Australasia (RCPA) by the Department of Health and Aged Care.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC supported the creation of new Medicare Benefits Schedule (MBS) items for the development and subsequent use of patient-specific quantitative molecular assays to detect measurable residual disease (MRD) in patients with acute lymphoblastic leukaemia (ALL). MSAC recalled it had already supported public funding of MRD testing using flow cytometry and next-generation sequencing (NGS) methods, and considered that testing using quantitative molecular methods is complementary to these methods. MSAC supported public funding of MRD testing using quantitative molecular methods because it recognised the clinical benefit of MRD testing, and accepted that MRD testing in patients with ALL had non-inferior safety and provided diagnostic, prognostic and/or predictive utility. MSAC also considered that MRD testing is the established standard of care in Australia for both paediatric and adult ALL patients, and public funding would improve equity of access to Pharmaceutical Benefits Scheme (PBS)-listed blinatumomab. MSAC advised MRD testing using quantitative molecular methods had acceptable cost-effectiveness and financial cost to the MBS. MSAC also considered that peripheral blood samples are acceptable for the development and use of the quantitative molecular assay in situations where a bone marrow sample is not obtainable.

Table 1 MSAC's supported MBS item descriptors

Category 6 – Pathology Services	Group P7 Genetics
MBS item CCCC Development of a quantitative patient-specific molecular assay for measurable residual disease (MRD) based on the diagnostic bone marrow specimen (or a peripheral blood sample if bone marrow cannot be collected) from a patient diagnosed with acute lymphoblastic leukaemia (ALL) treated with combination chemotherapy or after salvage therapy, requested by a specialist or consultant physician practising as a haematologist or oncologist. Includes use on the first MRD specimen for one test described in item DDDD. Not to be performed in conjunction with a service to which DDDD applies. Applicable not more than once per patient per episode of disease or per relapse. Fee: $3,000.00 Benefit: 75% = $2,250.00 85% = $2,906.80	
MBS item DDDD Measurable residual disease testing by a quantitative patient-specific molecular assay on bone marrow (or in a patient with T-cell acute lymphoblastic leukaemia (ALL), a peripheral blood sample if bone marrow cannot be collected) from a patient diagnosed with acute lymphoblastic leukaemia (ALL) treated with combination chemotherapy or after salvage therapy, requested by a specialist or consultant physician practising as a haematologist or oncologist. Not to be performed in conjunction with a service to which CCCC applies. Fee: $780.00 Benefit: 75% = $585.00 $85% = $686.80	
Practice Note (CCCC, DDDD): 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.	

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

Consumer summary

This was an application from the Royal College of Pathologists of Australasia (RCPA) requesting Medicare Benefits Schedule (MBS) listing of measurable residual disease testing in patients who have a type of blood cancer called acute lymphoblastic leukaemia or ALL.

ALL is caused when a genetic variant (genetic difference) arises in a person's white blood cells that makes the cells multiply more than they should. There are lots of different genetic variants that can do this, and the one that has arisen is often different from one patient to the next. Patients get treatment to try and kill the cancer cells, then to check how well it has worked. There are tests that either look for cells with the specific genetic variant that is causing the cancer in that patient, or look at a range of genetic variants that can cause ALL. These tests usually use a bone marrow sample because the bone marrow is where white blood cells are made.

When a patient has measurable residual disease (or MRD), this means they have a small number of cancer cells that cannot be seen with a microscope, but can be detected using genetic tests. Detecting measurable residual disease means a patient's cancer is more likely to return (known as relapse), and patients and clinicians can use this information to change the patient's treatment.

There are several scientific methods that can be used to test for measurable residual disease in a laboratory, including multiparametric flow cytometry (mpFC), next-generation sequencing (NGS) and quantitative polymerase chain reaction (qPCR). Measuring MRD using qPCR requires the laboratory to develop a qPCR assay (test) specifically for the genetic variant that is causing each patient's ALL. Not all types of cancer-causing genetic variants can be detected

Consumer summary
using every testing method, so one MRD testing method will not work for all patients, and different MRD testing method options need to be available. MSAC already supported public funding of MRD testing using mpFC and NGS methods in November 2022, so the method left to be considered under this application was qPCR. MSAC previously accepted that testing for measurable residual disease is routine health care in Australia for patients with ALL, and that measuring measurable residual disease results in better health outcomes for patients, including longer survival and access to the Pharmaceutical Benefits Scheme (PBS)-funded treatment blinatumomab. MRD testing is safe as it usually doesn't require any extra bone marrow samples to be collected. MSAC considered that MRD testing using qPCR was also better than only looking to see if there are cancer cells left using cell morphology (looking under a microscope). MSAC advised it was important that multiple MRD testing methods be funded, because not all methods will work for all patients. MSAC considered that MRD testing using qPCR methods was acceptably cost-effective, and that the financial cost to the MBS of MRD testing overall across all three methods would be acceptable. Therefore, MSAC supported public funding of measurable residual disease testing using qPCR methods. While MRD testing usually uses bone marrow samples, when a patient is first diagnosed with ALL there are also many cancerous white blood cells in their blood, so MSAC advised that blood samples could also be used to develop the qPCR assay to detect that patient's specific genetic variant. Then later after treatment when MRD testing is being used, there will be a small number of patients who will not be able to provide a bone marrow sample. MSAC advised that in patients with a type of ALL called T-ALL and where a bone marrow sample is not obtainable, a blood sample could also be used for MRD testing using qPCR methods. **MSAC's advice to the Commonwealth Minister for Health and Aged Care** MSAC supported listing measurable residual disease (MRD) testing using qPCR on the MBS for patients with ALL, including an item to develop the patient-specific assay and use it the first time, and an item to subsequently use the developed MRD assay. MSAC considered MRD testing using qPCR methods to be safe, effective, good value for money, and to have an acceptable total financial cost to the MBS.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that this application from the Royal College of Pathologists of Australasia (RCPA) was initially for MBS items for testing for MRD in patients with ALL using multiparametric flow cytometry (mpFC; item AAAA), NGS (item BBBB), and the development and first use (item CCCC) and subsequent use (item DDDD) of a patient-specific quantitative polymerase chain reaction (qPCR) MRD assay. MSAC recalled it had already supported MRD testing using mpFC and NGS methods at its November 2022 meeting (MSAC application 1707)[1]. Therefore, only MRD testing using qPCR methods, i.e. items CCCC and DDDD, remained for MSAC's consideration under Application 1703.

MSAC recalled that, for Application 1707, it had already accepted that:

- MRD testing in patients with ALL had non-inferior safety; provided diagnostic, prognostic and/or predictive utility; and had acceptable cost-effectiveness using mpFC and NGS methods.

[1] MSAC 1707 PSD, available at: http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1707-public

- MRD testing represented established standard of care for patients with ALL, and public funding would improve inequity of access to PBS-listed blinatumomab.
- Having multiple methods of MRD testing available to patients is important as they are complementary; one method alone will not detect the variant present in every patient.
- Requestors should be restricted to haematologists and oncologists.
- There was unlikely to be overuse of MRD testing or utilisation outside the intended population of patients with ALL.

MSAC noted consultation feedback from the Leukaemia Foundation suggested that eligibility for the proposed services could be extended to patients with acute myeloid leukaemia (AML), however MSAC considered that the proposed MRD testing would not be able to detect the types of variants found in patients with AML so advised that including AML within this consideration would not be appropriate. MSAC noted that no evidence for MRD testing in patients with AML or other haematological malignancies was considered in this application, as the PICO defined the population as patients with ALL only. However, once evidence is available, an MSAC application could be lodged for other populations.

MSAC recalled that it advised that the proposed maximum of 12 services per episode of disease is appropriate and should apply across all testing modalities, and that an episode of disease may be difficult to define, and it should be made clear that cancer relapse is considered a new episode of disease. In November 2022, MSAC recommended that these details move from the MBS item descriptor to a Practice Note.

MSAC noted ESC's concerns around whether the methodology for the intervention had been defined inconsistently given it was variously presented as PCR, qPCR and ASO-qPCR in the DCAR, and queried whether the proposed MBS item was intended to be restricted to ASO-qPCR given its proposed fee was based on the cost to conduct ASO-qPCR. MSAC noted that in the pre-MSAC response the applicant clarified that it had not intended to limit the MBS item to ASO-qPCR: any qPCR methodology would be appropriate (but not RT-PCR). Therefore the applicant proposed the wording 'quantitative patient-specific molecular assay'. MSAC considered that the intervention was therefore MRD testing using qPCR methods in general (including but not limited to ASO-qPCR), and agreed the item descriptor should describe this method as a "quantitative patient-specific molecular assay". MSAC considered that while typically MBS item descriptors are method-agnostic, it was appropriate to state the method in this case because there are multiple MRD testing methodology options available at different fees.

MSAC also noted ESC had raised whether peripheral blood samples could be an alternative sample type both to develop the assay and to subsequently use it, because at diagnosis there are high levels of blasts in the blood, and for subsequent MRD testing not all patients are able to provide a bone marrow sample. MSAC noted the Haematology Society of Australia and New Zealand (HSANZ) commented that the molecular abnormality is the same in both bone marrow and peripheral blood, and so agreed that it would be appropriate to permit a peripheral blood sample to be used both for assay development and subsequent MRD testing where a bone marrow sample is not available, and that the literature supported this. In the pre-MSAC response, the applicant agreed blood samples could be used for assay development, but for subsequent MRD testing commented that there was poor concordance between blood and bone marrow for patients with B-ALL so blood samples should only be permitted for MRD testing in patients with T-ALL. MSAC considered that a bone marrow sample was preferred so this sample type should remain the default, although the use of peripheral blood where a bone marrow sample was unavailable was acceptable for qPCR assay development in all ALL patients, and for subsequent MRD testing in patients with T-ALL. MSAC considered that there was insufficient evidence for it to

advise whether peripheral blood samples could also be used for MRD testing using mpFC or NGS methods, and noted the department was planning to seek advice from the sector on this.

MSAC noted that in the pre-MSAC response, the applicant justified the proposed fee of $3,000 for item CCCC (development and first use of patient-specific qPCR assay) by providing details of the substantial workflow required to develop patient-specific assays. MSAC considered the proposed fees for CCCC and DDDD were appropriate.

MSAC recalled that under application 1707, it had supported moving the maximum of 12 MRD tests "per episode of disease or per relapse" from the item descriptor to a practice note. MSAC considered that the proposed maximum of 12 services per episode of disease should apply across all testing modalities. MSAC noted the practice note clarified that relapse is also considered a new episode of disease, and considered that was important to make clear that relapse was also considered to be an "episode of disease", warranting up to a further 12 MRD tests. MSAC supported the practice note for MRD testing using mpFC and NGS methods also applying to items CCCC and DDDD for MRD testing using qPCR methods.

MSAC noted that the intervention and the comparator (morphological assessment ± cytogenetic analysis) both required bone marrow sampling so typically no additional clinical procedures are needed to allow MRD testing to take place. Consequently MSAC considered it unlikely that the qPCR assay introduces any additional safety concerns. MSAC noted that one study showed that MRD-directed chemotherapy reduced infection-related morbidity in children with ALL compared to conventional chemotherapy, and considered that MRD testing may have superior safety.

