

Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1707 – clonoSEQ® and mpFC for the detection of measurable residual disease (MRD) in acute lymphoblastic leukaemia (ALL)

Applicant: Adaptive Biotechnologies™

Date of MSAC consideration: 24-25 November 2022

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

1. Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of polymerase chain reaction (PCR)- and next generation sequencing (NGS)- based testing using the clonoSEQ® assay, and multi-parametric flow cytometry (mpFC), for the detection of measurable residual disease (MRD) in patients with de novo or relapsed acute lymphoblastic leukaemia (ALL), was received from Adaptive Biotechnologies™ 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 detection of measurable residual disease (MRD) in patients with acute lymphoblastic leukaemia (ALL), using flow cytometry and next-generation sequencing (NGS) methods. MSAC supported public funding of MRD testing because it is the established standard of care in these patients, and to correct the current inequity of access to the testing required to access PBS-listed blinatumomab. MSAC recognised the clinical benefit of MRD testing, accepted that MRD testing in patients with ALL had non-inferior safety, provided diagnostic, prognostic and/or predictive utility, and had acceptable cost-effectiveness. MSAC considered that the evidence had not demonstrated the clonoSEQ® test to be superior to other molecular methods, so there was no justification for a higher fee. The evidence also did not justify why MBS-funded testing should be limited to the gene variants detected by the clonoSEQ®, test so MSAC advised a generic item for MRD testing using NGS methods was appropriate. MSAC advised that this testing would have a modest financial impact to the MBS.

Table 1 MSAC’s supported MBS item descriptors

Category 6 – Pathology services (Group P4 Immunology)
<p>AAAA</p> <p>Measurable residual disease (MRD) testing by flow cytometry, performed on bone marrow from a patient diagnosed with acute lymphoblastic leukaemia (ALL) for the purposes of determining baseline MRD or facilitating the determination of MRD following combination chemotherapy or after salvage therapy, requested by a specialist or consultant physician practising as a haematologist or oncologist.</p> <p>Fee: \$550.00 Benefit: 75% = \$412.50 85% = \$467.50</p>
Category 6 – Pathology services (Group P7 Genetics)
<p>EEEE</p> <p>Measurable residual disease (MRD) testing by next-generation sequencing, performed on bone marrow from a patient diagnosed with acute lymphoblastic leukaemia (ALL) for the purposes of determining baseline MRD or facilitating the determination of MRD following combination chemotherapy or after salvage therapy, requested by a specialist or consultant physician practising as a haematologist or oncologist.</p> <p>Fee: \$1,550.00 Benefit: 75% = \$1,162.50 85% = \$1,456.80</p>

Where relevant, 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).

Practice Note (AAAA, EEEE): 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.

<p>Consumer summary</p> <p>This was an application from Adaptive Biotechnologies 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 when a genetic variant that arises in a person’s white blood cells 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 use a bone marrow sample because the bone marrow is where white blood cells are made.</p> <p>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.</p> <p>There are several methods that can be used to test for measurable residual disease, including multiparametric flow cytometry (mpFC) and next-generation sequencing (NGS). Not all types of cancer-causing genetic variant can be detected using one testing method, so one MRD testing method will not work for all patients, and different MRD testing method options will need to be available. This application requested two methods be listed on the MBS for patients with ALL: mpFC, and NGS-based testing using only the clonoSEQ® brand assay.</p> <p>Testing for measurable residual disease is already routine healthcare in Australia for patients with ALL, but it is not currently funded on the MBS. Patients either pay for it themselves or the test is funded by public hospitals. In particular, the Pharmaceutical Benefits Scheme (PBS) has a rule that patients with ALL need to test positive for MRD before they can access a drug called</p>

Consumer summary

blinatumomab, so MSAC considered that it was important to fund MRD testing on the MBS so that all patients can access blinatumomab.

MSAC considered that measuring MRD results in better health outcomes for patients, including longer survival, and provides good value for money. MSAC recommended that MRD testing using mpFC and any NGS method should be added to the MBS, and considered that the financial cost to the MBS would be acceptable.

Because the evidence had not justified restricting MRD testing that uses NGS methods to only the clonoSEQ® brand of assay, MSAC advised that MRD testing using NGS methods should be generic: in other words, it should also include other brands of NGS test, and non-branded NGS tests too. The fee that Adaptive Biotechnologies had proposed was higher than the fee proposed in a similar application for generic NGS MRD testing in patients with ALL, and because the evidence did not justify the higher fee MSAC reduced the fee to align with the fee proposed for generic NGS MRD testing.

MSAC's advice to the Commonwealth Minister for Health and Aged Care

MSAC supported listing of mpFC and generic NGS-based MRD testing on the MBS for patients with acute lymphoblastic leukaemia. MSAC considered MRD testing to be safe, effective, good value for money, and to have an acceptable cost to the MBS.

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

MSAC noted that this application from Adaptive Biotechnologies was requesting MBS listing of clonoSEQ® and multiparametric flow cytometry (mpFC) for the detection of measurable residual disease (MRD) in patients with acute lymphoblastic leukaemia (ALL). MSAC noted that MRD was previously described as “minimal residual disease”, but that the accepted terminology is now “measurable residual disease”.

MSAC noted that MRD testing is already the established standard of care for patients with *de-novo* or relapsed ALL in Australia. MRD testing is required before a patient can access Pharmaceutical Benefits Scheme (PBS)-subsidised blinatumomab therapy. As MRD testing is not currently funded under the MBS, patients currently either pay out-of-pocket or the test is funded through state or territory hospitals.

MSAC noted that the Royal College of Pathologists of Australasia (RCPA) also submitted an application (MSAC application 1703) proposing generic (i.e., non-proprietary) MBS items for three methods for detection of MRD in patients with ALL (mpFC, allele-specific oligonucleotide quantitative PCR (ASO-qPCR), and next-generation sequencing (NGS) methods), and that applications 1703 and 1707 had shared a PICO. Application 1707 proposed MBS items for MRD testing in patients with ALL by PCR- and NGS-based methods (specifically using the clonoSEQ® assay), and using mpFC.

MSAC noted that MRD test results are used to predict the risk of relapse in patients with ALL (and stratify patients based on this risk), decide on appropriate treatment, and provide access to treatments including PBS-subsided blinatumomab. MSAC considered that at present there is inequity of access to PBS-listed blinatumomab, and that listing MRD testing on the MBS would correct this inequity. MSAC considered that incorporation of MRD testing into the care pathway was of prognostic significance and that the MRD test results changed patient management. This conclusion was based on the evidence presented from two randomised controlled trials, two retrospective cohort studies and three prospective cohort studies ($n = 3,126$). MSAC considered

that MRD testing can detect patients who are in morphological remission but have residual disease, and this allows timely treatment that improves survival.

MSAC noted that mpFC has a faster turnaround time but must be performed on viable cells, whereas molecular methods have a slower turnaround time but are more robust. MSAC agreed that molecular methods and mpFC are complementary as one method alone will not be able to detect the types of clonal variants present in all patients. MSAC noted that once a patient's clonal marker is successfully measured with one method, the patient is likely to continue to have their MRD tested using that method.

MSAC noted that MRD testing would be performed in addition to the comparator, bone marrow morphological assessment \pm cytogenetic analysis. MSAC noted that the applicant-developed assessment report (ADAR)'s primary comparator was bone marrow morphological assessment \pm cytogenetic analysis, referred to as "no MRD testing", and that the secondary (near-horizon) comparator was other molecular methods of MRD testing, such as other proprietary forms of NGS assay or ASO-qPCR. MSAC considered that the ADAR did not characterise the different methods in its secondary comparator, or provide sufficient comparison of clonoSEQ[®] with these methods. MSAC also noted that the ADAR's economic and financial analyses also considered no MRD testing to be the comparator.

MSAC noted that PASC had advised that the test options proposed by both 1703 and 1707 should be compared with each other as well as with the current comparator, to justify the difference in proposed fees between the two applications. ESC considered that the ADAR for 1707 had not conducted all comparisons as requested by PASC, and the evidence provided did not sufficiently justify the higher fee in application 1707 compared to the generic molecular methods proposed in application 1703. MSAC considered that the ADAR's assumption that other MRD testing methods besides mpFC and clonoSEQ[®] will not be used was not reasonable.

MSAC considered that while the evidence presented by the ADAR had demonstrated that MRD testing was superior to no MRD testing, it had not demonstrated that MRD testing using clonoSEQ[®] was superior to other MRD testing using other quantitative molecular methods. MSAC noted that the ADAR proposed NGS testing specifically using clonoSEQ[®], and made statements claiming clonoSEQ[®] was superior to other molecular methods, but provided no additional evidence to support its claim of superiority. MSAC considered that the evidence presented did not provide sufficient argument as to why MBS-funded testing using NGS methods should be restricted to clonoSEQ[®], nor justify why the proposed wording in the item descriptor be limited to NGS testing of the gene variants detectable by clonoSEQ[®]. MSAC noted consultation feedback stating that the descriptor for item EEEE should not list which markers need to be reported, as this may prevent clinicians from exercising clinical judgement, and also may lead to the item descriptor quickly becoming outdated and superseded by future developments in clinical practice. MSAC therefore advised that MRD testing using NGS methods should not be restricted to clonoSEQ[®], and supported an MBS item for generic NGS-based testing, in addition to an MBS item for MRD testing using mpFC. MSAC noted that item BBBB from the 1703 PICO was stated to be for generic NGS however only proposed that "a quantitative molecular methodology" be specified, so was not specific to NGS methods. MSAC considered that the generic NGS MBS item supported for 1707 should clearly exclude ASO-qPCR, which is a less resource-intensive molecular method that should have a commensurately lower fee. Hence MSAC advised the wording for the item arising from 1707 should specify NGS methods rather than any molecular method.

MSAC noted that the proposed proprietary clonoSEQ[®] assay had not been approved for use in Australia, though the applicant advised it had a concurrent application under assessment by the Therapeutic Goods Administration (TGA). MSAC considered that it would therefore have to defer

advice on funding for clonoSEQ® specifically, however such deferral was not necessary for the MSAC-supported generic NGS item.

MSAC noted the applicant's proposed fee for NGS testing using clonoSEQ® specifically was \$2,100, which it considered to be high and insufficiently justified. MSAC considered that the evidence presented by the ADAR had not demonstrated a benefit over MRD testing using other molecular methodologies, and so a higher fee than that for generic NGS methods proposed under application 1703 (BBBB fee: originally proposed at \$1,150, then revised by the 1703 applicant to \$1,550 to reflect less efficient batching in smaller laboratories) was not warranted. MSAC further noted that the applicant advised in its pre-MSAC response that at 100% Illumina sequencer capacity the cost of testing using clonoSEQ® was \$1,583. MSAC recalled it has previously supported several other genomic tests at a fee of \$1,200, and that a fee of \$1,550 would be higher than this, though may be justified as a higher read depth is required. MSAC considered that the appropriate fee for NGS-based MRD testing should also be consistent with the department's ongoing reforms to align the fees for comparable genomic tests. On balance, MSAC advised that the appropriate fee for generic NGS-based MRD testing was \$1,550.

MSAC agreed that haematologists and oncologists are the appropriate requestors for MRD testing.

MSAC considered that while the proposed restriction to 12 instances of use per episode of disease was clinically appropriate, it cannot currently be automatically enforced through Medicare payment systems prior to the payment of benefits, and may only be enforced through post-payment compliance activity. MSAC noted ESC's advice that overservicing would be highly unlikely because the standard clinical management algorithms for high-risk and relapsed children and adults used seven or fewer tests, and bone marrow testing requires a surgical procedure that is usually avoided if possible. MSAC therefore advised moving the restriction of maximum 12 tests per course of disease from the item descriptor to a practice note. MSAC considered that the 'average' number of tests per episode of disease was not a meaningful description on a per-patient basis, and removed the word 'average' from the practice note.

MSAC considered that there were no additional safety concerns because MRD testing is performed in addition to bone marrow morphological assessment ± cytogenetic analysis, which already requires a bone marrow sample. Therefore, as typically no additional clinical procedures are needed to allow MRD testing to take place, it is considered to have non-inferior safety.

MSAC noted the ADAR presented clinical evidence supporting that MRD testing allows better prognostication, and risk stratification to better inform treatment. MSAC was confident that the data presented showed MRD testing resulted in a change in patient management, compared to no MRD testing. MSC noted that the evidence presented on accuracy was not entirely applicable, as it compared MRD using clonoSEQ® against mpFC, even though the PICO had specified the comparison should be molecular and mpFC methods against current testing. MSAC noted the data from Gupta 2018 demonstrated the incremental prognostic value of MRD testing over current bone marrow morphological testing (Table 10). MSAC noted the concordance studies comparing MRD detection using clonoSEQ® compared to mpFC showed concordance was between 68% to 87%.

MSAC noted that the economic evaluation was a cost-utility analysis and a cost-effectiveness analysis. MSAC noted the ADAR reported the incremental cost-effectiveness ratios (ICERs) for MRD testing compared to no MRD testing were \$29,517 per quality-adjusted life year (QALY) for the paediatric population and \$12,332 per QALY for the adult population, but that ESC had considered it was appropriate to correct the economic model to include the price of blinatumomab. Applying the PBS listed price for blinatumomab increased the ICER for the paediatric population to \$62,694/QALY and for the adult population to \$42,189/QALY (with

ICERs lower than this when the effective price of blinatumomab was applied). MSAC considered that the cost-effectiveness of MRD testing against no MRD testing had been demonstrated, and advised that MRD testing was cost-effective. MSAC noted the cost-effectiveness results were relatively robust against changes to inputs except downstream inputs related to blinatumomab.

MSAC noted that the ADAR did not compare clonoSEQ® testing versus other NGS methods in its main economic model as requested by PASC. The pre-MSAC response stated this was because clonoSEQ® is the only brand of NGS MRD assay seeking TGA approval at this time, and MSAC has previously expressed a strong preference for TGA-approved genetic panel tests. MSAC considered that while regulatory approval is important for tests that require it, omission of the requested comparisons from the ADAR meant that the applicant had not demonstrated that clonoSEQ® to be superior to other molecular methods of NGS testing. MSAC was not persuaded by the applicant's claim that the evidence base for clonoSEQ® would not be generalisable to generic NGS methods. MSAC noted that the ADAR compared clonoSEQ® with ASO-qPCR and yielded very high ICERs (\$721,379 for paediatrics and \$100,299 for adults), however there were no supporting data or calculations provided for these figures, so they could not be verified, and were not further discussed by the ADAR. MSAC further noted the ADAR assumed ASO-qPCR had equal cost-effectiveness to mpFC. MSAC considered that the economic analysis did not establish any incremental benefit or cost-effectiveness of clonoSEQ® compared with other molecular methods.