MSAC agreed with ESC's conclusions that "the limited available evidence showed qPCR performed better than morphological assessment in detecting MRD, although was insufficient to determine whether NGS or qPCR was superior as it was comprised of studies with small sample sizes that reported variable concordance rates" and that "the heterogeneity between studies made it difficult to conclude the most effective threshold of sensitivity for qPCR, although it showed that qPCR was more effective at higher thresholds of sensitivity of detection rather than lower when compared with morphological assessment". MSAC considered it was difficult to draw conclusions on concordance between mpFC, qPCR and NGS methods due to heterogeneity among studies. MSAC noted that qPCR is the method of choice in international ALL trials registered in Europe. MSAC considered that different MRD testing methodologies were complementary, and that publicly funding qPCR in addition to mpFC and NGS methods was important for improving access to methods that may be required for some patients.

MSAC considered that MRD testing overall was effective, because MRD positivity directed more intense treatments compared to MRD negativity, resulting in improved health outcomes, greater survival benefits and lower likelihood of relapse. MRD positivity is also required to be able to access PBS-listed blinatumomab, so publicly funding MRD testing will improve access to this publicly funded drug. Overall, MSAC agreed that MRD testing (using mpFC, qPCR or NGS methods) resulted in superior effectiveness and non-inferior safety compared to the comparator (morphological assessment ± cytogenetic analysis).

MSAC noted that the economic evaluation was a cost-utility analysis and a cost-effectiveness analysis of MRD testing against morphological assessment alone, and the model included three test methods, up to four lines of treatment, and both paediatric and adult populations. MSAC noted that incremental cost-effectiveness ratios (ICERs) per quality-adjusted life year (QALY) were presented separately for each method and combined across all three methods, and that the ICERs for qPCR alone were $7,334 and $30,821 for adult and paediatric patients, respectively (including post-ESC updates to include a re-biopsy rate of 4%). MSAC noted that in the sensitivity analysis, the highest ICERs were $16,500/QALY for adults and about $45,000/QALY for the paediatric population. MSAC noted that the ICER for all three MRD methods combined was a little

higher than for qPCR alone, although considered that MRD testing overall was highly cost-effective. MSAC noted that using the effective price of blinatumomab rather than the PBS-listed price further improved the cost-effectiveness of MRD testing.

MSAC noted that whereas under application 1707 the estimated service volumes (and cost to the MBS) of MRD testing had been divided across only two methods, with its support for qPCR under 1703 splitting the total service volume across three methods was now appropriate. MSAC noted the Department-contracted assessment report (DCAR) had estimated mpFC = 24%, NGS = 38% and qPCR = 38%. MSAC considered that whilst there was little evidence supporting these estimates, the estimated split across the three methods was acceptable for the current consideration. MSAC considered data on the relative use of the MRD testing methods could be examined through post-listing review, and for this reason recommended a review of all three MRD testing items in the future that includes the relative usage of the three methods.

MSAC noted the annual budget impact of MRD testing to the MBS (including revisions to incorporate ESC's advice) ranged from $2.4 million to $2.7 million. MSAC noted that estimated utilisation had been estimated in the DCAR to be a little lower than the estimates in Application 1707, but that updates to address ESC's advice (to add a re-biopsy rate of 4% and patients relapsing within the first two years) resulted in the total cost of MRD testing to the MBS now essentially aligning across the two applications. MSAC advised the financial cost of MRD testing to the MBS was acceptable.

MSAC noted that ESC had considered it unclear whether an external quality assurance (EQA) programme was available internationally, and that in the pre-MSAC response the applicant had clarified that one international EQA has been run by the EuroMRD network since 2001, which includes at least one MRD PCR laboratory in Australia.

4. Background

Application 1707 also requested MBS funding for MRD testing, specifically using the clonoSEQ® and/or mpFC. The PICOs for 1703 and 1707 were jointly considered by PASC in April 2022. Application 1707 was considered by ESC in October 2022 and MSAC in November 2022.

The applicant stated that MRD testing is currently undertaken in addition to morphological assessment and/or cytogenetic analysis in inpatient and outpatient settings using a range of techniques, and has been standard practice for children with ALL in Australia for over 10 years (MSAC application form 1703, RCPA 2022). However, the cost of MRD testing is currently borne by patients through out-of-pocket expenses, or hospitals and oncology departments through donated funds (RCPA comment, Ratified PICO 1703, pg. 17), and therefore issues surrounding equity of access to MRD testing through existing funding are apparent. With MBS funding, it is expected that within a short period of time bone marrow morphology would be completely replaced by other MRD testing methods for the purpose of identifying MRD in patients with ALL. Bone marrow morphology and cytogenetic testing will still be performed in addition to MRD testing to establish baseline and comparative patient samples for testing.

5. Prerequisites to implementation of any funding advice

The National Pathology Accreditation Advisory Council (NPAAC) advised that key implementation issues are that the selected assay will need to be validated to establish it meets the required sensitivity level according to NPAAC In House IVD Standard and overseen by the Therapeutic Goods Administration (TGA) and the National Association of Testing Authorities (NATA), and the need for an EQA program, which may be available internationally.

6. Proposal for public funding

The applicant proposed the intervention be publicly funded through the MBS.

The proposed MBS item descriptors as advised by PASC are presented in Table 2 (mpFC AAAA, generic NGS BBBB, qPCR assay design and first use CCCC, and qPCR assay subsequent use DDDD). Note that the item descriptors as advised by PASC (in April 2022) and assessed by the DCAR do not reflect MSAC's subsequent support for MRD testing using mpFC and NGS methods (under application 1707 in November 2022).

Table 2 MBS item proposed for MRD testing

Category 6 – Pathology services **Group P4 Immunology**
MBS item AAAA Measurable residual disease testing by flow cytometry performed on bone marrow from a patient diagnosed with acute lymphoblastic leukaemia (ALL) treated with combination chemotherapy treatment or after salvage therapy, requested by a specialist or consultant physician practising as a haematologist or oncologist. Maximum of 12 per course of disease for AAAA, BBBB, CCCC, DDDD, and EEEE combined
Fee: $550.00 Benefit: 75% = $412.50 85% = $467.50
Category 6 – Pathology services Group P7 Genetics
MBS item BBBB Measurable residual disease testing by a quantitative molecular methodology on bone marrow from a patient diagnosed with acute lymphoblastic leukaemia (ALL) treated with combination chemotherapy or after salvage therapy, requested by a specialist or consultant physician practising as a haematologist or oncologist other than a service to which item CCCC, DDDD or EEEE applies. Maximum of 12 per course of disease for AAAA, BBBB, CCCC, DDDD, and EEEE combined Fee: $1,550.00 Benefit: 75% = $1,162.50 85% = $1,456.80*
MBS item CCCC Development of a patient-specific quantitative assay for measurable residual disease (MRD) based on the diagnostic bone marrow specimen from a patient diagnosed with acute lymphoblastic leukaemia (ALL) treated with combination chemotherapy or after salvage therapy, requested by a specialist or consultant physician practising as a haematologist or oncologist, and use on the first MRD specimen for one test described in item DDDD. Applicable not more than once per patient per course of disease Maximum of 12 per course of disease for AAAA, BBBB, CCCC, DDDD, and EEEE combined Fee: $3,000.00 Benefit: 75% = $2,250.00 85% = $2,906.80*
MBS item DDDD Measurable residual disease testing by a quantitative patient-specific assay on bone marrow from a patient diagnosed with acute lymphoblastic leukaemia (ALL) treated with combination chemotherapy or after salvage therapy, requested by a specialist or consultant physician practising as a haematologist or oncologist. Maximum of 12 per course of disease for AAAA, BBBB, CCCC, DDDD, and EEEE combined Fee: $780.00 Benefit: 75% = $585.00 $85% = $686.80*

* 85% benefit reflects the 1 November 2022 Greatest Permissible Gap (GPG) of $93.20. All out-of-hospital Medicare services that have an MBS fee of $621.50 or more will attract a benefit that is greater than 85% of the MBS fee – being the schedule fee less the GPG amount. The GPG amount is indexed annually on 1 November in line with the Consumer Price Index (CPI) (June quarter).
Source: MSAC application 1703 and Ratified PICO 1703
Abbreviations: ALL, acute lymphoblastic leukaemia

The proposed MBS fee for MRD testing by mpFC is $550 (benefit: 75% = $412.50, 85% = $467.50), which factors in the cost of cell processing and data capture, reagents used, scientific labour cost and instrument amortisation.

MRD testing by mpFC is expected to take two days after sampling.

The significant costs associated with developing a patient-specific qPCR assay drew concern regarding out-of-pocket costs potentially borne by patients. As such, PASC suggested three separate MBS items to describe molecular methods for the detection of MRD including generic NGS (BBBB) and initial (CCCC) and subsequent (DDDD) ASO-qPCR MBS items. Both the RCPA (applicant for 1703) and Adaptive Biotechnologies (applicant for 1707) commented that they expect that if the proposed MBS items are listed with the proposed fees, there will be no out-of-pocket costs for patients.

MSAC application 1703 initially proposed that testing using any molecular method should have a fee of $1,150, which was a weighted estimate proposed on the bases that it was equivalent to what NGS was suggested to cost, lower than the suggested initial ASO-qPCR cost, and higher than the cost of subsequent ASO-qPCR testing (after the patient-specific assay has been developed). Prior to PASC consideration, the applicant increased its proposed fee for generic NGS testing to $1,550 to reflect that batching of samples was unlikely to take place in smaller laboratories.

Furthermore, the additional ASO-qPCR items include an item for development of the patient specific assay for qPCR and the first test using this assay with a fee of $3,000.00 and an item for subsequent testing using the patient specific assay for qPCR with a fee of $780.00.

7. Population

One PICO set was defined in the PICO confirmation.

The target population for this application are patients diagnosed with acute lymphoblastic leukaemia (ALL) being monitored for response to treatment or suspected ALL relapse. The World Health Organization (WHO) has classified ALL into B-cell ALL (B-ALL) with genetic abnormalities, B-cell ALL not otherwise specified, and T-cell ALL (T-ALL).

MRD testing is currently undertaken in addition to morphological assessment and/or cytogenetic analysis. MRD testing is expected to be conducted in addition to bone marrow morphology and/or cytogenetic testing.

Flow cytometry and molecular methods for MRD detection are considered complementary as many individuals may be followed with both methodologies, but in some ALL cases only one of these methods is able to identify the patient's dominant leukaemic clone. Once a marker has been identified using one method, then patients are likely to continue to have their MRD tested using that method, though some patients may switch during the course of their disease. The applicant expects that most patients would have MRD monitored by one or both of the proposed methods.

8. Comparator

In the absence of MRD testing, patients with ALL are diagnosed with relapse via bone marrow morphology, with or without cytogenetic analysis, which is nominated as the comparator (Ratified PICO 1703). Patients undergo bone marrow extractions after each subsequent treatment phase to provide evidence of treatment response. Bone marrow morphological testing can detect morphological relapse but not MRD, because MRD is defined as being sub-microscopic. Cytogenetic testing includes methods such as fluorescence in situ hybridisation (FISH).

The MBS items relevant to morphological assessment and cytogenetic analysis are described in Table 3. Note that the below items are nonspecific to ALL; thus, MBS statistics are unable to provide data on the number of services performed per year specifically for patients with ALL.

Table 3 MBS items for morphological assessment and cytogenetic analysis

MBS items relevant to comparator for Application 1703
MBS item 65087 Bone marrow - examination of aspirated material (including clot sections where necessary), including (if performed): any test described in item 65060, 65066 or 65070 Fee: $83.10 Benefit: 75% = $62.35 85% = $70.65
MBS item 73290 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
MBS item 73314 Characterisation of gene rearrangement or the identification of mutations within a known gene rearrangement, in the diagnosis and monitoring of patients with laboratory evidence of: (a) acute myeloid leukaemia; or (b) acute promyelocytic leukaemia; or (c) acute lymphoid leukaemia; or (d) chronic myeloid leukaemia; Fee: $230.95 Benefit: 75% = $173.25 85% = $196.35
MBS item 73315 A test described in item 73314, if rendered by a receiving APP - 1 or more tests (Item is subject to rule 18) Fee: $230.95 Benefit: 75% = $173.25 85% = $196.35
MBS item numbers used for services performed to obtain the bone marrow sample
MBS item number 20440 INITIATION OF MANAGEMENT OF ANAESTHESIA for percutaneous bone marrow biopsy of the sternum (4 basic units) Fee: $82.40 Benefit: 75% = $61.80 85% = $70.05
MBS item number 21112 INITIATION OF MANAGEMENT OF ANAESTHESIA for percutaneous bone marrow biopsy of the anterior iliac crest (4 basic units) Fee: $82.40 Benefit: 75% = $61.80 85% = $70.05
MBS item number 21114 INITIATION OF MANAGEMENT OF ANAESTHESIA for percutaneous bone marrow biopsy of the posterior iliac crest (5 basic units) Fee: $103.00 Benefit: 75% = $77.25 85% = $87.55
MBS item number 21116 INITIATION OF MANAGEMENT OF ANAESTHESIA for percutaneous bone marrow harvesting from the pelvis (6 basic units) Fee: $123.60 Benefit: 75% = $92.70 85% = $105.10
MBS item number 30081 DIAGNOSTIC BIOPSY OF BONE MARROW by trephine using open approach, where the biopsy specimen is sent for pathological examination (Anaes.) Fee: $114.30 Benefit: 75% = $85.75 85% = $97.20
MBS item number 30084 DIAGNOSTIC BIOPSY OF BONE MARROW by trephine using percutaneous approach where the biopsy is sent for pathological examination (Anaes.) Fee: $61.20 Benefit: 75% = $45.90 85% = $52.05

MBS item number 30087 DIAGNOSTIC BIOPSY OF BONE MARROW by aspiration or PUNCH BIOPSY OF SYNOVIAL MEMBRANE, where the biopsy is sent for pathological examination (Anaes.) Fee: $30.60 Benefit: 75% = $22.95 85% = $26.05

Source: Ratified PICO 1703

9. Summary of public consultation input

Consultation input was received from six (6) professional organisations, one (1) consumer organisation and two (2) health professionals. The organisations that submitted input on application 1703 were:

- Australian and New Zealand Children's Haematology and Oncology Group (ANZCHOG)
- Australian Leukaemia and Lymphoma Group (ALLG)
- Australian Pathology (AP)
- Department of Haematology, Prince of Wales Hospital
- Haematology Society of Australia and New Zealand (HSANZ)
- Leukaemia Foundation (LF)
- PathWest Laboratory Medicine WA (PathWest)

The consultation feedback received was broadly supportive of public funding for MSAC application 1703. Feedback comments included that MRD testing by flow cytometric and/or molecular methodology for patients with ALL is the current standard of care for risk stratification and to guide prognosis and treatment. Feedback also commented that public funding would ensure equity of access for patients.

The main benefits of public funding stated in the consultation feedback included:

- benefits to the individual and their family through more accurate prognostication and tailored treatment, avoiding treatment toxicity in those that do not require therapy and limiting risk of relapse in treated patients
- encouraging local testing capability and facilitating access to MRD testing for all patients/specialists
- avoidance of costly allogeneic stem cell transplants, which are also associated with substantial cost to the patient
- equitable access for patients.

The main disadvantages of public funding stated in the consultation feedback included:

- additional bone marrow biopsies may still be required in select patients, with associated side effects
- travel associated with accessing the MRD testing for patients and families.

The department also sought further advice from HSANZ at ESC's request, regarding the potential use of peripheral blood samples in MRD testing. HSANZ commented that the molecular abnormality is the same in bone marrow and peripheral blood, and so it agreed with ESC that peripheral blood samples could also be used for MRD testing where a bone marrow sample is unobtainable. HSANZ added that studies have been published showing that peripheral blood is an appropriate and equivalent substitute for bone marrow.

10. Characteristics of the evidence base

Key features of the evidence base are summarised in Table 4.

Table 4 Key features of the included evidence

Criterion	Type of evidence supplied	Extent of evidence supplied	Overall risk of bias in evidence base
Accuracy and performance of the test (cross-sectional accuracy)	35 cohort studies	☒ k=35 n=16,233patients, 10,475 samples*	14 studies at high risk of bias, 2 studies at low risk, and 19 studies with unclear risk of bias; 19 studies with high concern of applicability, 11 studies with low concern of applicability and 5 studies with unclear concern.
Prognostic evidence (longitudinal accuracy)	Overview of systematic reviews	☒ k=5 n=NA	Low confidence
MRD-guided treatment/management (Change in patient management)	Linked evidence: 1 RCT, 12 cohort studies	☒ k=13 n=9,773	Linked: 1 RCT low risk of bias, 9 of 12 cohort studies poor/fair quality.
Health outcomes Predictive effect (treatment effect variation)	Direct evidence: 1 RCT, 4 cohort studies Linked evidence: 24 cohort studies** NA	☒ k=5 (direct) n= 2,243 (direct) ☒ k=24 (linked) n= 7,971 (linked)	Direct: Serious concern Linked: 11 of 24 poor/fair quality.
Other	NA		

k = number of studies, n = number of patients; NA = not applicable

*Samples included in the concordance studies were variable. Some studies reported data for patients, while others reported concordance based on MRD status of bone marrow samples without describing number of patients, where a single patient could contribute more than one bone marrow sample.

Linked evidence for health outcomes included 1 RCT and 36 cohort studies as per **Error! Reference source not found.. The 37 studies included 24 cohort studies reporting health outcomes and 13 studies (1 RCT and 12 cohort) reporting MRD-directed treatment versus no MRD-directed treatment.

11. Comparative safety

Specific evidence comparing the safety of MRD testing compared to morphological assessment ± cytogenetic analysis was not identified in the systematic literature search. The application proposed MRD testing to be performed on a bone marrow sample. A bone marrow sample also needs to be acquired for the comparator test, morphological assessment ± cytogenetic analysis for assessing morphological remission. It is therefore expected that the proposed test does not present additional safety concerns for patients with ALL.

One study compared the impact of MRD-directed chemotherapy to conventional chemotherapy on infection-related morbidity in children with ALL[2]. Individuals who were MRD(-) after an induction and high-dose methotrexate phase were considered standard risk and received reduced intensification /maintenance chemotherapy, compared to those MRD(+) individuals who were considered medium risk and received conventional intensive intensification/maintenance chemotherapy. The results of the study are summarised in Table 5. Patients treated with reduced treatment protocol experienced less infection-related morbidity than patients who received conventional (intensified) treatment, fewer outpatient episodes of fever and of shorter duration, lower proportion of febrile episodes resulting in hospitalisation and intensive care unit admission, less chemotherapy interruptions, fewer intravenous antibiotic courses and shorter hospital stays. One patient in the medium-risk group died of an infection; no infection-related deaths were reported in the standard-risk group.

Table 5 **Results of safety of MRD-directed chemotherapy versus conventional chemotherapy in children with ALL van Tilburg et al. (2011)**

Outcome measure	MRD-directed treatment reduction (standard-risk patients) n with event/N	Conventional chemotherapy (medium-risk patients) n with event/N	Relative difference p-value
Outpatient episodes of fever	88/31* Median 1	360/72* Median 4	p=0.002
Proportion of febrile episodes resulting in hospitalisation	10%	35%	p<0.001
Hospital admission for fever	20/54* Median 0	272/117* Median 2	p<0.001
Length of hospitalisation for fever	Median 0 days Range 0-14 days	Median 10 days Range 0-225 days	p<0.001
Duration of fever	Median 0 days Range 0-9 days	Median 2 days Range 0-38 days	p<0.001

*more than one event may have been experienced by each patient
Abbreviations: MRD, measurable residual disease

12. Comparative effectiveness

Please note for studies reporting PCR, PCR was reported as follows, real time quantitative polymerase chain reaction and quantitative polymerase chain reaction are reported as qPCR, allele-specific oligonucleotide real time quantitative polymerase chain reaction is reported as ASO-qPCR, and reverse transcriptase quantitative polymerase chain reaction as RT-qPCR. Further, some studies did not report the type of PCR.

For studies comparing bone marrow morphology a threshold of <5% was used.

[2] van Tilburg (2011), et al. Reduced versus intensive chemotherapy for childhood acute lymphoblastic leukemia: impact on lymphocyte compartment composition. *Leuk Res.* 35.4 484-491.

Direct from test to health outcome evidence

Direct test to health outcome evidence was reported in five studies:

- One study (UKALL2003) was a two-in-one randomised controlled trial (RCT) where patients were randomised to different treatments based on MRD stratification (low-risk or high-risk groups)[3,4,5]. Aim of the study was to test tailoring of treatment intensity based on MRD status in clinically standard and intermediate risk patients. Event-free survival (EFS), overall survival (OS) and relapse were reported at 5-year and 10-year follow-up.
- Three cohort studies were included all in paediatric and young adult population[6,7,8]. The cohort studies aimed to determine if treatment changes based on MRD status improved health outcomes compared with historical controls that received treatment independent of the MRD status. Outcomes reported included EFS, OS, relapse-free survival (RFS), and cumulative incidence of relapse (CIR).

Paediatric and young adult population results

- Two cohort studies reported improved EFS in groups that had treatment amended according to the MRD stratification compared with standard of care (Eckert et al., 2013b; Pieters et al., 2016). In the UKALL2003 study, there were no differences in EFS between the standard and reduced treatment groups in the MRD low risk population and in the MRD high risk population, 5-year EFS improved when treatment was augmented (hazard ratio, HR 0.61, 95% confidence interval, CI 0.39–0.98).
- OS results were similar to the EFS results in two retrospective reports. In the UKALL2003 study there were no significant differences in OS between standard and intervention treatments in either MRD-low-risk or MRD-high-risk populations.
- Two retrospective studies reported reduced CID in groups that received treatment guided by MRD levels (Eckert et al., 2013b; Pieters et al., 2016). In the UKALL2003 study, lower rates of relapse (5-year and 10-year follow-up) were observed in the MRD high-risk population that received augmented treatment compared with standard treatment.