MSAC noted that the financial impact depended on the utilisation rate and the MBS fee. MSAC noted the ADAR estimated 10% of MRD testing to use clonoSEQ® in Year 1 (with the remainder using mpFC), with clonoSEQ® use increasing by 10 percentage points each year until stabilising at 50%. MSAC considered that as clonoSEQ® can only be used by patients with B-ALL, the share of testing using clonoSEQ® specifically could not exceed 85%. MSAC noted the ADAR had excluded 10% of adult patients from being eligible for MRD testing using any method because they had T-ALL, which MSAC considered was not appropriate. MSAC revised the utilisation and financials to include 100% of adult patients being eligible for MRD testing using any method, before the split into mpFC and NGS. MSAC noted the ADAR's financial modelling showed MRD testing would have a net cost to the MBS of \$1.44 million in Year 1 up to \$3.60 million in Year 6, though had not applied the greatest permissible gap (GPG) correctly in its calculations. MSAC considered that at its supported fees and using the November 2022 GPG amount, the revised estimate of the financial cost to the MBS would be \$1.38 million in Year 1 up to \$2.94 million in Year 6 (see updated rows in Table 18). MSAC considered this financial impact to the MBS to be modest and acceptable. MSAC further considered that even at the ceiling of 85% utilisation of clonoSEQ® (that is, all patients with B-cell ALL), at its revised fees the annual cost to the MBS would be \$2.9 to \$4.0 million. MSAC noted that no other financial impacts of listing MRD testing on the MBS were proposed, and considered this to be reasonable as MRD testing is already standard of care. MSAC considered that although MBS listing does not fund testing for public patients in public hospitals, it would increase equity of access for private patients, including private patients treated at public hospitals.

MSAC noted that some blinatumomab listings on the PBS for patients with ALL require patients to have "minimal residual disease defined as at least 10^{-4} (0.01%) blasts based on measurement in bone marrow". MSAC considered that NGS methods are reported to have a lower threshold of detection than this, and that while rates of relapse were not expected to change, if the PBS allowed a lower threshold of detection then this would potentially lead to earlier use of blinatumomab and other agents in the setting of ALL. MSAC considered that the PBAC should consider reviewing its restrictions to bring them in line with the lowered threshold for the detection of MRD.

MSAC recommended the MBS items be reviewed after two years, as there is a high level of uncertainty (potential under and overutilisation) regarding the likely uptake of molecular methods in this setting.

4. Background

MSAC has not previously considered MRD testing.

5. Prerequisites to implementation of any funding advice

The applicant was concurrently seeking Therapeutic Goods Administration (TGA) approval for the clonoSEQ® assay, a next generation sequencing (NGS)-based test for MRD in patients with acute lymphoblastic leukemia (ALL).

6. Proposal for public funding

The ADAR proposed use of two methods for the detection of MRD: mpFC, and PCR- and NGS-based testing via clonoSEQ® assay. The ADAR stated that a complex disease such as ALL required a range of MRD tests to cover all use cases. Therefore, both clonoSEQ® and mpFC were proposed as interventions to manage the patient variability and ensure all patients have access to an MRD test best suited for their needs.

The ADAR used the MBS fee for MRD testing by mpFC of \$550 (benefit: 75% = \$412.50, 85% = \$467.50) as proposed by the RCPA as applicant for MSAC application 1703 and agreed by PASC, which factors in the cost of cell processing and data capture, reagents used, scientific labour cost and instrument amortisation. The ADAR's proposed MBS item for the use of mpFC to detect MRD, and a breakdown of the costs associated with mpFC, are presented in Table 2 and Table 3 respectively. The Commentary found that the ADAR's item descriptor differed from that in the Ratified PICO in several ways: it stated "Minimal" instead of "Measurable", "patients" instead of "a patient", omits "requested by a specialist or consultant physician practising as a haematologist or oncologist", and stated "per episode of disease" instead of "per course of disease".

Table 2 ADAR's proposed MBS item for mpFC for MRD testing

Category 6 – Pathology services Group 1 Haematology, Group P6 Cytology
MBS item AAAA
Minimal residual disease testing by flow cytometry in patients diagnosed with acute lymphoblastic leukaemia (ALL) treated with combination chemotherapy treatment or after salvage therapy.
Maximum of 12 per episode of disease for AAAA and BBBB combined
Fee: \$550.00 Benefit: 75% = \$412.50 85% = \$467.50

Source: Table 15, page 47 of MSAC 1707 ADAR

Abbreviations: ALL, acute lymphoblastic leukaemia

Table 3 Breakdown and overall cost of mpFC

Cost component	mpFC
Cell processing and data capture / sample processing	\$160
Reagents including fluorochrome-labelled antibodies / other consumables	\$110
Scientific labour cost	\$280
Instrument amortisation	-
Total cost	\$550
Proposed MBS fee (AAAA)	\$550

Source: Table 16, page 47 of MSAC 1707 ADAR in the ADAR

Abbreviations: MBS, Medicare Benefits Schedule; mpFC, multi-parametric flow cytometry

The ADAR proposed that the MBS item descriptor for the NGS test be formulated to reflect and support the use of the clonoSEQ[®] assay. The proposed MBS fee for MRD testing by clonoSEQ[®] was \$2,100 (benefit: 75% = \$1,575, 85% = \$2,012.10), which factors in the cost of reagents, scientific labour and instrument amortisation. The proposed MBS item for the use of clonoSEQ[®] to detect MRD and a breakdown of the costs associated with clonoSEQ[®] (as presented in the ADAR) are presented in Table 4 and Table 5, respectively. The NGS-based MRD testing using the clonoSEQ[®] assay is expected to take between 7 to 14 days from receiving the sample.

The Commentary found that this item descriptor differed from that in the Ratified PICO in several ways: it abbreviated “B-cell receptor gene” to “BCR”, it stated “measurable/minimal” instead of “measurable”, it stated “bone marrow aspirate or peripheral blood” instead of “bone marrow”, it stated the test is “requested on behalf of, a specialist physician” instead of “requested by a specialist or consultant physician practising as a haematologist or oncologist”, it added “for the purpose of guiding treatment decisions”, and it stated “per episode of disease” instead of “per course of disease”. Further, the description of the population in the ADAR indicated that the maximum number of MRD tests per patient per course of disease will be greater than 12 in cases where patients require more than one type of MRD testing. Examples for this increased number were those requiring subsequent mpFC tests after a clonoSEQ[®], or those requiring other molecular tests in addition to the two interventions considered in this ADAR.

The Commentary found that the proposed MBS item descriptors would allow any patient with ALL to be tested with mpFC or clonoSEQ[®], however the ADAR described that only patients with B-ALL would be tested with clonoSEQ[®], patients with T-ALL tested with mpFC and patients with B-ALL without molecular variants identifiable by the clonoSEQ[®] assay would be tested with mpFC. The identification of patients without molecular variants that are identifiable by clonoSEQ[®] was not defined within the ADAR, and it was uncertain whether patients would be tested by clonoSEQ[®] to determine whether these patients do not have these molecular variations. This would impact the number of tests required by patient. The total maximum number of tests per patient per course of disease (n=12 as indicated in Table 15 of the ADAR) did not account for these patients who would undergo both mpFC and clonoSEQ[®] testing. The number of tests per course of disease was also inconsistent with Table 10 in the ADAR, which lists a maximum of n=17 tests in paediatric population and n=12 tests in adults. The ADAR did not clarify why it proposed additional mpFC tests would be required in the paediatric populations and the reasons to do so.

Table 4 ADAR’s proposed MBS item for clonoSEQ® assay for MRD testing

Category 6 – Pathology services (Group P7 Genetics)
MBS item EEEE
Identification and quantitation of rearranged BCR sequences (including IgH [VDJ], IgH [DJ], IgK, IgL, translocated BCL1/IgH [J] and BCL2/IgH [J] sequences), for the evaluation of measurable/minimal residual disease (MRD) using multiplex polymerase chain reaction (PCR) and massively parallel sequencing (also referred to as next generation sequencing) performed on DNA extracted from bone marrow aspirate or peripheral blood from a patient diagnosed with acute lymphoblastic leukaemia, as requested on behalf of, a specialist or consulting physician, for the purpose of guiding treatment decisions.
Maximum of 12 per episode of disease
Fee: \$2,100.00 Benefit: 75% = \$1,575.00 85% = \$2,012.10*

Source: Table 17 page 48 of MSAC 1707 ADAR

* Reflects the 1 November 2021 Greatest Permissible Gap (GPG) of \$87.90. All out-of-hospital Medicare services that have an MBS fee of \$586.20 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).

Table 5 Breakdown and overall cost of clonoSEQ®

Cost component	clonoSEQ®
Cell processing and data capture / sample processing	-
Reagents and other consumables	
Scientific labour cost	
Instrument amortisation	
Total cost	\$2100
Proposed MBS fee (EEEE)	\$2100

Source: Table 18 page 48 of MSAC 1707 ADAR.

Abbreviations: MBS, Medicare Benefits Schedule

7. Population

PASC noted that both this application and MSAC application 1703 were explicit that the proposed populations were patients with ALL, and not acute myeloid leukaemia (AML).

The ADAR specified that clonoSEQ® assay is available only for patients with B-cell ALL, which constitutes 85% of ALL cases, noting that a large proportion of the literature provides evidence to support the use of clonoSEQ® in this population (Jean Marcus 2016). Given the current availability of the clonoSEQ® assay, the ADAR proposed the following population for the primary intervention (clonoSEQ®): paediatric and adult patients with B-ALL with IgH (VDJ), IgH (DJ), IgK and IgL receptor gene sequences or translocated BCL1/IgH (J) and BCL2/IgH (J) sequences. The ADAR proposed the population for the secondary intervention (mpFC) as paediatric and adult patients with B-ALL without molecular variants identifiable by the clonoSEQ® assay or other molecular methods; additionally, the population receiving mpFC would also comprise paediatric and adult patients with T-ALL.

The Commentary noted that the clinical management algorithm did not differentiate between the populations, either in the ratified PICO or in the ADAR. The clinical management algorithm did not show how patients are clinically determined to be tested with either clonoSEQ® or mpFC. Additionally, the ADAR stated that “It is important that clinicians have choice in MRD tests, which can be due to reasons such as variable sensitivities and reliability between tests, or clinician preference.” However, the ADAR also stated that patients who have B-ALL (with specific variants)

would be tested with clonoSEQ® whereas other patients, such as those with T-ALL, would be tested with mpFC – thus indicating clinician preference is irrelevant. If clinician preference influences the choice of MRD test method, then this has not been considered in the ADAR in either the economic or financial analyses.

The ADAR described the current clinical management as including only bone marrow morphological testing and not MRD testing with clonoSEQ® or mpFC. The proposed clinical management algorithm (Figure 1) adds MRD testing using either intervention (clonoSEQ® or mpFC) to bone marrow morphological testing. For newly diagnosed patients, MRD test results will guide treatment decisions including risk group allocation and treatment intensity and identification of patients who would benefit from intensified therapy. Therefore, MRD testing influences the proportion of patients who receive different treatments (and the timing of these treatments) and is also used to determine access to blinatumomab, HSCT and CAR-T therapy (and the timing of this access).

The proposed algorithm indicated that standard risk (SR) cases (defined at diagnosis) with evidence of MRD during induction or consolidation would receive intensified chemotherapy. Because of the envisaged higher sensitivity of the intervention technologies for MRD detection, compared with bone marrow morphology alone, a greater proportion of SR patients would be identified as high risk (HR), and a greater proportion overall would be determined as HR during the initial risk stratification. This might result in a change in management for these patients.

Among those who are HR at diagnosis, all patients initiate treatment on HR chemotherapy protocol. The ADAR further proposed that for patients who receive MRD testing by clonoSEQ®, a baseline MRD test (called the ID or clonality test) must be performed to determine the baseline assessment, a reference for future MRD test results. However, the Commentary did not identify the timing of this initial baseline testing in the proposed clinical algorithm, nor in the proposed MBS item descriptor.

The ADAR described a higher analytical sensitivity of clonoSEQ® in identifying more MRD positive cases compared with mpFC (10^{-6} vs 10^{-4} , respectively). The supportive evidence suggested that clonoSEQ® demonstrates greater analytical accuracy at detecting MRD compared with mpFC at 10^{-4} , such that approximately 10% of patients are found to be discordant when comparing the two methods. However, the Commentary noted that the sensitivity reported in the ADAR refers to analytical sensitivity (1 cancer cell in 10,000 bone marrow cells or 10^{-4}) rather than diagnostic sensitivity (e.g. true positives and false negatives). Additionally, as the PBS restriction for blinatumomab defines MRD positivity at 10^{-4} , the commentary considered it is this sensitivity threshold that should have been used in the ADAR. However, there are other PBS-listed therapies available, specific to ALL, such as imatinib, ponatinib, inotuzumab ozogamicin, rituximab, and dasatinib which the ADAR failed to identify or discuss. The ADAR explored the potential health benefit to patients of a lower MRD detection threshold leading to earlier use of therapies such as HSCT (see longitudinal accuracy). The ADAR further overlooked the fact that MRD testing would be performed irrespective of what treatment a patient is receiving.

Downstream from MRD detection, the ADAR suggested that MRD testing with clonoSEQ® may increase the proportion of patients who are eligible to initiate treatment with blinatumomab compared with mpFC, because it will detect more MRD positive cases compared with mpFC. The Commentary noted that the PBS restriction for blinatumomab (PBS item numbers 11850Q, 11867N) specifically require MRD testing with PCR or flow cytometry. As such if testing with clonoSEQ® was listed on the MBS, patients would still not be able to gain access to blinatumomab treatment unless there were changes to PBS restrictions for blinatumomab.

Furthermore, patients who receive HSCT will have MRD testing performed before and after the procedure (NCCN 2021). In patients with HR ALL, relapsed ALL and those receiving

immunotherapy or HSCT, MRD monitoring during and after treatment identified patients with a higher risk of treatment failure and relapse (Eckert et al. 2013).

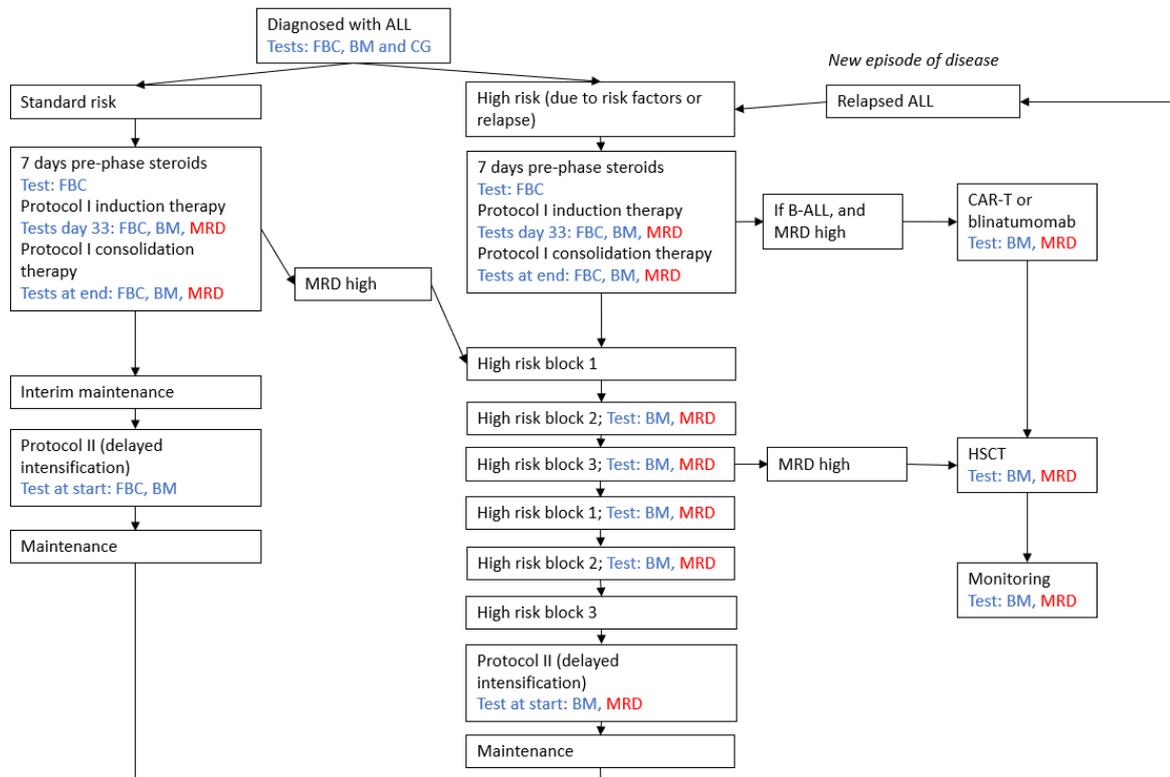


Figure 1 Proposed clinical management algorithm for patients with ALL (with MRD)

Source: Figure 7 page 45 of MSAC 1707 ADAR

Abbreviations: ALL, acute lymphoblastic leukaemia; BM, bone marrow morphology; CAR-T, chimeric antigen receptor T-Cell; CG, Cytogenetics; FBC, full blood count; HSCT, Haematopoietic stem cell transplantation; MRD, measurable residual disease

Overall, the Commentary found that the interventions and the clinical algorithms described in the ADAR aligned with the ratified PICO.

8. Comparator

The ADAR defined bone marrow morphology (morphological assessment ± cytogenetic analysis) as the primary comparator. For this method of testing, patients must undergo bone marrow extractions after each subsequent treatment phase to provide evidence of treatment response. The bone marrow sample is used to prepare a slide so its morphology is examined with a microscope. Cytogenetic analysis may also be performed using a stained slide and microscope, to examine the banded pattern of chromosomes during the metaphase of the cell cycle. The MBS items related to bone marrow morphology testing are listed in Table 6. These MBS items are not specific to ALL.

The Commentary noted that the ADAR stated “However, given MRD testing is not listed on the MBS, the primary comparator is no MRD testing (i.e. morphological assessment ± cytogenetic analysis for assessing morphological remission)”. As such, the ADAR defines no MRD testing as morphological assessment ± cytogenetic analysis for assessing morphological remission and assumes this occurs whether reported in any studies or not.

Table 6 MBS items for bone marrow morphological assessment and cytogenetic analysis

MBS items relevant to comparator for 1703 and primary comparator for 1707
<p>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</p>
<p>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</p>
MBS item numbers used for services performed to obtain the bone marrow aspirate
<p>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</p>
<p>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</p>
<p>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</p>
<p>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</p>

Source: Table 13 page 39 of MSAC 1707 ADAR

MBS fees reported in this ADAR are those applied in 2021-22. Non-pathology MBS items listed are subject to indexation so the fees are no longer accurate.

Table 7 MBS items not included in the ADAR but confirmed in the Ratified PICO

MBS items relevant to comparator for 1703 and primary comparator for 1707
<p>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</p>
<p>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</p>

MBS item numbers used for services performed to obtain the bone marrow sample
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: Table 3 of the ratified PICO (Pg9-10) and Commentary table 1 in the ADAR.

The ADAR proposed the secondary comparator to be other molecular methods of MRD testing. This involves any molecular methods of MRD testing likely to be used in the near-term in Australia such as allele-specific oligonucleotide (ASO) quantitative real-time PCR (qPCR), or other NGS assays. The Commentary noted that the ADAR did not describe the types of these secondary comparators, and their characteristics. Specifically, there is little information on how these technologies are different from the interventions.

The ADAR did not include five MBS items in the comparator description, that were included in the Ratified PICO (Table 7): two MBS items that are relevant to comparator for 1703 and primary comparator for 1707 – 73314 and 73315; three MBS items related to obtaining diagnostic biopsy of the bone marrow – 30081, 30084 and 30087.

While the ADAR listed the comparators adequately in relation to the ratified PICO, it did not align with the ratified PICO in its entirety because it excluded five MBS items. Further, the Commentary noted that in the Executive Summary of the ADAR the comparator was described as “no MRD testing” as opposed to either bone marrow morphology (primary comparator) or molecular methods of MRD testing (pg 12 of the ADAR). The economic and financial analyses of the ADAR also employed this approach of no MRD testing.

9. Summary of public consultation input

Consultation input was received from two (2) professional organisations and one (1) individual who was a researcher. No feedback was received from consumer organisations or individual consumers or carers for this application.

The following organisations submitted input on application 1707:

- PathWest laboratory medicine WA (PathWest)
- Australian Pathology (AP).

The consultation feedback received was broadly supportive of public funding for MRD testing, though disagreed with aspects of the intervention and comparator as proposed in the 1707 application form.

Clinical need and public health significance

The main benefits of public funding suggested by the consultation feedback included:

- more accurate prognostication regarding risk of relapse in ALL
- allows for tailored treatment, avoiding treatment toxicity for those that do not require treatment and limiting risk of relapse in treated patients
- increased equity of access.

The main disadvantages of public funding suggested by the consultation feedback included:

- Uncommonly, additional bone marrow sampling may be required for MRD testing, with discomfort/inconvenience to the patient.
- Specifying particular proprietary technologies for publicly funded testing would come at the expense of the development or use of other cheaper alternatives.
- It is uncertain that equity of access would be achieved as clonoSEQ® testing and the associated expertise may not be widely accessible across Australia.
- The clonoSEQ® may not provide an MRD assay suitable for most patients as it appears to be limited to B cell receptor rearrangements.

Indication(s) for the proposed medical service and clinical claim

The consultation feedback agreed with the proposed population and was mixed with respect to the proposed comparator.

PathWest noted that multi-parameter flow cytometry, the nominated comparator for 1707, is not the only method for MRD testing, and uses a fundamentally different technology to molecular testing. PathWest considered that allele-specific oligonucleotide qPCR is also a relevant technology and should also be included in the comparison. The researcher disagreed with the proposed comparator as it is not currently publicly funded and not routinely done.

The consultation feedback agreed with the clinical claim. The following key points were raised:

- AP considered that molecular genetic testing would be more accurate than flow cytometry, but noted the value of flow cytometry-based methods, which it commented should continue to be publicly funded and not be replaced by genetic testing.
- PathWest agreed that there is significant clinical benefit in identifying patients with ALL who are MRD-positive after treatment, and that this would inform treatment decisions, such as intensive chemotherapy, treatment with blinatumomab, or allogeneic stem cell transplant. Patients who are MRD-negative may successfully avoid intensive treatment/stem cell transplants.
- The researcher disagreed with the claim of superiority of the proposed service over mpFC and considered that there was no substantiation of the clonoSEQ® determined NGS-MRD results specifically benefiting patient outcomes or being of greater benefit than other available approaches.

Cost information for the proposed medical service

Consultation feedback on the proposed service widely supported broadening the intervention to encompass testing methods beyond clonoSEQ®, and raised the following points:

- PathWest considered that publicly funding any multiplex PCR/next generation sequencing test for MRD would allow or encourage other centres to implement similar methodologies, which would mitigate existing geographic and logistical access issues.

- The researcher noted that the clonoSEQ® approach for MRD testing appeared to be limited to B cell receptor rearrangements, which would mean that a significant number of patients would not be able to have their MRD measured. Other test types should be added to capture other MRD markers, such as T cell receptor rearrangements and microdeletions, to broaden the scope of patients who would benefit from testing and to increase equity for patients.
- The AP considered that while it may be useful to specify the use of a particular method, on balance it preferred a method-agnostic item descriptor, adding that this would aid in future proofing the item descriptor.
- PathWest considered that there may be value in restricting the number of episodes under which this item may be billed, to restrict unnecessary/inappropriate serial testing.

The consultation feedback ranged from ‘disagreeing’ to ‘strongly agreeing’ with the proposed service fee, and raised the following points:

- PathWest noted the difference in fees between MSAC application 1707 and 1703, with the applicant for 1707 proposing a much higher fee.
- The AP considered that the descriptor as drafted would require a higher fee.

10. Characteristics of the evidence base

The key features of the included evidence, as presented in the ADAR, are summarised in Table 8 and Figure 2.

The ADAR presented a linked evidence approach to the assessment. A systematic search for studies of cross-sectional and longitudinal accuracy was conducted for the comparison of clonoSEQ® and mpFC. This approach was considered appropriate by the Commentary.

Additionally, a search strategy restricted to systematic reviews and prospective comparative studies was conducted to identify evidence for other MRD detection methods (mainly mpFC and qPCR). Several irregularities and inconsistencies in the search methods and study selection were detected and discussed by the Commentary. The ADAR included one primary study and five systematic reviews as evidence of the longitudinal accuracy of mpFC and/or qPCR. The ADAR stated that these studies presented evidence for the comparison of MRD versus bone marrow morphology, with the implicit assumption that if the intervention consisted of “MRD + morphological assessment ± cytogenetics” and the comparator of “morphological assessment ± cytogenetics”, this comparison could be reduced to “MRD versus no testing”. However, this approach overestimated the incremental benefit of MRD as it assumed that all cases of residual disease are detected through MRD and none would have been detected by the comparator test.

The body of evidence for change in patient management consisted of seven studies that stratified patients based on their MRD test results and assigned them to receive either standard treatment, reduced regimen or augmented intensity treatment including more intensive chemotherapy, blinatumomab and HSCT. Although the ADAR claimed that these studies contributed comparative evidence for clonoSEQ® versus mpFC, none of the studies used clonoSEQ® or compared MRD detection methods. MRD was tested by mpFC or qPCR, or by case-specific molecular probes in one study¹. While the study protocols did assign treatments based on MRD test results, the Commentary considered that none of the studies were designed to assess the change in clinical practice.

¹ Bassan R et al. (2019) A systematic literature review and metaanalysis of minimal residual disease as a prognostic indicator in adult B-cell acute lymphoblastic leukemia. *Haematologica*, **104**(10):2028-2039.

The body of evidence for health outcomes of MRD testing consisted of seven studies describing long-term outcomes (survival, relapse risk) in patients who received modified treatment (reduced regimen or augmented intensity treatment including more intensive chemotherapy, blinatumomab and HSCT) based on the results of their MRD tests. None of the included studies for health outcomes used clonoSEQ® to measure MRD. Two studies were randomised controlled trials (RCTs), three studies used historical cohorts for the comparison; these studies were considered relevant to the assessment. Two studies^{2,3} involved CAR-T therapy and HSCT for persistent/recurrent MRD(+) ALL but as the treatment allocation mechanism for transplantation was unclear and some comparisons needed to respond to the question at hand (e.g., to compare the outcomes of MRD(+) and MRD(-) individuals) were missing, the Commentary considered they were not entirely relevant as evidence of health outcomes of MRD-guided treatment.

Additionally, two reproducibility studies were presented, one for clonoSEQ® and one for mpFC.

Table 8 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)	6 retrospective cohort studies 1 prospective cohort study	k=7 n=1,027	k=6/7 studies were at risk of bias and k=6/7 studies had applicability concerns
Prognostic evidence (longitudinal accuracy)	4 retrospective cohort studies 1 prospective cohort study	k=5 n=903	k=4/5 studies at high risk of bias and k=1/5 at moderate risk of bias
Change in patient management	2 RCTs 2 retrospective cohort studies 3 prospective cohort studies	k=7 n=3,209	k=2 RCTs at low risk of bias k=2 retrospective cohort studies, one at low and one at high risk of bias k=3 prospective cohort studies, risk of bias not assessed in the ADAR
Health outcomes	2 RCTs 5 retrospective cohort studies 3 prospective cohort studies	k=7 n=3,126	k=2 RCTs at low risk of bias k=5 retrospective cohort studies, two at low, two at moderate and one at high risk of bias
Other	Reproducibility studies for clonoSEQ® and mpFC	k=2 n=NA	Not assessed

ADAR=Applicant Developed Assessment Report; k=number of studies, n=number of patients; NA=not applicable; RCT=randomised controlled trial.

Source: Table 21 p 60, Table 41 p 119, Table 45 p 127 of MSAC 1707 ADAR

² Hu GH et al. (2022) Chimeric antigens receptor t cell therapy improve the prognosis of pediatric acute lymphoblastic leukemia with persistent/recurrent minimal residual disease in first complete remission. *Front Immunol.* **12**:731435.