Adult population results

- No direct evidence studies were identified in the adult population.

---

[3] Moorman AV et al. (2022). Time to Cure for Childhood and Young Adult Acute Lymphoblastic Leukemia Is Independent of Early Risk Factors: Long-Term Follow-Up of the UKALL2003 Trial. *Journal of Clinical Oncology*, JCO2200245.

[4] Vora A et al (2014) Augmented post-remission therapy for a minimal residual disease-defined high-risk subgroup of children and young people with clinical standard-risk and intermediate-risk acute lymphoblastic leukaemia (UKALL 2003): a randomised controlled trial. *Lancet Oncol.* Jul;15(8):809-18.

[5] Vora A, et al. (2013) Treatment reduction for children and young adults with low-risk acute lymphoblastic leukaemia defined by minimal residual disease (UKALL 2003): a randomised controlled trial. *Lancet Oncol*. Mar;14(3):199-209.

[6] Eckert, C et al (2013). 'Use of allogeneic hematopoietic stem-cell transplantation based on minimal residual disease response improves outcomes for children with relapsed acute lymphoblastic leukemia in the intermediate-risk group'. *J Clin Oncol*, 31 (21), 2736-42

[7] Pieters, R (2016). 'Successful Therapy Reduction and Intensification for Childhood Acute Lymphoblastic Leukemia Based on Minimal Residual Disease Monitoring: Study ALL10 From the Dutch Childhood Oncology Group'. *J Clin Oncol*, 34 (22), 2591-601.

[8] van Tilburg (2011), et al. Reduced versus intensive chemotherapy for childhood acute lymphoblastic leukemia: impact on lymphocyte compartment composition. *Leuk Res.* 35.4 484-491.

Linked evidence of test accuracy

Cross-sectional accuracy

The systematic review identified 35 studies that reported concordance between morphological analysis and MRD testing technologies: mpFC compared with bone marrow morphology, qPCR compared with bone marrow morphology, qPCR compared with mpFC, NGS compared with mpFC, and NGS compared with qPCR.

Overall, mpFC and qPCR both performed better than bone marrow morphology in detecting MRD in ALL patients, i.e. detected more MRD positive cases than bone marrow morphology. However, the evidence suggests that mpFC and qPCR may be used as complementary MRD technologies in early days and later after therapy. From the available evidence NGS performed better than mpFC, but evidence was conflicting on performance of NGS against qPCR. These results have implications for health outcomes of ALL patients. Knowing that MRD positivity can predict risk of relapse and poor health outcomes, ascertaining the status of MRD early in the treatment cycle using a sensitive technique such as NGS, qPCR or mpFC can guide treatment and prevent morbidity and mortality.

Studies comparing mpFC with bone marrow morphology reported an average positive percent agreement (PPA) of 92%, negative percent agreement (NPA) of 59%, and concordance of 62.5%. The evidence suggested that mpFC identified MRD positive cases that bone marrow morphological assessment found to be negative. With low concordance rates, mpFC may be superior to bone marrow morphology in detecting MRD. However, it may be difficult to conclude the precise timing of measurement and sensitivity threshold of mpFC that is the most effective. The main text presents the concordance between various MRD technologies for the different sensitivity thresholds.

Studies comparing qPCR with bone marrow morphology reported an average PPA of 88%, NPA of 45%, and concordance of 58%. The evidence suggested that qPCR identified MRD positive cases that bone marrow morphological assessment found to be negative, at MRD detection thresholds that were higher than those of morphology. The low NPA and low concordance rates suggest that qPCR may be superior to bone marrow morphology in detecting MRD at higher sensitivity thresholds.

Studies comparing mpFC with qPCR comprised most of the evidence on concordance. The studies reported an average PPA of 87%, NPA of 77%, and concordance of 84%— these high rates persisted at all sensitivity thresholds, on day 15 and later in therapy cycle. Further, the concordance was higher in patients with B-ALL than T-ALL.

Because of higher overall concordance and high PPA between qPCR (real-time PCR or RT-qPCR or ASO-qPCR) and mpFC, along with a relatively lower NPA, the two technologies may be complementary to each other in MRD detection, with a qPCR technique (qPCR or RT-qPCR or ASO-qPCR) better able to exclude MRD negatives than an mpFC. These results were specifically observed on day 15 or end of induction and late in the therapy cycle (for example after haematopoietic stem cell transplant (HSCT) or day 106), at a higher sensitivity threshold for MRD detection, in patients with B-ALL.

Studies comparing NGS and mpFC reported an average PPA of 99%, NPA of 62% and concordance of 63%. The low concordance and high PPA, especially at higher MRD detection sensitivity thresholds of NGS, compared with mpFC, suggests that NGS may be superior to mpFC in detecting MRD at higher sensitivity thresholds.,

Studies comparing NGS and qPCR reported an average PPA of 79%, NPA of 78% and concordance of 71%. Overall, the evidence was not conclusive on whether NGS performs better or worse than qPCR in detecting MRD. More robust evidence is required to conclude if NGS performs better or worse than qPCR in detecting MRD.

Prognostic accuracy

The assessment of prognostic accuracy of MRD testing was approached as an overview of systematic reviews. Due to the heterogeneity in populations, MRD detection techniques, detection thresholds and timepoints, evidence from the five included systematic reviews was only synthesised qualitatively.

Five systematic reviews were identified: one for children and young adults, one for adult population and three for mixed paediatric and adult populations. Two of the reviews focused specifically on the prognostic effect of pre-HSCT MRD testing on health outcomes after HSCT.

All five identified systematic reviews reported that MRD assessment had an independent prognostic value, and MRD positive patients had worse health outcomes than patients without MRD, even when measured in different populations (children and adults, B-cell and T-cell ALL, *de novo* and relapsed/refractory disease), across different timepoints and regardless of treatment administered.

Predictive accuracy

Linked evidence of change of management

The role of MRD testing in ALL clinical practice guidelines for patients with ALL is well established (e.g., NCCN Guidelines for ALL[9], ESMO guidelines for ALL[10], EuroMRD[11]). Studies that used MRD assessment to direct treatment (less intensive treatment regimens for patients who achieve MRD negativity to decrease toxicity without compromising survival, and treatment intensification for patients who are MRD(+) to improve their survival) are discussed in Direct from test to health outcomes evidence and in Linked evidence of health outcomes.

Linked evidence of health outcomes

Thirty-seven studies met the inclusion criteria for assessing evidence of changes in health outcomes resulting from changes in management (e.g., survival, rate of remission) and changes in treatment strategies based on MRD testing compared with no MRD testing.

Within the identified studies the description of the comparative arm to MRD testing was mixed some studies explicitly stated morphological assessment while others alluded to this comparison.

---

[9] NCCN. (2021). Acute Lymphoblastic Leukemia. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/all.pdf

[10] Hoelzer, D., Bassan, R. et al (2016). 'Acute lymphoblastic leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up'. *Ann Oncol*, 27 (suppl 5), v69-v82.

[11] van der Velden VH et al (2007) European Study Group on MRD detection in ALL (ESG-MRD-ALL). Analysis of minimal residual disease by Ig/TCR gene rearrangements: guidelines for interpretation of real-time quantitative PCR data. *Leukemia.* 21(4):604-11.

As morphological assessment is a part of NCCN risk assessment [12] any study that reported NCCN risk stratification and reported a no MRD testing arm was assumed to have completed morphological assessment.

- Five studies compared (mpFC) versus qPCR testing
- Fourteen studies compared morphological assessment versus mpFC or qPCR testing
- Four studies compared NGS versus mpFC or RT-qPCR testing
- Thirteen studies reported changes in treatment strategies based on MRD testing
- One study reported different testing thresholds for mpFC.

Articles included 18 paediatric, five paediatric and adults, and 14 adult population studies.

Health outcomes, including EFS and OS, were more favourable for qPCR versus mpFC testing at similar MRD testing detection thresholds (e.g., 10^{-3}, 10^{-4}). Additionally, when MRD positivity was detected later in the treatment pathway, for example, in week 11 versus day 26, event free and overall survival outcomes were worse.

Studies grouping patients as standard/low risk or with low MRD versus high risk or with high MRD individuals found those in higher risk groups had significantly worse survival outcomes.

Health outcomes including EFS, were more favourable for qPCR/mpFC testing at similar MRD testing detection thresholds (e.g. 10^{-3}, 10^{-4}) compared to bone marrow morphology alone.

Health outcomes including relapse rates for MRD(-) patients, were more favourable for NGS versus mpFC, however, noting that the NGS testing detection thresholds were $<10^{-6}$ (more sensitive) compared to mpFC detection thresholds of 10^{-4} (less sensitive) [13]Health outcomes including risk of relapse rates and OS, were more favourable for mpFC or RT-qPCR versus NGS, when testing thresholds were comparative at 10^{-4}.

Overall, MRD positivity directed more intense treatments compared to MRD negativity, resulting in improved outcomes, greater survival benefits and lower likelihood of relapse.

Clinical claim

The use of MRD testing (mpFC or molecular methods) with morphological assessment ± cytogenetic analysis results in superior effectiveness compared with morphological assessment ± cytogenetic analysis alone.

The use of MRD testing (mpFC or molecular methods) with morphological assessment ± cytogenetic analysis results in non-inferior safety compared with morphological assessment ± cytogenetic analysis alone.

13. Economic evaluation

The economic model assessed MRD testing compared with morphological assessment only by indirectly comparing the survival functions, and hazard rates (i.e., proportional hazards modelling) of EFS/RFS and OS outcomes based on respective tests and treatments. Up to four lines of treatment were modelled, along with three tests (mpFC, NGS, qPCR) in both the adult and paediatric populations. The time horizon of the model was 30 years, chosen as this is likely to

[12] Brown PA et al (2021) Acute Lymphoblastic Leukemia, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. ;19(9):1079-1109.

[13] Pulsipher et al (2022) Next-Generation Sequencing of Minimal Residual Disease for Predicting Relapse after Tisagenlecleucel in Children and Young Adults with Acute Lymphoblastic Leukemia. *Blood Cancer Discov*.3(1):66-81.

capture important difference in costs and outcomes, and has been previously accepted in PBAC submissions for ALL treatment (Blinatumomab PBAC PSD, July 2018, July 2019). A summary of the economic evaluation is shown in Table 6.