³ Zhao H et al. (2020) Pre-transplant MRD negativity predicts favorable outcomes of CAR-T therapy followed by haploidentical HSCT for relapsed/refractory acute lymphoblastic leukemia: a multi-center retrospective study. *J Hematol Oncol*, **13**(1):42

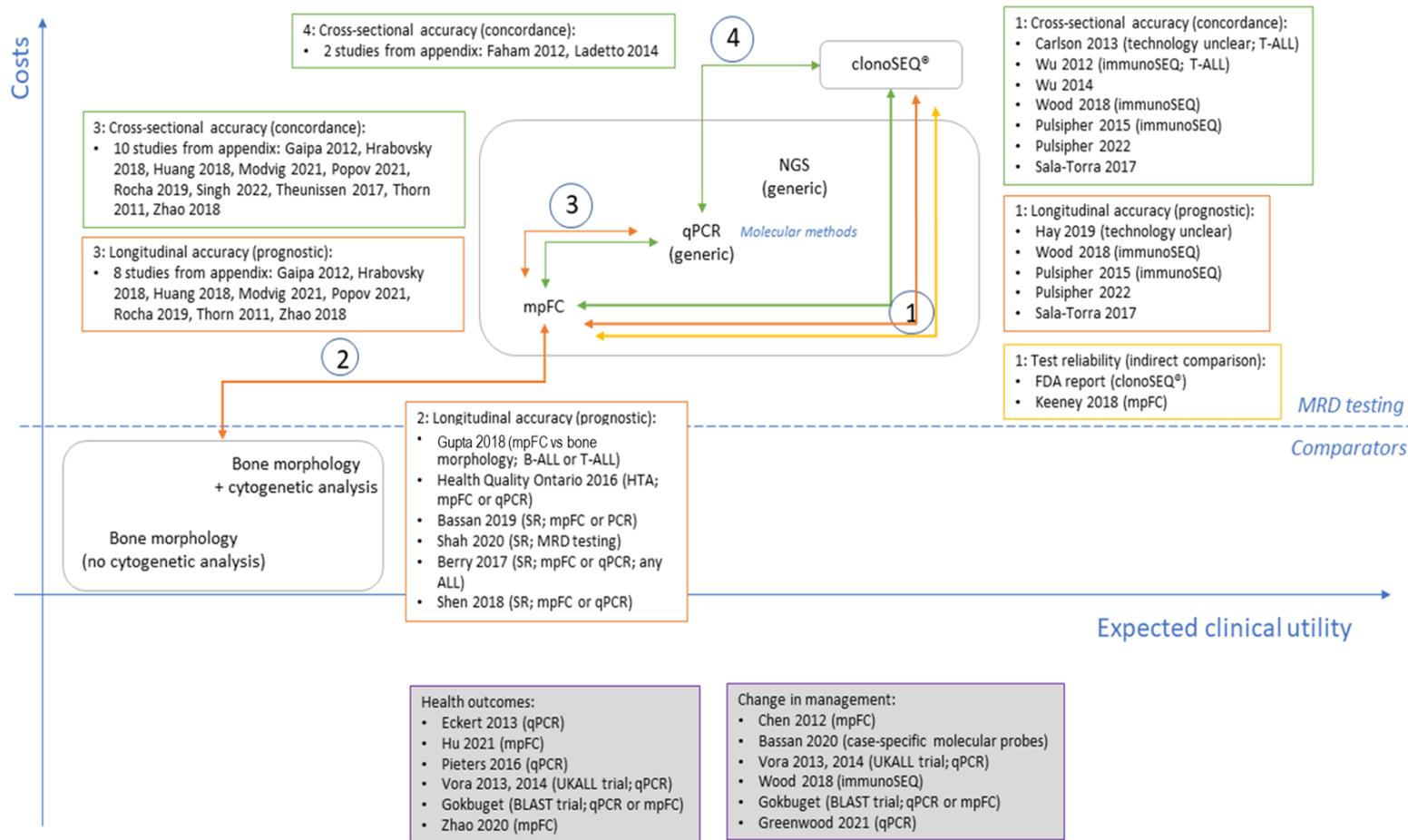


Figure 2 Summary of evidence presented in the ADAR

Source: Developed by the Assessment Group for the Commentary

ALL=acute lymphoblastic leukaemia B-ALL=B-cell acute lymphoblastic leukaemia; FDA=Food and Drug Administration; HTA=health technology assessment; mpFC=multiparametric flow cytometry; MRD=measurable residual disease; NGS=next generation sequencing; PCR=polymerase chain reaction; qPCR=quantitative polymerase chain reaction; SR=systematic review; T-ALL=T-cell acute lymphoblastic leukaemia

11. Comparative safety

The ADAR stated that because the same type of sample (bone marrow biopsy) is used for the proposed intervention and comparator test, the use of clonoSEQ® was not expected to introduce any additional direct safety concerns to patients with ALL.

12. Comparative effectiveness

Diagnostic accuracy

The results of cross-sectional diagnostic accuracy studies of clonoSEQ® compared with mpFC are summarised in Table 9. The positive predictive agreement (PPA) ranged from 50% to 100%, negative predictive agreement (NPA) ranged from 33% to 88%, and concordance between the two methods of MRD detection ranged between 68% and 87%. Most studies were at risk of bias and had applicability concerns.

Table 9 Results of cross-sectional key diagnostic accuracy trials comparing MRD detection via clonoSEQ® compared to MRD detection against the reference standard (mpFC)

Study ID <i>Risk of bias</i>	N samples	Biomarker investigated	Intervention, sensitivity ^a Comparator, sensitivity	Sample(s) tested	PPA NPA Concordance
Wood 2018 ^a <i>At risk of bias</i> <i>Applicability concerns</i>	551 NR	MRD	clonoSEQ, 10 ⁻⁴ mpFC, 10 ⁻⁴	BM	84% 88% 87%
Carlson 2013 <i>At risk of bias</i> <i>Applicability concerns</i>	36 NR	MRD	clonoSEQ, <10 ⁻⁵ mpFC, 10 ⁻⁴	BM	100% 33% 69%
Pulsipher 2015 ^a <i>At risk of bias</i> <i>Applicability concerns</i>	53 125	MRD	immunoSEQ, 10 ⁻⁴ mpFC, 10 ⁻⁴	BM	50% 76% 73%
Pulsipher 2022 <i>At risk of bias</i>	95 287	MRD	clonoSEQ, >10 ⁻⁶ mpFC, 10 ⁻⁴	BM, PB	100% 81% 84%
Sala Torra 2017 <i>At risk of bias</i> <i>Applicability concerns</i>	25 61	MRD	clonoSEQ, >10 ⁻⁶ mpFC, 10 ⁻⁴	BM	95% 78% 84%
Wu 2012 ^a Low <i>Applicability concerns</i>	31 NR	MRD	immunoSEQ, <10 ⁻⁵ mpFC, 10 ⁻⁴	BM	100% 47% 68%
Wu 2014 <i>At risk of bias</i> <i>Applicability concerns</i>	91 NR	MRD	clonoSEQ, >10 ⁻⁶ mpFC, 10 ⁻⁴	BM	100% 59% 69%

Source: Table 28, pg 78 of MSAC 1707 ADAR + *Commentary corrections in blue italics*

Abbreviations: BM=bone marrow; mpFC=multi-parameter flow cytometry; MRD=measurable residual disease; NPA=negative percent agreement; NR=not reported; PB=peripheral blood; PPA=positive percent agreement

^a clonoSEQ® sensitivity is defined by the input of the featured concordance analysis, not the analytical sensitivity of the test

Longitudinal prognostic accuracy

The ADAR presented evidence for the longitudinal prognostic accuracy of MRD as measured by mpFC or qPCR. This comparison is incorrectly presented in the ADAR as “mpFC versus bone [marrow] morphology”, however, only one primary study conducted a non-randomised comparison of mpFC versus bone marrow morphological assessment⁴. The study examined 5-year event-free survival (EFS) and overall survival (OS) in patients concordant and discordant for remission according to flow cytometry and bone marrow morphological assessment (Table 10). In patients with B-ALL, patients in morphological remission but with MRD detected using flow cytometry had significantly shorter EFS than patients who both methods determined were in remission ($p < 0.0001$). The same was true for EFS in patients with T-ALL, though the difference was smaller ($p = 0.01$). Similar results were also reported for OS. The authors concluded that “Patients with morphologic remission but MRD $\geq 5\%$ have outcomes similar to those who fail to achieve morphological remission, and significantly inferior to those with M1 marrows and concordant MRD, suggesting that flow cytometry should augment the [morphological] definition of remission in ALL.”.

Table 10 Event-free survival and overall survival among patients concordant in remission, and in morphological remission but MRD detected using flow cytometry

	ALL type	Patients in concordant remission (M1/MRD<5%)	Patients in morphological remission but MRD detected by flow cytometry (M1/MRD $\geq 5\%$)	P value for comparison
Event-free survival	B-ALL	87.1 \pm 0.4 (n = 7,682)	59.1 \pm 6.5 (n = 66)	p < 0.0001
	T-ALL	87.6 \pm 1.5 (n = 1,303)	80.3 \pm 7.3 (n = 97)	p = 0.01
Overall survival	B-ALL	93.8 \pm 0.3 (n = 7,682)	77.2 \pm 5.6 (n = 66)	p < 0.0001
	T-ALL	91.9 \pm 1.3 (n = 1,303)	83.4 \pm 6.8 (n = 97)	p = 0.005

Source: Gupta 2018, Table 4.

Abbreviations: B-ALL = B-precursor acute lymphoblastic leukaemia; M1 = morphological remission, defined as less than 5% of lymphoblasts; MRD = measurable residual disease; MRD<5% = remission according to flow cytometry; MRD $\geq 5\%$ = not in remission according to flow cytometry; T-ALL = T-precursor acute lymphoblastic leukaemia.

Despite the inconsistencies and inaccuracies detected in the ADAR, the Commentary considered that this body of evidence supports the premise that MRD (measured by mpFC or clonoSEQ[®] or qPCR at various time points of the disease) is an independent prognostic factor for patients with B-cell ALL.

The rest of the evidence, five systematic reviews at high risk of bias, provide a comparison of “MRD by mpFC or qPCR”. The results of longitudinal prognostic accuracy studies comparing clonoSEQ[®] with mpFC are summarised in Table 11 and Table 12.

⁴ Gupta S et al. (2018) Flow cytometric vs morphologic assessment of remission in childhood acute lymphoblastic leukemia: a report from the Children’s Oncology Group (COG). *Leukemia*; **32**(6):1370–1379.

Table 11 Results of longitudinal prognostic accuracy in patients with ALL (allcomers) who have undergone MRD testing: EFS as determined by clonoSEQ® against mpFC

Study ID <i>Risk of bias</i>	Timepoint measured	Duration of EFS	Population	MRD status (sensitivity) ^a	EFS %		p-value
					MRD +ve	MRD -ve	
Wood 2018 ^a <i>High</i>	Day 29	5 years	Allcomers ^b	clonoSEQ®(10 ⁻⁴)	76	91	NR
				clonoSEQ®(<10 ⁻⁴)	NR	NR	0.0118
				mpFC (10 ⁻⁴)	73	90	NR
			Standard risk	clonoSEQ®(10 ⁻⁴)	NR	NR	0.0009
				clonoSEQ®(<10 ⁻⁴)	NR	98.1	0.0226
			High risk	clonoSEQ®(10 ⁻⁴)	NR	NR	0.0002
				clonoSEQ®(<10 ⁻⁴)	NR	92.7	0.1021
Pulsipher 2015 ^a <i>High</i>	pre-HSCT	2 years	IgH-V(D)J (all)	clonoSEQ®(10 ⁻⁴)	47	100	<0.0001
				mpFC (10 ⁻⁴)	54	84	0.02
	post-HSCT (any timepoint)	2 years	IgH-V(D)J (all)	clonoSEQ®(10 ⁻⁴)	27	87	<0.0001
				mpFC (10 ⁻⁴)	33	75	<0.0001
	post-HSCT (30 days)	2 years	IgH-V(D)J (all)	clonoSEQ®(10 ⁻⁴)	65	NR	0.91
				mpFC (10 ⁻⁴)	NR	NR	<0.0001
	post-HSCT (100 days)	2 years	IgH-V(D)J (all)	clonoSEQ®(10 ⁻⁴)	NR	NR	0.45
				mpFC (10 ⁻⁴)	NR	NR	0.0009
	post-HSCT (8 months)	2 years	IgH-V(D)J (all)	clonoSEQ®(10 ⁻⁴)	NR	NR	0.0009
				mpFC (10 ⁻⁴)	NR	NR	0.01

Study ID <i>Risk of bias</i>	Timepoint measured	Duration of EFS	Population	MRD status (sensitivity) ^a	EFS %		p-value
					MRD +ve	MRD -ve	
Pulsipher 2022 <i>High</i>	post CAR-T (day 28)	2 years	CR/CRI	clonoSEQ®(>10 ⁻⁶)	70	63	0.53
				clonoSEQ®(<10 ⁻⁶)	40	74	0.00047
	post CAR-T (3 months)	2 years	CR/CRI	clonoSEQ®(<10 ⁻⁶)	36	71	<0.0001
	post CAR-T (6 months)	2 years	CR/CRI	clonoSEQ®(<10 ⁻⁶)	31	74	<0.0001
	post CAR-T (any timepoint)	2 years	Allcomers	clonoSEQ®(>10 ⁻⁶)	NR	69	NR
				clonoSEQ®(<10 ⁻⁶)	NR	100	NR
mpFC (10 ⁻⁴)				NR	50	NR	
Hay 2019 <i>Moderate</i>	3 weeks post CAR-T	NR	Allcomers ^c	mpFC (10 ⁻⁴)	0	34	<0.0001
Sala Torra 2017 <i>High</i>	Second induction chemotherapy	5 years	Allcomers ^d	clonoSEQ®(10 ⁻⁶)	7	86	0.018
				mpFC (10 ⁻⁴)	0	58	0.032

Source: Table 30, pg 88-89 of MSAC 1707 ADAR + *Commentary corrections in blue italics*

Abbreviations: +ve, positive; -ve, negative; ALL, acute lymphoblastic leukaemia; CAR-T, chimeric antigen receptor T-cell; CR/CRI, complete remission/ complete remission with incomplete haematologic recovery; EFS, event free survival; HSCT, haematopoietic stem cell transplant; ID, identification; mpFC, multi-parameter flow cytometry; MRD, measurable residual disease; N/A, not applicable; NR, not reported

^a clonoSEQ® sensitivity defined as the input used in the featured analysis, not the test itself

^b EFS was calculated from digitalised survival curves from Wood et al. 2018 Figure 1A

^c EFS was calculated from digitalised survival curves from Hay et al. 2019 Figure 1A

^d EFS was calculated from digitalised survival curves from Sala Torra et al. 2017 Figure 3C and 3D

Table 12 Results of longitudinal prognostic accuracy in patients with ALL (allcomers) who have undergone MRD testing: OS as determined by clonoSEQ® against mpFC

Study ID <i>Risk of bias</i>	Timepoint measured	Duration of EFS	Population	MRD status (sensitivity) ^a	OS %		p-value
					MRD +ve	MRD -ve	
Wood 2018 ^a <i>High</i>	Day 29	5 years	Allcomers ^b	clonoSEQ®(10 ⁻⁴)	79	96	NR
				mpFC (10 ⁻⁴)	68	97	NR
			Standard risk	clonoSEQ®(10 ⁻⁴)	NR	NR	0.0199
				clonoSEQ®(<10 ⁻⁴)	NR	100	0.1260
			High risk	clonoSEQ®(10 ⁻⁴)	NR	NR	0.0694
				clonoSEQ®(<10 ⁻⁴)	NR	95.1	0.3594
Pulsipher 2015 ^a <i>High</i>	pre-HSCT	2 years	IgH-V(D)J (all)	clonoSEQ®(10 ⁻⁴)	48	96	0.003
				mpFC (10 ⁻⁴)	61	77	NR
	post-HSCT (any timepoint)	2 years	IgH-V(D)J (all)	clonoSEQ®(10 ⁻⁴)	NR	NR	0.005
Pulsipher 2022 <i>High</i>	post CAR-T (day 28)	2 years	CR/CRi ^c	clonoSEQ®(>10 ⁻⁶)	60	72	0.46
				clonoSEQ®(<10 ⁻⁶)	47	84	0.0038
	post CAR-T (3 months)	2 years	CR/CRi ^c	clonoSEQ®(>10 ⁻⁶)	29	81	<0.0001
	post CAR-T (6 months)	2 years	CR/CRi ^c	clonoSEQ®(>10 ⁻⁶)	46	83	0.029
Hay 2019 <i>Moderate</i>	3 weeks post CAR-T	NR	Allcomers ^d	mpFC (10 ⁻⁴)	12	44	0.014

Source: Table 32, pg 97 of MSAC 1707 ADAR + *Commentary corrections in blue italics*

Abbreviations: +ve, positive; -ve, negative; ALL, acute lymphoblastic leukaemia; CAR-T, chimeric antigen receptor T-cell; CR/CRi, complete remission/ complete remission with incomplete haematologic recovery; ID, identification; mpFC, multi-parameter flow cytometry; MRD, measurable residual disease; N/A, not applicable; NR, not reported; OS, overall survival; RR, risk ratio

^a clonoSEQ sensitivity is defined as the input used in the featured analysis and does not represent the analytical threshold of the test itself.