Table 6 Summary of the economic evaluation

Component	Description
Perspective	Health care system perspective
Population	Patients with Acute Lymphoblastic Leukemia (ALL) • Adult • Paediatric
Prior testing	(Morphology and Full Blood Count)
Intervention(s)	Measurement of MRD using: • Multi-parametric flow cytometry (mpFC) • Polymerase chain reaction (PCR) • Next-generation sequencing (NGS)
Comparator	Bone marrow morphology (+/- cytogenetics)
Type(s) of analysis	Cost-Utility Analysis Cost-Effectiveness Analysis
Outcomes	Life-years gained Quality-adjusted life years gained
Time horizon	30 years
Computational method	Partitioned survival analysis Proportional hazards modelling
Generation of the base case	Modelled
Health states	Newly Diagnosed ALL Chemotherapy Tx (SR/HR) 1L Blinatumomab 1L HSCT 2L CAR-T 2L HSCT 2L Blinatumomab 3L CAR-T 3L HSCT 4L CAR-T 4L HSCT Relapsed Dead
Cycle length	1 month
Transition probabilities	Transition Probabilities were sourced from studies either reporting Kaplan Meier data for EFS/RFS or OS or Hazard Ratios and were transformed into time-dependent transitions probabilities through proportional hazards modelling. These transformations were discussed in further detail below.
Discount rate	5% costs and benefits
Software	Microsoft Excel

Abbreviations: ALL, acute lymphoblastic leukaemia; CAR-T, Chimeric antigen receptor T-cell; EFS, event free survival; HSCT, haematopoietic stem cell transplantation; HR, high risk; mpFC, multiparametric flow cytometry; MRD, measurable residual disease; NGS, next-generation sequencing; OS, overall survival; qPCR, quantitative polymerase chain reaction; RFS, relapsed free survival; SR, standard risk; Tx, Treatment

The economic analysis adopted a stepped approach where the first step assessed the cost-effectiveness of each test, based on cost per LYs gained after 5 years. The second step quantified the cost per LYs gained compared with morphology only after 30 years, and the third step assessed the cost utility (cost per QALY gained) of each test after 30 years. These results are shown for qPCR in Table 7, and the overall results for all three methods are shown in Table 8. Post-ESC updated analyses adding patients relapsing in year 1 and year 2 and a re-biopsy rate of 4% in line with ESC's requests are shown in blue italicised font.

Table 7 Stepped presentation of results from the economic analysis (qPCR only)

	Cost	Incremental cost	Effectiveness	Incremental effectiveness	ICER
Adult: qPCR					
Step 1 (cost per LY gained- 5 year time horizon)					
MRD	$341,058	-$25,343	4.22	0.84	Dominant
No MRD	$366,401		3.38		-$30,267
Step 2 (cost per LY gained- 30 year time horizon)					
MRD	$418,846	$31,274	9.76	3.80	$8,220
No MRD	$387,572		5.95		
Step 3 (cost per QALY gained- 30 year time horizon)					
MRD	$418,846	$31,274	7.36	4.27	$7,318
No MRD	$387,572		3.08		
Paediatric: qPCR					
Step 1 (cost per LY gained- 5 year time horizon)					
MRD	$368,572	$24,680	4.02	0.61	$40,562
No MRD	$343,892		3.41		
Step 2 (cost per LY gained- 30 year time horizon)					
MRD	$427,329	$65,189	8.03	2.72	$23,951
No MRD	$362,139		5.30		
Step 3 (cost per QALY gained- 30 year time horizon)					
MRD	$427,329	$65,189	5.77	2.12	$30,788
No MRD	$362,139		3.65		

Table 8 Results of the economic analysis

	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	ICUR
Adult					
mpFC					
MRD	$424,295	$36,722	7.19	4.10	$8,948
No MRD	$387,572		3.08		
~~PCR~~					
~~MRD~~	~~$418,846~~	~~$31,274~~	~~7.36~~	~~4.27~~	~~$7,318~~
~~No MRD~~	~~$387,572~~	-	~~3.08~~	-	-
PCR – *post-ESC analysis revised to include a 4% re-biopsy rate*					
MRD	$418,916	$31,343	7.36	4.27	$7,334
No MRD	$387,572		3.08		
NGS					
MRD	$379,110	-$8,462	6.91	3.83	Dominant
No MRD	$387,572		3.08		-$2,211
Paediatric					
mpFC					
MRD	$402,255	$40,116	6.59	2.93	$13,680
No MRD	$362,139		3.65		
~~PCR~~					
~~MRD~~	~~$427,329~~	~~$65,189~~	~~5.77~~	~~2.12~~	~~$30,788~~
~~No MRD~~	~~$362,139~~	-	~~3.65~~	-	-
PCR – *post-ESC analysis revised to include a 4% re-biopsy rate*					
MRD	$427,398	$65,259	5.77	2.12	$30,821
No MRD	$362,139		3.65		
NGS					
MRD	$356,900	-$5,240	6.21	2.56	Dominant
No MRD	$362,139		3.65		-$2,050

Abbreviations: ICUR, incremental cost-utility ratio; mpFC, multiparametric flow cytometry; MRD, measurable residual disease; NGS, next-generation sequencing; PCR, polymerase chain reaction

When all MRD tests were combined (using weight based on the proportion of mpFC, NGS and PCR expected to be used – discussed further in the financial analysis), the economic model demonstrated that there was a greater accrual of quality of life for MRD testing in both the adult and paediatric populations. In both the adult and paediatric populations, the cost-effectiveness and cost-utility was less than $15,000/QALY (Table 9).

Table 9 Results of the economic evaluation

Parameter	MRD testing	Morphology Only	Increment
Paediatric patients			
Costs	$394,548	$362,139	$32,408
Life years	8.33	5.30	3.03
QALYs	6.13	3.65	2.48
Incremental cost per life year gained			**$10,713**
Incremental cost per QALY gained			**$13,070**
Adult patients			
Costs	$405,054	$387,572	$17,482
Life years	9.42	5.95	3.47
QALYs	7.15	3.08	4.06
Incremental cost per life year gained			**$5,040**
Incremental cost per QALY gained			**$4,302**

Abbreviations: MRD, measurable residual disease; QALY, quality-adjusted life year.

Sensitivity analyses

A One Way Sensitivity Analysis (OWSA) was conducted to assess the main drivers of the model. Pairwise comparisons of each MRD testing method against morphology only were individually assessed for both the paediatric and adult population. The comparison of NGS compared with morphology only had the largest impact when varying each parameter by ±20% as the base case ICUR.

All parameters were reduced and increased by 20% to assess the impact on the model. For all comparisons, the hazard ratios used in the model had the greatest impact, and of these hazard ratios, the hazard ratios relating to mpFC, the discordant rate, or standard risk versus high risk had the greatest impact. In the paediatric population, the utility values for the relapse free health state and the Australian general population also had an impact.

The reason the HR related to mpFC had the greatest impact was due to the structure of the model. The base comparison for each indirect comparison is based on blinatumomab MRD+ v chemotherapy MRD+, however central within the network of comparisons is the mpFC comparison. This position within the network of comparisons therefore increased the impact of the importance and dominance of the data point within the overall comparison.

However, while the mpFC MRD+/MRD- HR had the greatest impact, it was also the parameter with the greatest certainty, as it was sourced from a systematic review by Berry et al[14].

Additionally, an analysis was conducted to assess the impact of FISH when included with morphological assessment, i.e. the comparator of morphological assessment plus cytogenetics. Assuming the increment of FISH testing over qPCR is the same as the increment of FISH testing over morphological assessment, then when FISH is added to morphological assessment, the ICER for mpFC, NGS and PCR increased by 54.2% in the adult population and 75.4% in the paediatric population, however this estimate needs to be used with caution due to limitations in the study design and base assumptions used with the study underpinning this analysis.

[14] Berry, D. A., Zhou, S. et al (2017). 'Association of Minimal Residual Disease With Clinical Outcome in Pediatric and Adult Acute Lymphoblastic Leukemia: A Meta-analysis'. *JAMA Oncol*, 3 (7), e170580.

14. Financial/budgetary impacts

The financial model used an epidemiological approach to estimate the cost of listing MRD testing for mpFC and other molecular methods of MRD testing (including ASO-qPCR and NGS) on the MBS for the purposes of identifying MRD in patients with ALL. As the number of patients with ALL and rate of relapse was distributed unevenly across patients at different ages, the financial analysis considered financial outcomes of MRD testing for the paediatric and adult populations, where results are reported for each population separately and combined. The proposed populations were:

- Paediatric patients with de novo or relapsed B- or T-cell ALL, defined as those diagnosed between the ages of 0 to 14 years of age (inclusive).
- Adult patients with de novo or relapsed B- or T-cell ALL, defined as those diagnosed at age 15 and above.

The eligible population for patients with ALL was sourced from 2022 AIHW cancer data which reports actual age-standardised incident data from 1982 to 2018 (Australian Institute of Health and Welfare (AIHW), 2022). Projections were made to estimate the incidence of ALL cases in 2023, including the proportion of patients that relapse by MRD testing method, which were derived from outputs of the economic model. According to the AIHW Cancer Data, the proportion of the total population that are paediatric patients (aged 0-14 years) and adult patients (15 years and above) are 49% and 51% respectively.

Assumptions were made regarding the proportion of the population that are eligible for both bone marrow morphology and MRD testing (by mpFC, ASO-qPCR and NGS). Uptake was assumed to be 100% in the paediatric population and 90% in the adult population to account for patients that are not suitable for MRD testing (1703 Ratified PICO, pg. 6). Additionally, the uptake of bone marrow morphology is assumed to be 100% across both populations, whereas individual uptake rates are determined separately for each MRD testing method.

While the uptake of bone marrow morphology was assumed to be 100% across both populations, 15% of patients with T-ALL and 10% of patients with B-ALL that undertake NGS/ASO-qPCR testing were assumed to be ineligible for NGS or ASO-qPCR (1703 Application, pg. 2; 1707 Application, pg. 27). Therefore, a total of 23.5% of patients with ALL were not suitable for testing using NGS or ASO-qPCR (8.5% consisting of patients with B-ALL in addition to 15% consisting of patients with T-ALL patients). As such an uptake rate of 23.5% was assumed for mpFC with the remaining uptake of MRD testing methods split equally between NGS and ASO-qPCR. Due to limited availability of data, the uptake rate of MRD testing methods (mpFC, NGS and ASO-qPCR) were assumed to be consistent overtime despite the slow adoption of a newly approved TGA and MBS listing, however the rate of uptake remains highly uncertain.

The proportion of patients that fall under different risk stratification statuses (high risk, standard risk or relapsed) was determined separately for both paediatric and adult populations and was derived from outputs of the economic analysis. That is: for the paediatric population, the proportion of non-relapsed patients was calculated by deducting the relapsed population from the total prevalent population. Subsequently, the proportion of standard risk and high-risk patients reported by (Vora et al., 2014) were applied to the remaining non-relapsed patients to determine the overall proportion of standard risk, high risk and relapse. For the adult population, risk stratification was based on data from[15], aligning with the inputs of the economic analysis.

[15] Greenwood, M., Trahair, T. et al (2021). 'An MRD-stratified pediatric protocol is as deliverable in adolescents and young adults as children with ALL '. *Blood Adv* (Online ahead of print)

Although the RCPA's estimated relapse rates were included in the 1703 Ratified PICO, the financial model used time-dependent relapse rates sourced from the economic model, where the rates are reported by testing method, population (i.e. paediatric or adult) and year. To calculate the rates of relapse, the event-free survival (EFS) or risk-free survival (RFS) rates were applied to the risk stratification to determine the relapse rates per year for paediatric and adult patients. While patients are likely to relapse prior to 2 years, it was assumed that patients would continue treatment and not switch for the first two years, as defined within the clinical treatment algorithm presented in the PICO Confirmation, which aligns with inputs from the economic model (1703 Ratified PICO, Fig. 4).

The utilisation of each test, including bone marrow morphology, mpFC, NGS and ASO-qPCR along with the number of tests required for each patient were derived from treatment protocol ALL06 reflected in the proposed clinical management algorithm in the PICO (1703 Ratified PICO, Fig. 4). It is important to note that due to variability in patient response and treatments received, some patients may require more tests than others. Of note, treatments such as haematopoietic stem cell transplant (HSCT) and blinatumomab are associated with increased MRD testing, either to determine eligibility or during monitoring. Therefore, the number of tests required by each patient is uncertain and likely variable, due to the various treatment pathways a patient may follow. The inputs in the financial impact model endeavoured to provide a standardised estimate on the number of MRD tests required by each patient by risk stratification, assuming all patients who are classified within a risk category receive the same volume of MRD tests.

The financial implications to the MBS resulting from the proposed listing of mpFC, NGS and ASO-qPCR for paediatric and adult patients was an overall increase to the MBS budget as shown in Table 10. Post-ESC updated analyses incorporating patients relapsing in year 1 and year 2 and a re-biopsy rate of 4% in line with ESC's requests are shown in blue italicised font.

Table 10 Net financial implications of MRD testing to the MBS

Parameter	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Cost of MRD testing - world without MRD testing						
Paediatric population						
Cost of Bone Marrow Morphology	$96,402	$98,015	$132,485	$105,454	$104,649	$105,730
Adult population						
Cost of Bone Marrow Morphology	$102,457	$104,171	$143,060	$114,089	$111,956	$112,695
Total cost (paediatric patients and adults combined)	**$198,859**	**$202,186**	**$275,545**	**$219,543**	**$216,605**	**$218,425**
Cost of MRD testing - world with MRD testing						
Paediatric population						
Cost of Bone Marrow Morphology	$96,402	$98,015	$132,485	$105,454	$104,649	$105,730
Cost of MRD tests by mpFC (AAAA services)	$114,450	$116,365	$138,932	$135,276	$146,836	$154,046
Cost of MRD tests by NGS (BBBB services)	$580,494	$590,209	$671,893	$637,337	$636,219	$641,590
Cost of MRD tests by ASO-qPCR (CCCC services)	$227,113	$230,914	$234,778	$238,707	$242,702	$246,764
Cost of MRD tests by ASO-qPCR (DDDD services)	$220,010	$223,692	$276,071	$251,367	$247,060	$247,119
Total cost (paediatric patients)	$1,238,469	$1,259,195	$1,454,160	$1,368,142	$1,377,465	$1,395,248

Parameter	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Adult population						
Cost of Bone Marrow Morphology	$102,457	$104,171	$143,060	$114,089	$111,956	$112,695
Cost of MRD tests by mpFC (AAAA services)	$111,503	$113,369	$134,471	$125,028	$122,291	$124,338
Cost of MRD tests by NGS (BBBB services)	$565,546	$575,010	$665,225	$624,136	$621,410	$625,986
Cost of MRD tests by ASO-qPCR (CCCC services)	$210,926	$214,455	$218,044	$221,693	$225,403	$229,175
Cost of MRD tests by ASO-qPCR (DDDD services)	$216,787	$220,415	$268,819	$246,218	$242,684	$243,047
Total cost (adults)	$1,207,218	$1,227,421	$1,429,620	$1,331,164	$1,323,745	$1,335,241
Total cost (paediatric patients and adults combined)	**$2,445,688**	**$2,486,616**	**$2,883,780**	**$2,699,306**	**$2,701,210**	**$2,730,489**
Net cost of MRD testing to the MBS						
Paediatric population	$1,142,067	$1,161,180	$1,321,675	$1,262,688	$1,272,816	$1,289,518
Adult population	$1,104,762	$1,123,250	$1,286,560	$1,217,075	$1,211,789	$1,222,545
Total (net cost to the MBS per year)	**$2,246,829**	**$2,284,429**	**$2,608,235**	**$2,479,763**	**$2,484,605**	**$2,512,064**
Post-ESC revised analyses *(two relapse rate scenarios, each including re-biopsy)*						
Net cost of MRD testing to the MBS, *including 4% re-biopsy rate, and relapsing patients in year 1 (3%) and year 2 (17%)*	***$2,448,035***	***$2,489,002***	***$2,712,564***	***$2,578,954***	***$2,583,989***	***$2,612,546***
Net cost of MRD testing to the MBS, *including 4% re-biopsy rate, and relapsing patients in year 1 (10%) and year 2 (50%)*	***$2,671,123***	***$2,715,824***	***$2,712,564***	***$2,578,954***	***$2,583,989***	***$2,612,546***

Source: DCAR: Attachment 4_Financial estimates, worksheet 'Results Tables_DCAR'; and HTA group's post ESC updated analysis: 02b. 1703 DCAR Financial estimates_160222_UPDATED.
Post-ESC revised analyses are shown in blue italics; rows relating to MRD testing by qPCR are highlighted in pale grey.
Abbreviations: MBS, Medicare Benefits Schedule; MRD, measurable residual disease
*Year 1-6 reflects the annual years of 2023-2028

The results of the financial model demonstrate that the utilisation of bone marrow morphology does not change in the world with and without the listing of MRD testing on the MBS. As such, the increased cost to the MBS is directly related to the estimated use of MRD testing by mpFC and other molecular methods of MRD testing including NGS and ASO-qPCR (Table 11).

Table 11 Estimated use and change in cost of listing MRD testing on the MBS

Parameter	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Paediatric and adult populations combined						
Incidence of paediatric and adult patients with ALL	415	422	429	436	444	451
Number of paediatric and adult patients with ALL eligible for MRD testing	394	401	562	434	429	433
Estimated use and cost of the proposed health technology						
Number of people who receive bone marrow morphology	415	422	759	486	463	462
Number of bone marrow morphology tests	2815	2862	3900	3107	3066	3092
Number of people who receive MRD testing via mpFC	93	94	124	114	119	124
Number of MRD tests by mpFC (AAAA services)	483	491	585	557	576	595
Number of people who receive MRD testing via NGS	151	153	191	171	169	169
Number of MRD tests by NGS (BBBB services)	787	800	918	866	863	870
Number of people who receive MRD testing via ASO-qPCR	151	153	201	177	172	171
Number of MRD tests by ASO-qPCR (CCCC services)	151	153	156	158	161	164
Number of MRD tests by ASO-qPCR (DDDD services)	636	647	793	724	713	714
Cost of MRD testing to the MBS	$2,445,688	$2,486,616	$2,883,780	$2,699,306	$2,701,210	$2,730,489
Change in use and cost of other health technologies						
Change in use of bone marrow morphology	0	0	0	0	0	0
Cost of bone marrow morphology in the world without MRD testing	$198,859	$202,186	$275,545	$219,543	$216,605	$218,425
Net change in costs to the MBS	$2,246,829	$2,284,429	$2,608,235	$2,479,763	$2,484,605	$2,512,064
Net financial impact to the MBS (increased cost of MRD testing to the MBS)	**$2,246,829**	**$2,284,429**	**$2,608,235**	**$2,479,763**	**$2,484,605**	**$2,512,064**

Source: Attachment 4_Financial estimates, worksheet 'Results Tables_DCAR'
Rows relating to MRD testing by qPCR are highlighted in pale grey.
Abbreviations: ALL, acute lymphoblastic leukaemia; ASO-qPCR, allele-specific oligonucleotide real time quantitative polymerase chain reaction; BM, bone marrow morphology; MBS, Medicare Benefits Schedule; mpFC, multi-parametric flow cytometry flow cytometry; MRD, measurable residual disease; NGS, Next Generation Sequencing

The 1703 Ratified PICO included a comment from the applicant that "although MRD testing is routinely used in paediatric ALL, its use is currently funded by hospitals and oncology departments, usually using donated funds, or by patients paying out-of-pocket". As such, MRD

testing is not paid for by the states/territories and therefore the implications of cost-shifting to the MBS have not been assessed.

It is noted that as MRD testing is currently being paid for out-of-pocket/by hospital budgets, there is not expected to be a change in utilisation of therapies and therefore the cost of blinatumomab, CAR-T, HSCT have not been included in the financial impact model. While it is not expected to increase utilisation, if MRD testing is listed on the MBS there is possibility of a change in treatment only due to greater awareness of the treatments in the tests and therefore this has been tested for blinatumomab in the scenario analysis.

Sensitivity, threshold and scenario analysis were conducted to quantify uncertainty around all parameters used in the financial model. Firstly, all parameters were adjusted by ±10% in a sensitivity analysis to identify key drivers of the model in terms of impact on the change in the additional cost of listing MRD testing on the MBS over six years. In summary, the impact of parameters on the model were minimal at a 20% adjustment, where the maximum change in results were 15% across three parameters. The top three parameters were further assessed in a threshold analysis, with an additional analysis conducted for uptake rates given the uncertainty surrounding this parameter. The parameters tested in the threshold analysis include:

- Uptake rates for mpFC (including NGS and ASO-qPCR)
- Proportion of paediatric patients eligible for MRD testing
- Proportion of adult patients eligible for MRD testing

The results of the threshold analysis were consistent with the sensitivity analysis, and demonstrate that the top three drivers of the financial model have a minimal impact on the model, with a maximum change of 15% to the results at a 20% threshold for uptake rates.

Additionally, scenario analyses were conducted to test the following:

- RCPA reported relapse rates
- Increase in demand for blinatumomab

The RCPA provided method-agnostic relapse rates for adult and paediatric populations in the 1703 Ratified PICO, including a 50% relapse rate for infants aged ≤12 months and adults (age 15 years and above), and a 10% rate in children aged 1-18 years old. As such these relapse rates have been independently tested to assess the difference in the additional cost of listing mpFC and method-agnostic MRD testing on the MBS. Overall, with a paediatric relapse rate of 10% and 50% the results of the financial analysis change by 0.4% and 10% respectively. Similarly, with an adult relapse rate of 50%, the results of the financial analysis change by approximately 10%.

Two scenario analyses were considered to model the financial impact to the MBS, should the PBS restriction criteria be amended to reflect an analytical detection threshold of 10^{-6}: first to test the eligible population inclusive of standard risk, high risk and relapsed patients (total ALL population), and second to test the eligible population inclusive of high risk and relapsed patients to reflect the population eligible for blinatumomab in the clinical management algorithm (1703 Ratified PICO, Fig.4). Within each scenario, the impact of increased access to blinatumomab in 2% of the eligible MRD population is assessed. Both scenarios did not affect the financial impact to the MBS, as the rate of testing remained the same as was assumed in the base case.

In the first scenario, the increase in total cost of blinatumomab is equivalent to $112,240 over 6 years. This translates to a net total of $14,728,165 to the PBS government budget when increasing patient access to blinatumomab over six years. In the second scenario, the increase total cost of blinatumomab is equivalent to $58,121 over 6 years. This translates to a net total of

$14,674,046 to the government budget when increasing patient access to blinatumomab over six years.