^b OS was calculated from digitalised survival curves from Wood et al. 2018 Figure 1B

^c CR defined as <5% blasts in bone marrow or <1% in peripheral blood

^d OS was calculated from digitalised survival curves from Hay et al. 2019 Figure 1B

The ADAR suggested that this evidence supported clonoSEQ® as having higher analytical sensitivity compared with mpFC, at least partly due to its lower detection threshold. The Commentary considered that the certainty of evidence should likely be downgraded from high (as assessed by the ADAR) to moderate/low certainty due to presence of risk of bias and applicability issues in most studies and due to the type of studies available (“levels of evidence”). The Commentary therefore considered that the evidence presented in the ADAR did not allow the conclusion, as suggested in the ADAR, that clonoSEQ® has higher analytical sensitivity than other molecular methods of MRD detection.

Further, as a threshold of 10^{-4} is required for PBS access to blinatumomab therapy, any clinical utility benefit from a lower detection threshold has not been assessed and may not be realised in clinical practice, though other potentially affected therapies may not have an explicit MRD threshold.

Secondary comparison: mpFC or clonoSEQ® versus other molecular methods

The ADAR described secondary comparisons (mpFC or clonoSEQ® versus qPCR) in Appendix B of the ADAR, and indicate that only the ASO-qPCR was used as a comparator. The Commentary observed a lack of description of other molecular methods such as standalone NGS or qPCR methods, specified in the ratified PICO as secondary comparators. The ADAR does not describe if ASO-qPCR was the only comparator found in the published evidence that qualified for inclusion into the clinical evaluation of the ADAR, or if there was limited or no data on other comparators. Further, risk of bias assessment was not undertaken for any of the included studies in the secondary comparison. These comparisons, which should have been presented in the main text along with the primary comparisons, warrant the same level of evidence synthesis details as the primary comparisons.

In the secondary comparisons of mpFC versus qPCR, the ADAR found that eight of 10 included studies reported a concordance rate of >80%, and most discordance discrepancies occurred at levels close to sensitivity limits for mpFC (10^{-4}) and ASO-qPCR (10^{-5}). Seven studies that reported data on EFS indicate that mpFC and ASO-qPCR have similar prognostic accuracy for ALL. However, no studies presented data on OS.

The evidence on clonoSEQ® vs qPCR, based on two studies, indicates that the concordance rates are not based on the same level of sensitivity threshold. Secondly, no study reported on survival outcomes at all, making the incremental prognostic value of clonoSEQ® over qPCR, questionable.

Reproducibility

No comparative evidence of reproducibility was provided in the ADAR.

The ADAR supplied the clonoSEQ® report for the FDA, which included reproducibility data. Neither operator, instrument, reagent lot or extraction run had a significant effect on the reproducibility of the test. All samples passed the preestablished acceptance criteria and demonstrated a high-quality base call.

The evidence for mpFC included one study where reference bone marrow samples were tested by mpFC in different laboratories for concordance before and after educational feedback. The results suggested that discordance was initially relatively high (26%) and improved with training.

Change in management

The studies presented in the ADAR as evidence of change in management were not designed to study change in management. Instead, they are studies that used MRD for risk stratification and treatment allocation, generally in the setting of clinical trial protocols. The translation into medical practice is not discussed. No studies used clonoSEQ® for MRD testing, and the text of

the ADAR does not create a narrative that would link the different findings together. There is no mention in the ADAR that MRD is supported for treatment guidance by clinical practice guidelines, e.g., NCCN Guidelines for ALL⁵, ESMO guidelines for ALL⁶, EuroMRD⁷.

The only data presented in this section of the ADAR concerned the proportion of patients with discordant clinical risk grouping and MRD status (e.g., clinical standard risk but MRD(+)). The ADAR further argues that given the lower detection threshold of clonoSEQ[®], an even higher proportion of discordant patients would be detected by clonoSEQ[®] testing than what was reported in the included studies (using mpFC or qPCR).

The use of MRD in clinical practice is supported by several clinical practice guidelines, and the Commentary considered that it was reasonable to accept that MRD was being used to change management of patients with ALL in medical practice.

Health outcomes

The ADAR presented evidence that in newly diagnosed paediatric patients with ALL and standard or intermediate risk, MRD testing can lead to more favourable health outcomes if used to allocate MRD(-) patients to less intensive treatment (no worsening of EFS with less intensive treatment, difference in survival probability 1.1%, 95% CI -5.6% to 2.5%) and MRD(+) patients to augmented treatment regimens (5-year EFS 82.8% versus 89.9%, OR=0.61, 95% CI 0.39 to 0.98; p=0.04)⁸. The differences in the overall survival, however, were not significantly different.

Equally, MRD after the first and second course of therapy can be used to allocate paediatric patients to reduced intensity or increased intensity regimens based on their MRD risk and improve their health outcomes (5-year EFS 88.7% versus 83.3%, p=0.001, 5-year overall survival 93.9% versus 88.3%, p=0.002).⁹

The ADAR also presented evidence that in paediatric patients with ALL, MRD at the end of therapy can help identify higher-risk patients who benefit from transplantation¹⁰ (HR=0.28, 95% CI 0.17 to 0.48), and that in adults in complete remission (CR), MRD can help select patients who benefit from additional therapy with blinatumomab (HR=0.5, 95% CI 0.32 to 0.78).¹¹ The statistically significant difference in EFS did not translate to a benefit in overall survival, though.

⁵ Available at: https://www.nccn.org/professionals/physician_gls/pdf/all.pdf [accessed 28 July 2022].

⁶ Hoelzer D 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.

⁷ van der Velden VHJ et al. (2007) Analysis of minimal residual disease by Ig/TCR gene rearrangements: guidelines for interpretation of real-time quantitative PCR data. *Leukemia.* ;**21**(4):604-11

⁸ 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.* ;**14**(3):199-209.

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.* ;**15**(8):809-18.

⁹ Pieters R et al. (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

¹⁰ 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.

¹¹ BLAST trial. Gokbuget N et al. (2020) Blinatumomab vs historic standard-of-care treatment for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukaemia. *Eur J Haematol.* ;**104**(4):299-309.

The evidence for using MRD as a guide to timing HSCT and CAR-T therapy does not allow definitive conclusions to be made, as has been further discussed in the Commentary.

Clinical claim

The ADAR concluded that the use of clonoSEQ® or mpFC for the detection of MRD in patients with ALL results in superior effectiveness and non-inferior safety compared with bone marrow morphological assessment ± cytogenetics. The Commentary considered this conclusion appropriate.

However, the Commentary considered that the ADAR did not present sufficient evidence that clonoSEQ® would have superior effectiveness and non-inferior safety in patients with ALL compared to other molecular methods of MRD testing to justify the higher proposed fee over these other MRD options, including mpFC. The Commentary noted that although mpFC is part of the proposed intervention for 1707, PASC had advised that the test options proposed by both 1703 and 1707 should be compared with each other as well as with the comparator, as this is needed to justify the proposed different costs of testing per patient (1707 PICO, page 8-9).

13. Economic evaluation

The economic model presented in the ADAR is a Markov model using three health states – Relapse-free survival (RFS), Relapse and Death. The model aggregates the costs and benefits of clonoSEQ® and mpFC testing and compares these costs and benefits with the assumed no MRD testing comparator. The ADAR justified this approach by stating that MRD testing is not listed on the MBS and assumed no additional benefit for patients identified by bone marrow morphological assessment. The model was stratified by patient population (adult and paediatric populations) and by high and standard risk groups, as treatment management would change based on patients' risk profile.

While the model forecasts disease progression from a “relapsed-free” health state to a “relapsed” health state, the data used from these transition probabilities was from EFS data, as discussed in Section 2 of the in-line Commentary. RFS and EFS are similar in definition, and RFS is a subset of EFS. The supporting systematic review by Shah et al 2020 tabulated in an appendix the heterogeneous definitions of EFS and RFS used across studies, however according to the National Cancer Institute (US) the definition of RFS is when a patient survives without any signs or symptoms of that cancer, while EFS is when a patient remains free of certain complications or events that the treatment was intended to prevent or delay¹². Hence, EFS includes treatment related complications and RFS does not. The ADAR used EFS and RFS interchangeably. As the model uses relapse as a health state, RFS is the more appropriate outcome for the model. As relapse free and relapse are the defined health states within the model, the ADAR referred to the outcome of RFS rather than EFS in its Sections 3 and 4.

The model differentiated between the interventions (no MRD testing, mpFC testing and clonoSEQ® testing) by having a baseline risk profile for no MRD testing and applying adjustment factors for the proportions of patients with a change in clinical management due to the different results of mpFC and clonoSEQ® testing. These adjustment factors included a relapse reduction due to blinatumomab treatment for RFS high risk patients, a risk reduction for relapse in RFS standard risk patients and a “survival benefit for optimal identification of H[S]CT by clonoSEQ®” in RFS standard risk patients tested with clonoSEQ®. Transitioning from either RFS standard risk

¹² <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/relapse-free-survival> and <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/event-free-survival>

in patients who are MRD negative and tested by clonoSEQ® was reliant on the relapse reduction due to blinatumomab treatment. A discordant rate between clonoSEQ® and mpFC was also applied to patients transitioning from standard risk MRD negative to either relapse or death. This approach is not appropriate for mpFC. The ADAR stated in its Section 1 that clonoSEQ® is used in B-ALL patients, while mpFC is used in T-ALL patients (as well as other B-ALL patients without molecular variants identifiable by the clonoSEQ® assay). However, blinatumomab treatment on the PBS is only listed for B-precursor cell ALL and not T-ALL. Therefore, most patients tested with mpFC would be T-ALL patients and not have access to blinatumomab. The assumption that 50% of MRD positive paediatric patients and 60% of MRD positive adult patients tested with mpFC would be treated with blinatumomab was unfounded.

The baseline risk estimates for no MRD testing were based on the RFS Kaplan Meier data reported in Chen et al 2012 for the paediatric population, and Bassan et al 2020 in the adult population. RFS was stratified by risk (standard or high) and MRD status (positive or negative). These Kaplan Meier curves were extrapolated for the length of the time horizon of the model (30 years) and use a Kaplan + Parameterisation approach.

However, the subsequent adjustment factors used to generate the incremental consequences in the model may have limited applicability as the relapse reduction due to blinatumomab treatment factor is reliant on the proportion of patients treated with blinatumomab. However, as more patients are treated with blinatumomab, the cost also increases (and therefore the ICER becomes less cost-effective). The ADAR may have overestimated the proportion of patients treated with blinatumomab. However, other adjustment parameters applied in the model may have potentially biased the cost-effectiveness results in favour of MRD testing.

The risk reduction for relapse in RFS standard risk patients was sourced from a trial that had an additional treatment effect (as the study compared regimen A and B with regimen C) and therefore may not be representative of a risk reduction for relapse linked to MRD testing. Although MRD testing by clonoSEQ®/mpFC is expected to change the clinical management of more than one treatment option, additional treatment options (additional pegylated asparaginase, vincristine and escalated dose intravenous methotrexate without folic acid rescue) were only somewhat aligned with the high-risk treatment protocol.

The survival benefit for optimal identification of HSCT by clonoSEQ® in RFS standard risk patients tested with clonoSEQ® was obtained in a study primarily in high-risk patients (83%).

The Commentary considered it to be unclear why the transition from RFS standard risk MRD negative health state to relapse or death was dependant on the treatment effect of blinatumomab only in the clonoSEQ® arm.

The discordance rate between clonoSEQ® and mpFC was based on low numbers in the adult population (n=21 in total), had high uncertainty and may be significantly overestimated. Discordance was only captured where clonoSEQ®+/mpFC-, and this may be due to the small study population. Wood et al 2017 reported discordant cases where clonoSEQ®-/mpFC+ (n=17), however, Wood did not follow up on analysis of these patients. Nonetheless, this did suggest that discordance can also occur in favour of mpFC.

In the three interventions, a non-relapse mortality rate was applied, as well as background mortality and RFS. While this rate is applicable in determining the transition from RFS to death, this rate was included in the RFS analysis. RFS includes the time from date of treatment to the time of recurrence or death. As such, death may be double counted by not removing this non-relapsed mortality rate from the RFS.

The impacts of these parameters (with the exception of the double-counted mortality due to potential structural change required) were tested in an additional sensitivity analysis.

The ADAR consistently referred to an analytical sensitivity of 10^{-4} . However, this sensitivity refers to analytical sensitivity, the ability to detect 1 cancer cell in 10,000 bone marrow cells¹³. Diagnostic accuracy (e.g. true negatives, false positives etc), was not considered in the ADAR, however, as previously mentioned, the model does incorporate a discordance rate between clonoSEQ® and mpFC.