Additionally, a scenario analysis was conducted to assess the cost of baseline testing for all MRD testing methods in the case where this testing is included for public funding. The costs of baseline testing are detailed below.

Table 12 Scenario analysis - Baseline testing costs for MRD testing methods

Parameter	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Paediatric population						
mpFC baseline testing cost (AAAA)	$22,441	$22,817	$23,199	$23,587	$23,982	$24,383
NGS baseline testing cost (BBBB)	$113,822	$115,727	$117,664	$119,633	$121,635	$123,671
ASO-qPCR baseline testing cost (CCCC)	$227,113	$230,914	$234,778	$238,707	$242,702	$246,764
Adult population						
mpFC baseline testing cost (AAAA)	$20,842	$21,190	$21,545	$21,906	$22,272	$22,645
NGS baseline testing cost (BBBB)	$105,710	$107,479	$109,277	$111,106	$112,965	$114,856
ASO-qPCR baseline testing cost (CCCC)	$210,926	$214,455	$218,044	$221,693	$225,403	$229,175

15. Committee-in-confidence information

REDACTED

16. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues:

- At its November 2022 meeting MSAC supported measurable residual disease (MRD) testing using mpFC and NGS methods under application 1707, therefore only MRD testing using other molecular methods, including ASO-qPCR, remains for MSAC's consideration.
- The clinical need for MRD testing using molecular methods (and mpFC) is clear, and this is already standard of care in Australia.
- MRD testing using qPCR is complementary to other methodologies, and all are sufficiently sensitive to detect MRD for clinical purposes. There are clinical, technical and logistical reasons laboratories may wish to have more than one method available.
- Supporting MRD testing using molecular methods may improve equity of access.
- Bone marrow samples are preferred and usually available, but MSAC may want to consider not excluding the use of peripheral blood samples, especially for initial development of the patient-specific qPCR assay (item CCCC). Clinical expert advice should be sought to support MSAC's consideration of this issue.
- It was difficult to draw conclusions on concordance comparisons between mpFC, NGS and ASO-qPCR methodologies due to heterogeneity among studies.
- It is unclear if effectiveness was compromised by the variation in definition of this methodology (i.e., whether it is defined as ASO-PCR, qPCR, or PCR). If the clinical evidence was based on qPCR more broadly, then the assessment relied on indirect effectiveness data.

Economic issues

- The economic model was detailed and well thought through. Most assumptions made in the model seemed reasonable, and sensitivity analyses showed the ICER was robust. However the model should be interpreted with caution as it involved multiple indirect comparisons, and was not completely validated.
- The applicant had advised for the PICO that there are rare instances where there is insufficient tissue and a re-biopsy is required specifically for MRD testing, although a re-biopsy rate was not included in the model.
- Limited data exist to support the proportions of MRD testing using each method (the DCAR estimated 24% mpFC, 38% NGS, and 38% qPCR).
- There was a misalignment of the definition of the qPCR methodology across clinical, economic and financial analyses, as the applicant may have intended the request for MBS funding to be for ASO-qPCR specifically (and the CCCC/DDDD fees proposed based on ASO-qPCR costs were used), however studies used to inform the economic model were for qPCR more broadly.

Financial issues:

- The estimated utilisation of MRD testing was lower than under application 1707, and the figures in application 1703 appeared more appropriate.
- The financial impact to the MBS was $2.4-$2.7 million per year, depending on relapse rate.

ESC discussion

ESC noted that this application from the Royal College of Pathologists of Australasia (RCPA) was for Medicare Benefits Schedule (MBS) listing of measurable residual disease (MRD, formerly known as 'minimal residual disease') testing in patients with acute lymphoblastic leukemia (ALL).

ESC noted the PICO proposed MBS items for measurement of MRD using multiparametric flow cytometry (mpFC; item AAAA), next-generation sequencing (NGS; item BBBB), as well as the development and first use (item CCCC) and subsequent use (item DDDD) of a patient-specific quantitative polymerase chain reaction (qPCR) MRD assay. ESC noted MSAC had supported public funding for MRD testing using mpFC and generic NGS methods under previous Application 1707 at its November 2022 meeting, so considered that effectively only MRD testing using other molecular methods including allele-specific oligonucleotide quantitative polymerase chain reaction (ASO-qPCR) (i.e., items CCCC and DDDD) remains for MSAC's consideration under application 1703.

ESC considered that MRD testing is already standard of care for these patients, and that it is currently paid for by hospital departments or out-of-pocket by patients, and that the current lack of MBS funding creates inequity of access. ESC also considered that if the sample could be sent away by the treating unit for testing then the patient may not have to travel, noting travel is another potential equity concern.

ESC noted consultation feedback had queried whether MRD testing could be extended to include patients with acute myeloid leukemia (AML). ESC considered that MRD testing in patients with ALL primarily looks for variants in the immunoglobulin genes, whereas the genetic arrangements found in AML patients are different, so the tests proposed in this application are not suitable for patients with AML. ESC considered that sufficient evidence for MRD testing in patients with AML likely did not exist yet, although this could be proposed in a future application.

ESC noted that in the MRD testing items supported under application 1707 MSAC had agreed that the frequency of testing should be moved to a practice note, and considered the same was likely appropriate here. ESC also noted consultation feedback stated that "episode of disease"

(as per the PICO Confirmation and MSAC-supported practice note under 1707) was unclear, and considered that further clarification of this term may be needed.

ESC noted the development of the item descriptors was described in the PICO Confirmation and that the applicant had proposed fees for CCCC and DDDD based on the costings for ASO-qPCR specifically (see PICO Table 7), and considered that the applicant appeared to have intended only ASO-qPCR to be included under proposed MBS items CCCC and DDDD. However, as the final item descriptors in the PICO did not specify "using ASO-qPCR" or similar, the DCAR's clinical and economic evaluations combined evidence from different types of PCR: qPCR (in general), ASO-qPCR (specifically) and RT-PCR (which uses reverse transcription to look for gene fusions in RNA rather than in DNA and is not quantitative). ESC considered it was uncertain whether it was appropriate or necessary to include other types of PCR under MBS items CCCC and DDDD. ESC also considered that it would be more consistent to have "quantitative patient-specific" in the same order across CCCC and DDDD.

ESC noted that MSAC's supported item descriptors for MRD testing using mpFC and NGS methods stated the method within the item descriptor, but that the descriptor for development of a patient-specific assay (item CCCC) did not state the method to be used. ESC considered this presented a risk that less expensive methods could be conducted at the higher fee. ESC recommended molecular methods should be specified in CCCC and DDDD, for clarity and to be consistent with the method being stated in the MRD item descriptors supported by MSAC under Application 1707.

ESC's proposed revisions to the MBS item descriptors are shown below.

Table 13 ESC's proposed revisions to the MBS items for MRD testing using molecular methods other than NGS

Category 6 – Pathology services	Group P7 Genetics
MBS item CCCC Development of a *quantitative* patient-specific ~~quantitative~~ *molecular* assay for measurable residual disease (MRD) based on the diagnostic bone marrow specimen from a patient diagnosed with acute lymphoblastic leukaemia (ALL) treated with combination chemotherapy or after salvage therapy, requested by a specialist or consultant physician practising as a haematologist or oncologist, and use on the first MRD specimen for one test described in item DDDD. Applicable not more than once per patient per ~~course~~ *episode* of disease *or per relapse.* ~~Maximum of 12 per course of disease for AAAA, BBBB, CCCC, DDDD, and EEEE combined~~ Fee: $3,000.00 Benefit: 75% = $2,250.00 85% = $2,906.80*	
MBS item DDDD Measurable residual disease testing by a quantitative patient-specific *molecular* assay on bone marrow from a patient diagnosed with acute lymphoblastic leukaemia (ALL) treated with combination chemotherapy or after salvage therapy, requested by a specialist or consultant physician practising as a haematologist or oncologist. ~~Maximum of 12 per course of disease for AAAA, BBBB, CCCC, DDDD, and EEEE combined~~ Fee: $780.00 Benefit: 75% = $585.00 $85% = $686.80*	

New Practice Note (CCCC, DDDD): 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.

ESC's additions are shown in green italics, and deletions in strikethrough.
* 85% benefit reflects the 1 November 2022 Greatest Permissible Gap (GPG) of $93.20. All out-of-hospital Medicare services that have an MBS fee of $621.50 or more will attract a benefit that is greater than 85% of the MBS fee – being the schedule fee less the GPG amount. The GPG amount is indexed annually on 1 November in line with the Consumer Price Index (CPI) (June quarter). Source: MSAC Application 1703 and Ratified PICO 1703

ESC considered that the reasons to use ASO-qPCR methodology specifically are because this method uses a patient-specific assay to target the genetic mutation in each patient's dominant leukaemic clone, and it is a very sensitive method of MRD detection (more sensitive than mpFC but less sensitive than NGS). ESC noted that qPCR MRD testing is standardised for multi-site clinical trials through the EuroMRD group, and it is currently the method of choice for large international ALL trials registered in Europe. ESC noted the evidence suggested that mpFC and qPCR may be used as complementary MRD methodologies in early stages as well as in late stages after therapy, and there are clinical, technical and logistical reasons why laboratories may wish to have more than one publicly funded method available.

ESC noted that bone marrow (usually aspirate or occasionally biopsy) is the preferred sample type to perform MRD testing, and that PASC had considered the use of peripheral blood but had advised the assessment should be limited to bone marrow samples. ESC noted that at initial diagnosis the proportion of blasts in peripheral blood is typically high, so considered that restricting the sample to be used for assay development (item CCCC) to bone marrow samples may not be necessary. ESC further noted scientific literature that supported that peripheral blood may alternatively be used for MRD testing[16,17], especially for patients with T-ALL[18,19], and that in its experience peripheral blood samples were occasionally used when a bone marrow sample was unavailable, and that a positive MRD result from peripheral blood was likely a true positive, although the converse was not necessarily true. ESC noted that MRD levels tend to be higher in bone marrow than in peripheral blood, but considered that for some patients a bone marrow specimen may not be available and a peripheral blood sample could potentially be used to provide a positive MRD result. ESC considered there is a chance that the biomarker could differ between tissues, and while this was not examined by the assessment, noted that Coustan-Smith 2002 reported MRD testing in blood samples detected 100% (n=35) of bone marrow positives in patients with T-ALL, although only 36% (37/104) of bone marrow positives in patients with B-ALL. ESC requested the Department seek expert advice from organisations such as the HSANZ to inform MSAC's consideration of whether ASO-qPCR assay design and/or subsequent MRD testing could also use peripheral blood samples. ESC noted that occasionally when sampling bone marrow a "dry tap" occurs where no bone marrow cells are collected, and considered that it was reasonable to perform MRD testing on the sample collected by a bone marrow biopsy even if the sample was a dry tap.

On test sensitivity and accuracy, ESC noted MSAC had already accepted under application 1707 that MRD testing using mpFC or NGS was vastly more sensitive than morphological assessment (+/- cytogenetics) in patients with ALL. ESC noted the DCAR's analysis of 35 cohort studies showed poor concordance between qPCR and morphological assessment (average concordance 58%), and high concordance between qPCR and mpFC (average concordance 84%). ESC considered the limited available evidence showed qPCR performed better than morphological assessment in detecting MRD, although was insufficient to determine whether NGS or qPCR was superior as it was comprised of studies with small samples sizes that reported variable concordance rates. ESC noted the heterogeneity between studies made it difficult to conclude

[16] van der Velden VH et al (2002) Minimal residual disease levels in bone marrow and peripheral blood are comparable in children with T cell acute lymphoblastic leukemia (ALL), but not in precursor-B-ALL. *Leukemia,* **16**(8):1432-6.

[17] Muffly L et al (2021) Concordance of peripheral blood and bone marrow measurable residual disease in adult acute lymphoblastic leukemia. *Blood Adv,* **5**(16):3147-3151.

[18] Coustan-Smith E et al (2002) Use of peripheral blood instead of bone marrow to monitor residual disease in children with acute lymphoblastic leukemia. *Blood,* **100**(7): 2399-2402.

[19] Kotrova M et al (2020) Comparison of minimal residual disease levels in bone marrow and peripheral blood in adult acute lymphoblastic leukemia. *Leukemia*, **34**:1154–1157.

the most effective threshold of sensitivity for qPCR, although it showed that qPCR was more effective at higher thresholds of sensitivity of detection rather than lower when compared with morphological assessment.

ESC noted that the applicant had claimed that MRD testing is superior to bone marrow morphological assessment because it allows more appropriate treatment allocation. ESC agreed that the clinical utility of MRD testing is well established, and noted that in relation to application 1707 MSAC had already accepted "*that incorporation of MRD testing into the care pathway was of prognostic significance and that the MRD test results changed patient management*"[20]. ESC considered the DCAR presented evidence supporting the improved prognostic accuracy, changes in management and improved health outcomes with MRD testing compared to no MRD testing.

ESC noted that the MBS fee proposed for item CCCC was $3,000 and that the costing in the PICO showed this was mainly due to the high scientific labour cost to develop a patient-specific ASO-qPCR assay. ESC noted the fee for MBS item DDDD was lower at $780 to reflect the subsequent lower cost of running the developed patient-specific assay. ESC considered that ASO-qPCR is more expensive than other molecular methods because unique primers need to be developed for each patient to monitor the presence of disease. ESC considered it was uncertain whether the higher proposed fees for ASO-qPCR would also be appropriate for other qPCR methods. ESC also noted that ASO-qPCR is more labour-intensive than methods such as NGS and mpFC, and that not all laboratories will have the capacity to offer MRD testing using ASO-qPCR. ESC also noted that the specific primers and probes required for ASO-qPCR are not universally available, which could contribute to equity-of-access issues.

ESC noted that the economic evaluation was a cost-effectiveness analysis and a cost-utility analysis, and that the MRD testing methodology for items CCCC/DDDD was described as "PCR", which it considered was broad and encompassed any type of PCR. Overall, ESC considered the economic model was detailed and well considered, and most of its assumptions seemed reasonable. ESC compared the economic model against that from 1707, and noted that there were many similarities. The differences were that the intervention for 1703 also included PCR, and the 1703 model was a partitioned survival analysis using proportional hazards modelling. ESC noted there was no direct comparative evidence, so the DCAR had instead constructed a large network of multiple indirect comparisons. ESC also noted that the 1703 model had more health states, which it considered was appropriate. ESC considered the model was very detailed. ESC noted there had only been one previous published model: a Canadian model in 2016[21] that was more straightforward with only nine health states, and which did not include updated therapies. ESC considered the DCAR's model was therefore an improvement on previous published models.

ESC considered that the model's approach to model transition probabilities was unique, in that it digitised Kaplan-Meier curve data to derive the transition probabilities, then applied hazard ratios to those rates, and did so for relapse-free survival (RFS) for both adult and paediatric populations. ESC considered this approach was robust, valid and detailed. ESC noted baseline survival curves were validated against the model survival output.

ESC considered that other limitations of the model included that using this approach it could only include published data that contained Kaplan–Meier curves. ESC also considered that the model made assumptions, although most of these were reasonable. Assumptions included: that event-

[20] MSAC public summary document (PSD) for application 1707 - clonoSEQ® and mpFC for the detection of measurable residual disease (MRD) in acute lymphoblastic leukaemia (ALL).

[21] Health Quality Ontario (2016). Minimal Residual Disease Evaluation in Childhood Acute Lymphoblastic Leukemia: An Economic Analysis. *Ontario Health Technology Assessment Series,* **16**(8), 1-83.

free survival (EFS) was interchangeable with RFS; that studies reporting health outcomes in adults or children can be used for the other population when no data are available; and that disease progression with each therapy is independent of line of therapy. ESC considered that the relapse rates used in the model were quite high (29%) and uncertain given the applicant had estimated 50% relapse in infants aged under 12 months and 10% for patients aged 1-18 (PICO, page 5), although not per MRD test and the period to which the stated rates referred was uncertain. ESC noted the model had assumed a relapse rate in the paediatric population in year 3 from morphological analysis of 73%, which was higher than the applicant's advice. However, ESC considered that sensitivity analyses showed that the relapse rates did not significantly affect the ICERs. ESC also queried how the 6-month terminal care costs had been applied, and noted that the utilities for "high risk" patients were assumed to be half that of "standard risk" patients, which it considered to be uncertain.

Another limitation of the model was that it assumed there would be no relapsed patients in year 1 or 2, from patients diagnosed prior to year 1 or incident patients, which ESC considered was likely not realistic given the high relapse rates in some types of ALL. ESC also noted that very young and very old patients are more likely to relapse within two years. ESC considered that the proportion of patients who would relapse within the first two years should be included, as while it would likely not make a significant impact on the ICERs it would affect the financial impact.

ESC noted other limitations of the model, including the heterogeneous outcomes from the indirect comparisons and the assumptions used for the proportional hazards modelling approach, but considered the sensitivity analyses demonstrated that the ICERs were robust and none of the variations to inputs significantly affected the ICERs, or the financial analyses. However, due to the assumptions, there was still uncertainty associated with the model and the results should be interpreted with caution.

ESC noted stepped incremental cost-effectiveness ratios (ICERs) were presented separately by MRD testing method (Table 7). ESC noted that the effectiveness result for qPCR for adults in step 1 represented a 5-year survival of 67.5%, which it considered aligned very closely with the reported 69% 5-year survival. ESC also compared the CUA results between the different MRD testing methods, and noted that incremental QALYs for PCR were higher than other methods in adults but lower than other methods in children, whereas incremental costs for PCR were higher than other methods in children and between those of mpFC and NGS for adults (Table 8).

ESC noted the possibility of insufficient sample requiring a re-biopsy had not been considered by the DCAR, though the applicant had previously commented that "rebiopsies occur in very rare circumstances, and could occur for MRD testing alone" (PICO, page 8), and in relation to application 1707 MSAC had advised that "*typically no additional clinical procedures are needed to allow MRD testing to take place*" (1707 PSD, page 5). ESC considered that additional bone marrow sampling may be required to support the proposed services, though likely this would be rare and would not have a large impact on the ICERs. Post-ESC, the HTA group provided updated economic results for PCR methods including a re-biopsy rate of 4% per annum: these showed the ICER for adults increased from $7,318 to $7,334 per QALY (0.22% increase), and the ICER for the paediatric population increased from $30,788 to $30,821 per QALY (0.11% increase) (Table 8).

ESC noted that the sensitivity analyses showed that the ICERs were overall very stable; the main drivers were the hazard ratios and clinical parameters. ESC noted that the PICO defined the primary comparator as "morphological assessment ± cytogenetic analysis", and that the DCAR had mainly used morphological assessment without cytogenetics. ESC noted that the comparator 'morphological assessment plus cytogenetics' had been addressed through sensitivity analyses, and that using this comparator increased the ICER by 54.5% in adults and 75.4% in children. ESC

considered that the additional value of cytogenetic testing was uncertain, and that given MRD testing is commonly used this comparison may not be highly relevant. ESC noted that threshold analyses showed uptake rates and the proportion of patients eligible for testing changed the economic results by 15-20%.

ESC also compared the weighted cost-utility analysis results (for mpFC, PCR and NGS) against those from application 1707 (for mpFC and NGS), and considered that there were many differences between the two economic models. ESC noted that the adult and paediatric ICERs estimated in 1703 were approximately one third of those estimated in 1707.

ESC noted that the proportion of patients estimated to use each method of MRD testing was estimated by the DCAR to be 24% mpFC / 38% NGS /38% qPCR, although evidence for this was limited. The DCAR had based its estimated proportions on only 90% of the 85% of patients with B-ALL having sequences identifiable by the clonoSEQ® NGS assay according to the 1707 ADAR (and therefore the remaining patients could only receive mpFC MRD testing in the 1707 assessment as it did not include PCR), giving an estimated 23.5% of patients with ALL that were assumed in the 1703 DCAR to not be able to use NGS or ASO-qPCR methods, then dividing the remainder of patients equally between NGS and qPCR methods. However, ESC noted that in relation to application 1707 MSAC had considered the 15% of patients who have T-ALL would not be ineligible for MRD testing using generic NGS methods.

ESC noted that the estimated number of MRD services was lower than that previously reported in application 1707, and considered that the numbers of services presented in application 1703 were more accurate because they used an average growth rate of 1.7% based on the ALL-specific incidence, whereas 1707 had used an average growth rate of 3% based on all haematological cancers. However, ESC also considered that the omission of patients relapsing within years 1 and 2 as described above meant the utilisation and financial impact would have been underestimated in those years. Post-ESC, the HTA group provided financial analyses updated to include patients relapsing within years 1 and 2 as well as a re-biopsy rate of 4% per annum: these showed that the cost to the MBS would be approximately $100,000 per year higher in years 3-6, and depending on the relapse rate $200,000-$425,000 higher in years 1-2 (Table 10). ESC noted relapse rates were based on the applicant's estimated relapse rates as stated in the PICO, although because it was unclear what timeframe those rates were measured across scenarios were provided for year 1 and 2 relapse rates of either 3% and 17% per annum (for a 3-year relapse rate), or 10% and 50% per annum (for a 1-year relapse rate). ESC noted the revised financial impact to the MBS was approximately $2.4-$2.7 million per year, depending on relapse rate (Table 10).

Because the fees for MBS items CCCC and DDDD were proposed specifically for ASO-qPCR, ESC considered the financial analysis was therefore specific to ASO-qPCR, which may be misaligned with the broader set of PCR methodologies included in the clinical and economic evaluations.

ESC noted that the NPAAC had advised that the MRD assay needs to be validated so that it meets the required sensitivity level according to NPAAC's in-house in vitro diagnostic assay standard, and overseen by the TGA and NATA. ESC noted that NPAAC could not confirm whether an external quality assurance (EQA) program was available internationally.

17. Applicant comments on MSAC's Public Summary Document

The College's Working Party would like to express their delight in MSAC approving public funding of measurable residual disease in patients with acute lymphoblastic leukaemia, and would like to take this opportunity to thank the Department for its assistance throughout the assessment process.

18. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website