The model assumed a therapeutic benefit as patients gain access to blinatumomab treatment. HSCT and CAR-T therapies have also been included. However, the proportion of patients treated with CAR-T therapy was set at 0% in both arms of the modelled comparison and there are other PBS-listed therapies available, specific to ALL, such as imatinib, ponatinib, inotuzumab, ozogamicin, rituximab, and dasatinib which the ADAR fails to identify or discuss. MRD testing would be performed irrespective of what treatment the patient is receiving and the costs and benefits of MRD testing in these patients have not been quantified in the ADAR. A literature review was conducted to identify similar economic assessments. The ADAR identified one study by Health Quality Ontario (2016) that assessed MRD testing by mpFC. The model was similar to the ADAR's model, however, included the ability to relapse during treatment, as well as including HSCT and rescue chemotherapy as additional health states.

Utility values used to quantify quality of life in the model were obtained from the Health Quality Ontario (2016) report. However, these values were sourced from studies that may overestimate quality of life (QoL) as these values were not sourced from patients (paediatric utilities were sourced from parents, and adult utility sourced from the general population). These values appear unrealistically high, and may need to be adjusted to be reflective of the health states relative to the general population (i.e., adjusted for population norms).

The average age, gender and height/weight (for chemotherapy calculations) appeared to be miscalculated in the adult population. It appeared that the mean age used in the base case adult model (age = 23) was based on the overall population, not the adult population (i.e., age 15 and over). However, the impact of this miscalculation was tested in the sensitivity analysis and was minimal.

Hospitalisation costs were uncertain. These costs represented a significant proportion of total costs. Hospitalisation costs were dependent on the length of stay which were obtained from the Health Quality Ontario (2016) report, which subsequently identified hospital cost and resource use from personal communication with a Canadian healthcare researcher. Treatment options may have changed since 2016 and may be different in a different healthcare setting. Examples of these options were that blinatumomab is now an option and was not listed on the PBS in 2016. There were conflicting reports on how long patients stay in hospital due to ALL treatment in the Australian healthcare setting. The Commentary recommended further validation within the Australian healthcare setting.

The model was based on the Australian healthcare system perspective using a base case annual discount rate of 5% of costs and benefits. No half-cycle corrections were used. The base case time horizon was selected at 30 years, which is similar to time horizons used in ALL treatments recommended by the PBAC (such as blinatumomab). The incremental cost per life year gained (or incremental cost-effectiveness ratio; ICER) and the incremental cost per QALY gained (or incremental cost-utility ratio: ICUR) were primary outcomes of the economic analysis. A summary of the economic evaluation is presented in Table 13.

¹³ https://www.ils.org/sites/default/files/National/USA/Pdf/Publications/FS35_MRD_Final_2019.pdf

Table 13 Summary of the economic evaluation

Component	Description
Perspective	Australian healthcare system perspective
Population	Population 1: Paediatric patients (aged 0-14 years) with <i>de novo</i> or relapsed ALL Population 2: Adult patients (aged 15+ years) with <i>de novo</i> or relapsed ALL
Prior testing	Tests to diagnose ALL
Intervention	Intervention 1: clonoSEQ® Intervention 2: mpFC
Comparator	Bone marrow morphology (No MRD testing)
Type(s) of analysis	Cost utility analysis (CUA)/ Cost effectiveness analysis (CEA)
Outcomes	Change in management costs, QALYs, health state costs
Time horizon	30 years
Computational method	Markov model
Health states	RFS, relapse, death
Cycle length	1 month
Transition probabilities	Paediatric population: Chen 2012, Wood 2018, Blanco 2012, Vora 2014, BLAST trial Adult population: Bassan 2020, Sala Torra 2017, Blanco 2012, Vora 2014, Greenwood 2021, BLAST trial
Discount rate	5% for both costs and outcomes
Software	Microsoft Excel

Abbreviations: ALL, acute lymphoblastic leukaemia.; mpFC, multiparametric flow cytometry; QALY, quality adjusted life year; RFS, relapse-free survival

Source: Table 50 of MSAC 1707 ADAR

The PICO specified the comparator to be bone marrow morphological assessment with or without cytogenetic analysis for assessing morphological remission. As cytogenetic analysis was not considered in the ADAR, and it could be assumed that the addition of cytogenetic analysis could increase the clinical benefit of the comparator Any difference in the incremental benefit quantified in the ADAR would then be an overestimate and the real ICER would be increased (i.e., become less cost-effective).

The ADAR presented a stepped analysis presenting an analysis over a 5-year time horizon (Step 1), then presented costs per LY gained over 30 years and extrapolating trial data (Step 2), and then presented costs per QALY gained over 30 years using the same extrapolated trial data (Step 3). However, the ADAR presented data to suggest the most appropriate curves used in the extrapolation (based on Akaike's Information Criteria [AIC] and Bayesian Information Criteria [BIC] values) were not used in the base case analysis. The justification was that the AIC/BIC values were used to select the appropriate distribution, however, this statement was contradictory to the AIC/BIC values presented in the model and the ADAR.

The ADAR reported a decreasing ICER (when comparing life years gained) with increasing the time horizon, as evident when comparing Step 1 (cost/LY gained – 5 years) with an ICER of \$659,087/LY gained in the paediatric population and \$66,898 in the adult population, with Step 2 (cost/LY gained – 30 years) with an ICER of \$31,322/LY gained in the paediatric population and \$12,303/LY in the adult population. The impact of QoL on the LY gained was marginal (8.7% in the paediatric population and 0.2% in the adult population). The ICURs (cost/QALY gained) were reported as \$29,517/QALY gained in the paediatric population and \$12,332/QALY gained in the adult population. These results are shown in Table 14 and Table 15.

Table 14 Results of the stepped economic analysis clonoSEQ® and mpFC testing for MRD in ALL patients

Step	MRD testing	No MRD testing	Increment	ICER
Paediatric population				
Step 1 – cost per LY gained- 5 year time horizon				
Costs	\$151,183.56	\$139,055.15	\$12,128.41	
Effectiveness (LYs)	4.31	4.21	0.02	\$659,087.04
Step 2 – cost per LY gained- 30 year time horizon				
Costs	\$182,555.12	\$171,304.95	\$11,250.17	
Effectiveness (QALYs)	12.98	12.62	0.36	\$31,322.02
Step 3 – cost per QALY gained- 30 year time horizon				
Costs	\$182,555.12	\$171,304.95	\$11,250.17	
Appropriate management allocation	11.08	10.69	0.38	\$29,516.80
Adult population				
Step 1 – cost per LY gained- 5 year time horizon				
Costs	\$241,376.26	\$229,571.52	\$11,804.74	
Effectiveness (LYs)	3.83	3.65	0.18	\$66,897.76
Step 2 – cost per LY gained- 30 year time horizon				
Costs	\$292,316.59	\$276,753.05	\$15,563.54	
Effectiveness (QALYs)	8.71	7.45	1.27	\$12,302.56
Step 3 – cost per QALY gained- 30 year time horizon				
Costs	\$292,316.59	\$276,753.05	\$15,563.54	
Appropriate management allocation	6.30	5.04	1.26	\$12,331.77

Abbreviations: ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year.

Table 15 Results of the economic evaluation

Parameter	MRD testing	No MRD testing	Increment
Paediatric population			
Costs	\$182,555.12	\$171,304.95	\$11,250.17
Life years	12.98	12.62	0.36
QALYs	11.08	10.69	0.38
Incremental cost per life year gained			\$31,322.02
Incremental cost per QALY gained			\$29,516.80
Adult population			
Costs	\$292,316.59	\$276,753.05	\$15,563.54
Life years	8.71	7.45	1.27
QALYs	6.30	5.04	1.26
Incremental cost per life year gained			\$12,302.56
Incremental cost per QALY gained			\$12,331.77

Abbreviations: QALY = quality-adjusted life year.

The ADAR selected parameters to be tested in a sensitivity analysis. The key drivers identified in this sensitivity analysis are shown in Table 16.

Table 16 Key drivers of the model

Description	Method/Value	Base case (Paediatric): \$29,517/QALY gained	Impact Base case (Adult): \$12,332/QALY gained
Time horizon	The base case time horizon was 30 years.	High, favours no MRD testing A time horizon of 10 years increased the ICER to \$96,756/QALY gained. A time horizon of 50 years decreased the ICER to \$23,611/QALY gained	High, favours no MRD testing A time horizon of 10 years increased the ICER to \$18,125/QALY gained. A time horizon of 50 years decreased the ICER to \$11,657/QALY gained
Transition probabilities	Baseline probability of MRD status as per Chen 2012 (Vora et al 2014 used in base case)	High, favours no MRD testing Paediatric (only): A change in baseline probability of MRD status decreased the ICER to \$11,442/QALY gained.	-
Transition probabilities	Baseline risk stratification as per Bassan 2020 (Greenwood et al 2021 used in base case)	-	High, favours no MRD testing Adult (only): A change in baseline risk stratification results in a lower cost and higher benefit (-\$19,009/QALY gained; Dominant).
Discount rate	Base case is 5% for costs and benefits	A discount rate of 0% decreased the ICER to \$12,808/QALY gained.	High, favours MRD testing A discount rate of 0% decreased the ICER to \$8,772/QALY gained.
Baseline characteristics	Base case utilisation of clonoSEQ® (39%/36%) and mpFC (62%/64%) [paediatric/adult]	Utilisation of clonoSEQ®(80%) and mpFC (20%) The ICER increases to \$44,032/QALY gained	Utilisation of clonoSEQ®(80%) and mpFC (20%) The ICER increases to \$16,805/QALY gained
Costs	Cost of disease management and terminal care	+20% decreases the ICER to \$26,489/QALY gained. -20% increases the ICER to \$32,544/QALY gained.	+20% decreases the ICER to \$9,735/QALY gained. -20% increases the ICER to \$14,929/QALY gained.
Costs	Cost of first line treatment	+20% decreases the ICER to \$32,409/QALY gained. -20% increases the ICER to \$31,099/QALY gained.	+20% increases the ICER to \$14,404/QALY gained. -20% decreases the ICER to \$10,259/QALY gained.

Abbreviations: ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year.

The Commentary identified multiple parameters used in the model that were uncertain and required additional sensitivity testing. The results of key univariate sensitivity analyses are summarised below for both the paediatric and adult populations.

The parameters relating to a risk reduction due to blinatumomab treatment, and the proportion of patients tested with clonoSEQ® and mpFC decreased the cost-effectiveness of the two assessed MRD tests. MSAC and ESC may wish to consider the validity of these parameters in further detail.

Table 17: Parameters used in the economic model additionally tested in the sensitivity analysis

Parameter tested	Incremental cost	Incremental QALYs	ICUR (\$/QALY gained)	% change ICUR
Paediatric				
Baseline	\$11,250	0.38	\$29,517	-
Removal of RR in SR MRD+ve	\$13,831	0.25	\$55,060	86.5%
Removal of relapse risk reduction in SR MRD +ve blinatumomab patients (mpFC)	\$15,930	0.12	\$128,637	335.8%
Removal of relapse risk reduction in HR MRD +ve blinatumomab patients (mpFC and clonoSEQ®)	\$13,136	0.28	\$46,782	58.5%
Removal of relapse risk reduction in MRD +ve blinatumomab patients	\$15,957	0.12	\$130,470	342.0%
Removal of relapse risk reduction in SR blinatumomab patients	\$12,362	0.33	\$37,778	28.0%
Removal of survival benefit for optimal identification of HSCT by clonoSEQ®	\$11,092	0.39	\$28,512	-3.4%
Change extrapolation parameters based on AIC/BIC values	\$11,124	0.36	\$30,657	3.9%
Change in discordant rate to 10%	\$11,081	0.38	\$29,108	-1.4%
Change in discordant rate to 0%	\$9,934	0.38	\$26,275	-11.0%
Change in proportion of patients eligible for blinatumomab (10%)	-\$28,650	1.44	-\$19,916	-167.5%
Change in proportion of clonoSEQ® and mpFC to 85%/15%	\$17,702	0.39	\$45,755	55.0%
Change in extrapolation start time to end of KM data	\$11,155	0.38	\$29,551	0.1%
Utility values adjusted for population norms by 0.87	\$11,250	0.33	\$33,711	14.2%
No discordance between mpFC and clonoSEQ®	\$10,166	0.38	\$26,882	-8.9%
All changes	-\$15,894	0.94	-\$16,921	-157.3%
All changes (except proportion of patients on blinatumomab)	\$21,282	0.02	\$1,279,180	4233.73%
Adult				
Baseline	\$15,564	1.26	\$12,332	
Removal of RR in SR MRD+ve	\$20,590	0.97	\$21,138	71.4%
Removal of relapse risk reduction in SR MRD +ve blinatumomab patients (mpFC)	\$30,939	0.26	\$120,897	880.4%
Removal of relapse risk reduction in HR MRD +ve blinatumomab patients (mpFC and clonoSEQ®)	\$21,673	0.90	\$24,038	94.9%
Removal of relapse risk reduction in MRD +ve blinatumomab patients	\$31,213	0.24	\$130,725	960.1%
Removal of relapse risk reduction in SR blinatumomab patients	\$17,724	1.14	\$15,509	25.8%
Removal of survival benefit for optimal identification of HSCT by clonoSEQ®	\$13,794	1.36	\$10,157	-17.6%
Change extrapolation parameters based on AIC/BIC values	\$13,585	1.31	\$10,342	-16.1%
Change in discordant rate to 24%	\$15,058	1.26	\$11,976	-2.9%
Change in discordant rate to 0%	\$14,368	1.25	\$11,484	-6.9%
Change in proportion of patients eligible for blinatumomab (10%)	-\$50,726	1.68	-\$30,109	-344.2%

Parameter tested	Incremental cost	Incremental QALYs	ICUR (\$/QALY gained)	% change ICUR
Change in proportion of clonoSEQ® and mpFC to 85%/15%	\$22,563	1.30	\$17,302	40.3%
Change in extrapolation start time to end of KM data	\$13,243	1.35	\$9,839	-20.2%
Utility values adjusted for population norms by 0.87	\$15,564	1.11	\$14,011	13.6%
No discordance between mpFC and clonoSEQ®	\$14,368	1.25	\$11,484	-6.9%
Baseline years in adult population adjusted to 50 years	\$15,501	1.20	\$12,919	4.8%
All changes	-\$35,338	0.89	-\$39,811	-422.8%
All changes (except proportion of patients on blinatumomab)	\$38,298	0.06	\$622,906	4951.23%

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; HSCT, hematopoietic stem cell transplantation; HR, high risk; ICER, incremental cost effectiveness ratio; ICUR, incremental cost utility ratio; LY, life year; mpFC, multiparametric flow cytometry; MRD, measurable residual disease; QALY, quality-adjusted life year; RR, relative risk; SR, standard risk

14. Financial/budgetary impacts

Model population and approach

An epidemiological approach was used in the ADAR to estimate the financial implications of MBS listing for MRD testing by clonoSEQ® and mpFC in paediatric and adult patients with ALL. For both populations, the eligible population was calculated based on the projected number of new cases of ALL as per data from the Australian Institute of Health and Welfare (AIHW) in addition to the proportion of patients who experience relapse, derived from data from relevant locally applicable sources provided by the Royal College of Pathologists of Australasia (RCPA) and accepted by the PASC (Attachment 1_1707 Ratified PICO).

In 2021, the AIHW released the Australian Cancer Incidence and Mortality (ACIM) book (AIHW 2021)¹⁴, providing a wide range of cancer related statistics including historical data ranging back to 1982 and projections up to 2021. The epidemiological estimates used in the financial impact model in the ADAR were derived from the ACIM for ALL, which reported 364 new cases of ALL in 2017. Among these, 51% of cases were reported in children diagnosed between the age of 0 to 14, informing the proportion of paediatric patients in the budget impact analysis while the remaining 49% of cases represent the adult population.

The Commentary noted that the population was calculated using -ALL age-standardised data until 2017 reported by AIHW in 2021. However, a more recent AIHW dataset was released in July 2022 (cancer incidence counts, age-specific rates, age-standardised rates by sex, age group, actual data from 1982 to 2018 and projections to 2022)¹⁵, which reports ALL age-standardised data until 2018.

The Commentary calculated an annual growth rate of 3.1% among haematological malignancies using data from AIHW 2022. To project the number of incident cases of ALL for the duration of

¹⁴ Australian Cancer Incidence and Mortality (ACIM) book for Acute Lymphoblastic Leukaemia (ALL) 2021 (ICD-10 code C91.0). Available from: https://www.aihw.gov.au/getmedia/0f15c984-a6b0-43f0-85d1-7e24e6e61063/AIHW-CAN-122-ACIM_ALL.xlsx.aspx

¹⁵ Cancer Data in Australia 2022, AIHW Australian Cancer Database 2018, Book 1a – Cancer incidence (age-standardised rates and 5-year age groups). Available from: <https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/data>

the budget impact model, the annual growth rate was applied each year to the incidence reported in the ACIM for ALL 2021.

The Commentary noted difficulty in locating the source of the 3.1% in the ACIM 2021 data. Additionally, it noted that the projected ALL totals in 2022-2027 did not align with the projected ALL cases in the PICO (Ratified PICO, Table 2, Pg. 6). The latest ALL-specific incident growth rate from the AIHW (July 2022) was approximated as 1.9% when considering the average growth rate of the ALL incident population from 2008 to 2018. If using the 1.9% ALL incidence growth rate and the 2018 ALL totals to calculate the incidence rate from 2022-2027 for all persons, the results would differ slightly (400 in 2022 and 439 in 2027).

The Commentary considered that the proportion of patients that relapse was double counted in the method used to calculate the relapsed paediatric and adult patients in the financial model. As such, this was tested in a separate sensitivity analysis in the Commentary (results further detailed in Table 19).

Justification of the selection of approach and data sources

The base case of the financial estimates in the ADAR assumed that in 2022 (Year 1) of MBS listing, 10% of patients would receive clonoSEQ® while the remaining 90% would receive MRD testing by mpFC. This was supported by local clinician advice, which suggested that in lieu of MBS funding, patients currently receive MRD testing by mpFC funded either through out-of-pocket payments or through public hospital funding. It was expected that over time, the uptake of MRD testing by clonoSEQ® would increase with MBS listing, and would likely be utilised at the same rate as mpFC. Therefore, the financial estimates factored in these predictions such that the uptake of clonoSEQ® increased by 10 percentage points each year while the uptake of mpFC decreased accordingly. This was expected to stabilise at 50% uptake for each test by 2026 (Year 5).

The Commentary noted that the initial uptake rate of clonoSEQ® may be appropriate given the slow adoption of a recent TGA approval and MBS listing, however, the rate of uptake remained uncertain. The ADAR contextually described that 'Currently, the clonoSEQ® assay is available only for B-cell ALL which constitutes 85% of ALL cases, noting that a large proportion of the literature provides evidence to support the use of clonoSEQ® in this population (Jean Marcus 2016).' Therefore, although the clinical assessment in the Commentary has questioned whether clonoSEQ® is a superior test over mpFC, the utilisation of clonoSEQ® could be assumed to increase until 85%, with the remaining 15% ineligible for clonoSEQ® to undertake mpFC due to these patients having ALL other than B-ALL (i.e. T-ALL). Additionally, a sensitivity analysis was run to test different rates of uptake of clonoSEQ® and mpFC (30% vs 70% and 80% vs 20%, respectively), however the scenario for uptake rates of 85% and 15% was not tested. As such, a separate sensitivity analysis was conducted in the Commentary to assess the greatest viable impact of 85% clonoSEQ® and 15% mpFC uptake rates from 2022-2027 (Table 19).

The estimated proportion of patients that experience relapse varies in the literature. For the paediatric population, Australian data reporting on relapse rates in patients 0 to 18 years of age between 1998 to 2013 was provided by the RCPA and was applied to estimate the relapsed paediatric population in the financial estimates. For the adult population, the literature reported relapse rates ranging between 40% to 50%. The ADAR estimated the rate of relapse in the paediatric population to be 10%, increasing to 50% in the adult population and relapse was assumed to occur three years after the initial diagnosis as per the Application 1707 Ratified PICO (Attachment 1_1707 Ratified PICO).

The Commentary noted that while the RCPA stated in the Ratified PICO that the relapse rate for paediatric patients aged 1-18 years old is 10%, it also stated that for children aged less than or

equal to 12 months old the relapse rate is 50%. As the majority of ALL paediatric patients are aged between 0-4 years old (54% of the total paediatric population aged 0-14 years old in 2017 as per the ACIM data), the more conservative relapse rate of 50% should have been used in the model or tested in a sensitivity analysis. Instead, the relapse rates in the economic model for both populations (11.5% in paediatrics and 28.3% in adults) were tested as an alternative scenario in a sensitivity analysis (Table 19). If the paediatric relapse rate was increased to 50%, the net MBS cost of MRD testing would double to \$1,422,229 in the paediatrics population and increase to \$2,213,291 for adults and paediatrics combined.

Risk stratifications among both populations were derived from sources used in the economic analysis, accounting for the patients that relapse. 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 proportions of standard risk (SR) and high risk (HR) patients reported by Vora 2014 were applied to the remaining non-relapsed patients to determine the overall proportion of SR, HR and relapse. For the adult population, risk stratification was based on data from Greenwood et al. 2021, aligning with the inputs of the economic analysis.

The utilisation of each test, which includes clonoSEQ®, mpFC and bone marrow morphology, along with the number of tests required for each patient, was derived from local clinician advice (no further details provided). However, due to variability in patient response and treatments received, some patients may require more tests than others. For example, treatments such as H SCT and blinatumomab are associated with increased MRD testing, either to determine eligibility or during monitoring. Therefore, it is challenging to specify the number of tests required by each patient 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 received the same number of MRD tests.

The Commentary noted that whilst the number of tests has a degree of uncertainty, this was tested in a sensitivity analysis.

Net financial impact to the MBS

The estimated use, cost and incremental cost of listing clonoSEQ® and mpFC are detailed in Table 18. With the introduction of these services, the utilisation of bone marrow morphology would not change, however there would be an increase in cost where clonoSEQ® and mpFC are publicly funded under the MBS (calculated using the applicable 85% benefit rate) is applied to clonoSEQ® and mpFC. The Commentary noted that the costs of testing were marginally understated, as cost was calculated using a pure 85% rate rather than the 85% rate which involves rounding up to nearest \$0.05.

Additionally, the Commentary noted that the financial impact model did not consider MBS costs associated with anaesthesia, bone marrow biopsy and cytogenetic analysis (as identified in the Ratified PICO, Table 3), and patient episode initiation and bulk-billing incentive items. This however was appropriate as bone marrow samples would be taken regardless of being tested for MRD status or not, and as such, any costs associated with sample collection would be consumed regardless of the outcome and results of MSAC 1707.

Table 18 Utilisation and financial implications of MRD testing using mpFC and generic NGS to the MBS

Parameter	Year 1 (2022)	Year 2 (2023)	Year 3 (2024)	Year 4 (2025)	Year 5 (2026)	Year 6 (2027)
Estimated use and cost of the proposed health technology						
Number of patients eligible for MRD testing (includes new and relapsed)						
Number of paediatric patients eligible for MRD testing	236	244	251	259	267	275
Number of adult patients eligible for MRD testing (10% ineligible due to T-ALL presentation)	272	280	289	298	307	317
Number of adult patients eligible for MRD testing (<i>T-ALL presentation not ineligible</i>)	302	311	321	331	341	352
Number of services for the proposed MBS items (3-6 tests per patient per year)						
mpFC (90-50% uptake yr 1-6)	1,990	1,824	1,645	1,454	1,249	1,288
<i>mpFC (90-50% uptake yr 1-6)</i>	<i>2,113</i>	<i>1,936</i>	<i>1,747</i>	<i>1,544</i>	<i>1,326</i>	<i>1,367</i>
clonoSEQ (10-50% uptake yr 1-6)	256	528	816	1,121	1,445	1,490
<i>Generic NGS (10-50% uptake yr 1-6)</i>	<i>271</i>	<i>559</i>	<i>864</i>	<i>1,188</i>	<i>1,531</i>	<i>1,578</i>
Cost of services for the proposed MBS items						
mpFC at requested fee (\$550)	\$930,294	\$852,559	\$769,115	\$679,678	\$583,957	\$602,059
<i>mpFC at requested fee (\$550)</i>	<i>\$987,717</i>	<i>\$905,188</i>	<i>\$816,592</i>	<i>\$721,634</i>	<i>\$620,004</i>	<i>\$639,224</i>
clonoSEQ at requested fee (\$2,100) ^a	\$514,767	\$1,061,447	\$1,641,528	\$2,256,555	\$2,908,135	\$2,998,287
<i>Generic NGS at supported fee (\$1,550)^b</i>	<i>\$394,761</i>	<i>\$813,998</i>	<i>\$1,258,848</i>	<i>\$1,730,496</i>	<i>\$2,230,177</i>	<i>\$2,299,312</i>
Total cost to MBS (at requested fees)	\$1,445,057	\$1,914,007	\$2,410,644	\$2,936,233	\$3,492,092	\$3,600,347
<i>Total cost to MBS (at supported fees)</i>	<i>\$1,382,478</i>	<i>\$1,719,185</i>	<i>\$2,075,440</i>	<i>\$2,452,130</i>	<i>\$2,850,181</i>	<i>\$2,938,537</i>

^a 85% benefit reflects the 1 November 2021 Greatest Permissible Gap (GPG) of \$87.90.

^b 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).

Green italicised text indicates the Department's updates to the ADAR's financial analyses to reflect MSAC's advice.

Abbreviations: MBS, Medicare Benefits Schedule; mpFC, multi-parametric flow cytometry; MRD, measurable residual disease; NGS, next-generation sequencing.

The Commentary considered that there would be changes to the total cost of testing where the growth rate is amended to be ALL-specific, the paediatric relapse rate is changed to 50%, and where the uptake rate of each testing method is adjusted. The results of sensitivity analyses of these parameters are detailed in Table 19. The ADAR noted that MBS listing of clonoSEQ® and mpFC was not expected to result in change to other health budgets. This was because patients currently receive MRD testing despite a lack of MBS funding, through either out-of-pocket payments or public hospital funding.

The ADAR noted that current reliance on MRD testing is particularly true for access to blinatumomab on the PBS, which specifies that patients must be MRD positive at a sensitivity of 10⁻⁴ in order to receive treatment. The continuing criteria specify that to be eligible for subsequent rounds of treatment with blinatumomab, patients must be MRD negative. For the purpose of this application, the clinical utility of clonoSEQ® and mpFC and treatment decisions in

the base case of the economic model and financial estimates were modelled at a sensitivity threshold of 10^{-4} as this represents what is currently used in clinical practice. Two sensitivity analyses were conducted to model the impact should the PBS restriction criteria be amended to reflect an analytical threshold of 10^{-6} : first to test the impact of increased (rather than earlier) access to blinatumomab in 2% of the ALL population, and the second tested the opposite (2% decreased – rather than later – access to blinatumomab in the ALL population). Neither scenario affected the budget impact to the MBS, as the rate of testing remained the same as the base case. However, increasing patient access to blinatumomab resulted in an increase of \$ [REDACTED] to the PBS over the duration of the model, which translates to an overall net cost of \$ [REDACTED] to the Government. On the other hand, a reduction in patient access to blinatumomab resulted in an overall net cost of \$ [REDACTED] between 2022 and 2027.

Supplementary sensitivity analysis

A separate sensitivity analysis was conducted for the Commentary (Table 19) to test the impact of uncertain parameters in the financial model. The Commentary noted that the base case (scenario 1), incorrectly calculated the number of patients in each testing arm that relapsed for both populations (scenario 2) and used a non-specific ALL growth rate (scenario 3). As such, these parameters were tested alone (scenarios 2 and 3) and combined (scenario 4) in the model.

The results showed that of the three scenarios, recalculating relapse rates resulted in a \$2,137,270 reduction in the net cost to the MBS over 6 years compared to the base case. The combined scenario 4 resulted in a \$3,167,063 reduction in the net cost to the MBS over 6 years.

Additionally, the uptake rate of clonoSEQ® and mpFC (scenarios 5-6) and paediatric relapse rate (scenarios 7-8) were tested in both the base case and scenario 4 to reduce uncertainty around these parameters. When the uptake of clonoSEQ® was changed to 85% and mpFC to 15% from 2022 to 2027, there was a \$13,580,817 increase in the net cost to the MBS compared to the base case. A \$8,130,746 increase in net MBS costs was identified when the paediatric relapse rate was increased to 50%. The Commentary considered these results to be large changes in net MBS cost, though noted it may be difficult to predict the uptake of newly listed MBS items due to uncertainty surrounding behavioural responses and uptake fluctuations in the first few years after an item is listed.

The 1703 and 1707 PICO requests each assessment include a sensitivity analysis to incorporate the alternative application's utilisation estimates. This was not completed in the ADAR, and it was not possible for the Commentary to complete these analyses without further information about the number of tests per testing method by risk status. The ADAR tested the scenario where an additional MRD test per patient for clonoSEQ and mpFC is required.

Table 19 **Commentary Table – Alternative sensitivity and scenario analysis to assess the impact of uncertain parameters on the results of the financial model**

	2022	2023	2024	2025	2026	2027	TOTAL
Scenario 1: Base case							
Paediatric population	\$653,996	\$874,902	\$1,108,876	\$1,356,516	\$1,618,444	\$1,668,615	\$7,281,349
Adult population	\$791,061	\$1,039,105	\$1,301,768	\$1,579,717	\$1,873,648	\$1,931,731	\$8,517,032
Net cost to MBS	\$1,445,057	\$1,914,007	\$2,410,644	\$2,936,233	\$3,492,092	\$3,600,347	\$15,798,380
Difference	\$0	\$0	\$0	\$0	\$0	\$0	\$0
Scenario 2: Recalculation of relapse rates							
Paediatric population	\$637,132	\$853,198	\$1,082,047	\$1,324,266	\$1,580,462	\$1,629,456	\$7,106,560

	2022	2023	2024	2025	2026	2027	TOTAL
Adult population	\$601,719	\$795,414	\$1,000,540	\$1,217,620	\$1,447,196	\$1,492,060	\$6,554,550
Net cost to MBS	\$1,238,851	\$1,648,612	\$2,082,588	\$2,541,885	\$3,027,658	\$3,121,515	\$13,661,110
Difference	-\$206,205	-\$265,395	-\$328,057	-\$394,348	-\$464,434	-\$478,831	-\$2,137,270
Scenario 3: ALL-specific growth rate							
Paediatric population	\$618,655	\$817,991	\$1,024,679	\$1,238,926	\$1,460,944	\$1,488,701	\$6,649,896
Adult population	\$754,440	\$979,466	\$1,212,772	\$1,454,589	\$1,705,158	\$1,737,556	\$7,843,980
Net cost to MBS	\$1,373,095	\$1,797,458	\$2,237,451	\$2,693,515	\$3,166,101	\$3,226,257	\$14,493,876
Difference	-\$71,962	-\$116,550	-\$173,194	-\$242,719	-\$325,991	-\$374,090	-\$1,304,504
Scenario 4: Combined analysis (Scenarios 2 and 3 combined)							
Paediatric population	\$605,512	\$801,326	\$1,004,383	\$1,214,890	\$1,433,055	\$1,460,366	\$6,519,531
Adult population	\$581,316	\$759,290	\$943,837	\$1,135,141	\$1,333,395	\$1,358,806	\$6,111,786
Net cost to MBS	\$1,186,828	\$1,560,616	\$1,948,220	\$2,350,031	\$2,766,450	\$2,819,172	\$12,631,317
Difference	-\$258,229	-\$353,391	-\$462,424	-\$586,202	-\$725,642	-\$781,175	-\$3,167,063
Scenario 5: BASE CASE scenario analysis - change clonoSEQ®/mpFC uptake rate							
Paediatric population	\$2,113,495	\$2,179,013	\$2,246,563	\$2,316,206	\$2,388,009	\$2,462,037	\$13,705,324
Adult population	\$2,417,065	\$2,491,994	\$2,569,246	\$2,648,892	\$2,731,008	\$2,815,669	\$15,673,873
Net cost to MBS	\$4,530,560	\$4,671,007	\$4,815,808	\$4,965,099	\$5,119,017	\$5,277,706	\$29,379,197
Difference	\$3,085,503	\$2,757,000	\$2,405,164	\$2,028,865	\$1,626,925	\$1,677,359	\$13,580,817
Scenario 6: SCENARIO 4 scenario analysis - clonoSEQ®/mpFC uptake rate							
Paediatric population	\$1,961,723	\$1,999,109	\$2,037,208	\$2,076,033	\$2,115,597	\$2,155,916	\$12,345,586
Adult population	\$1,809,623	\$1,844,110	\$1,879,255	\$1,915,069	\$1,951,566	\$1,988,758	\$11,388,382
Net cost to MBS	\$3,771,346	\$3,843,220	\$3,916,463	\$3,991,102	\$4,067,163	\$4,144,674	\$23,733,968
Difference	\$2,326,290	\$1,929,212	\$1,505,819	\$1,054,869	\$575,071	\$544,327	\$7,935,588
Scenario 7: BASE CASE paediatric relapse rate 50%							
Paediatric population	\$1,422,229	\$1,874,750	\$2,353,960	\$2,861,080	\$3,397,378	\$3,502,697	\$15,412,095
Adult population	\$791,061	\$1,039,105	\$1,301,768	\$1,579,717	\$1,873,648	\$1,931,731	\$8,517,032
Net cost to MBS	\$2,213,291	\$2,913,855	\$3,655,728	\$4,440,797	\$5,271,027	\$5,434,429	\$23,929,126
Difference	\$768,234	\$999,848	\$1,245,084	\$1,504,564	\$1,778,935	\$1,834,082	\$8,130,746
Scenario 8: SCENARIO 4 paediatric relapse rate 50%							
Paediatric population	\$1,121,960	\$1,469,034	\$1,828,930	\$2,202,010	\$2,588,646	\$2,637,980	\$11,848,561
Adult population	\$581,316	\$759,290	\$943,837	\$1,135,141	\$1,333,395	\$1,358,806	\$6,111,786
Net cost to MBS	\$1,703,276	\$2,228,325	\$2,772,767	\$3,337,152	\$3,922,041	\$3,996,787	\$17,960,347
Difference	\$258,219	\$314,317	\$362,123	\$400,919	\$429,949	\$396,440	\$2,161,967

Source: Commentary Table 1, pg. 219 of the Commentary on MSAC 1707 ADAR

15. Other relevant information

Nil.

16. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues:

- MRD testing is already established as the standard of care for patients with ALL and is fully disseminated in Australia.
- Baseline testing to establish the patient's biomarker (i.e., determine their dominant leukaemic clone) should be included. The maximum of 12 tests per episode of disease would not need to be increased to account for this.
- The term "episode of disease" or "course of disease" is potentially confusing and it should be clarified in the item descriptor that this refers to both initial disease and relapse.
- A different laboratory-developed test (immunoSEQ) was used in the supporting evidence than the proposed clinical test (clonoSEQ®). The concordance between the two is uncertain, but an unpublished clinical validation report provided by the applicant indicates 91.8% concordance.
- Proposing both mpFC and a molecular method is appropriate, as some patients' biomarkers will not be detectable with one method. mpFC and molecular methods are complementary.

Economic issues:

- Some inputs to the economic model were uncertain, including the age of the adult population, and relapse rate in babies under 12 months of age.
- The hospital length-of-stay cost was not validated in the Australian healthcare setting.
- The cost of blinatumomab over an episode of treatment had been miscalculated. When this was corrected, the ICER increased substantially.

Financial issues:

- The appropriate fee for MRD testing using clonoSEQ® is uncertain. There was insufficient justification for the higher cost of testing using clonoSEQ® compared to other methods.
- The assumption that other MRD testing methods besides mpFC and clonoSEQ® will not be used is not reasonable.
- The utilisation of clonoSEQ® was potentially underestimated as an expected utilisation of 10-50% was used over 6 years, however the ADAR stated that up to 85% of B-ALL patients could be eligible for clonoSEQ®.
- Utilisation was underestimated as the 50% relapse rate in children aged 0-12 months was not incorporated into estimated service volumes for paediatric patients.
- The utilisation was overestimated by the ADAR double counting patients that relapsed, and not using the ALL-specific growth rate.
- Utilisation also may have been overestimated because the annual growth rate of the incidence of haematological malignancies was based on general population growth (3%), rather than the ALL-specific incidence (approximately 1.9%).

ESC discussion

ESC noted that this was an application from Adaptive Biotechnologies requesting Medicare Benefits Schedule (MBS) listing of PCR- and next generation sequencing (NGS)-based testing using the clonoSEQ® assay, and multi-parametric flow cytometry (mpFC), for the detection of

measurable residual disease (MRD; previously termed minimal residual disease) in patients with de novo or relapsed acute lymphoblastic leukaemia (ALL). ESC also noted that [Application 1703](#) was submitted by the Royal College of Pathologists of Australasia (RCPA) for methodology-agnostic molecular methods for the detection of MRD in patients with ALL: mpFC, allele-specific oligonucleotide real time quantitative polymerase chain reaction (ASO-qPCR), and generic NGS. Application 1703 is expected to be considered by ESC in February 2023.

ESC noted that MRD testing detects the presence of, and quantifies, residual malignant B- or T-cells in a patient's body below that detectable by morphological assessment, following commencement of treatment. MRD testing can detect malignant cells at a sensitivity of between 0.01% and 0.001% of cells (i.e., $<10^{-4}$ and $<10^{-6}$) depending on the technique used.

ESC noted the value that consumers placed on knowing prognosis, and that MRD testing might help plan future treatment. Regarding access for remote and rural patients, ESC considered that people with ALL were already linked to a hospital unit that had access to centralised testing, so considered access issues were unlikely. ESC noted that although it is not currently MBS listed, MRD testing has been the standard of care for children with ALL in Australia for more than 10 years. In addition, MRD-directed therapy was also recommended in adults in Australian clinical practice. However, to receive MRD testing, many patients (particularly adults) currently pay out-of-pocket costs. ESC noted that blinatumomab is a PBS-listed treatment for patients undergoing B-ALL treatment and who relapsed early, and that access under the current PBS restriction requires MRD to have been demonstrated at a level of 10^{-4} blasts, as measured by PCR (which may include clonoSEQ®) or mpFC. However, a diagnostic test for MRD to detect an early relapse in these patients is not MBS funded, so patients currently pay out-of-pocket for MRD testing in order to access PBS-listed blinatumomab. ESC therefore considered that publicly funding MRD testing would promote equitable access to this PBS-listed therapy.

ESC noted that the ADAR's item descriptors did not align with those in the PICO, however that in the pre-ESC response, the applicant had accepted amendments to the descriptors to align with the PICO.

ESC noted the item descriptors stated the patient must have been "treated with combination chemotherapy treatment or after salvage therapy", which it considered excluded baseline testing that occurs prior to chemotherapy or salvage treatment in order to identify the dominant leukaemic clone that can then be tracked in MRD testing, ESC considered that it would not be appropriate to exclude baseline testing from public funding, given its clinical importance in establishing the MRD assay successfully measures a patient's biomarker. ESC noted that the upper limit of 12 services per course of disease reflected the view of the RCPA, stated in the application form for MSAC Application 1703, that the average number of MRD tests per patient would not exceed four per year for three years (i.e., 12 services in total). However, ESC considered that according to the standard clinical management algorithms for patients with ALL (summarised in the applications), the total number of MRD tests that might be required in high risk and relapse settings were 5 and 7 tests respectively for children, and 4 and 6 tests respectively for adults. ESC therefore considered that overservicing would be highly unlikely – even more so because testing is restricted to bone marrow samples, which require an unpleasant procedure to obtain that patients and clinicians avoid when possible. Therefore, ESC further considered that baseline testing could be included as part of the proposed 12 tests per course of disease without needing to increase the maximum number. ESC proposed revising the item descriptors to make this unambiguous, by adding "or facilitating the determination of MRD in the future". ESC noted Medicare data does not have a concept of 'episode of disease' or 'course of disease' and that the potential overservicing of patients (i.e., repeat services beyond the proposed upper limit of 12 services per course of disease) would therefore be managed through Medicare compliance activity.

ESC agreed with the PICO Advisory Sub-Committee (PASC) that both proposed MBS items should be restricted to bone marrow (aspirate or biopsy) samples, to exclude usage of peripheral blood samples to determine MRD as this was much less sensitive. ESC noted the applicant-developed assessment report (ADAR) had not addressed whether aspirate and biopsy are interchangeable but considered that interchangeability was clinically reasonable.

ESC noted that the terms “episode of disease” or “course of disease” could be confusing and that the descriptor should be amended to clarify that this was intended to describe both initial disease and relapsed disease, with a maximum of 12 MRD tests each. ESC considered that ‘episode of disease’ would be clearer than ‘course of disease’, because clinically ‘course’ tends to mean first presentation and relapse.

ESC suggested the following edits to the proposed item descriptors:

Category 6 – Pathology services (Group P4 Immunology)
<p>MBS item AAAA</p> <p>Measurable residual disease (MRD) 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, <i>for the purposes of determining MRD or facilitating the determination of MRD following combination chemotherapy or after salvage therapy</i>, requested by a specialist or consultant physician practising as a haematologist or oncologist.</p> <p>Maximum of 12 per course <i>episode</i> of disease <i>or per relapse</i> for AAAA and EEEE combined</p> <p>Fee: \$550.00 Benefit: 75% = \$412.50 85% = \$467.50</p>
Category 6 – Pathology services (Group P7 Genetics)
<p>MBS item EEEE</p> <p>Identification and quantitation of rearranged B-cell receptor gene sequences (including IgH [VDJ], IgH [DJ], IgK, IgL, translocated BCL1/IgH [J] and BCL2/IgH [J] sequences), for the evaluation purposes <i>of determining measurable residual disease (MRD) or facilitating the determination of MRD following combination chemotherapy or after salvage therapy</i>, using multiplex polymerase chain reaction (PCR) and massively parallel sequencing (also referred to as next generation sequencing) performed on DNA extracted from bone marrow from a patient diagnosed with acute lymphoblastic leukaemia, requested by a specialist or consultant physician practising as a haematologist or oncologist.</p> <p>Maximum of 12 per course <i>episode</i> of disease <i>or per relapse</i> for AAAA and EEEE combined.</p> <p>Fee: \$2,100.00 Benefit: 75% = \$1,575.00 85% = \$2,012.10*</p>

Source: ESC. Red italics and red strikethrough indicate additions and deletions (respectively) proposed by ESC.

Abbreviations: ALL, acute lymphoblastic leukaemia. Italics (Red font) indicate changes proposed by ESC.

* Reflects the 1 November 2021 Greatest Permissible Gap (GPG) of \$87.90. All out-of-hospital Medicare services that have an MBS fee of \$586.20 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).

ESC noted that MRD status was the most important prognostic marker for relapse and overall survival (OS) in both newly diagnosed and relapsed patients with ALL. ESC noted that the ADAR concluded that the use of clonoSEQ® or mpFC for the detection of MRD in patients with ALL resulted in superior effectiveness and non-inferior safety compared with bone marrow morphological assessment ± cytogenetics, and that the commentary considered this conclusion was appropriate. ESC considered it was reasonable that using mpFC and/or molecular methods to detect MRD was superior to bone marrow morphology.

Regarding the proposed MBS fees, ESC noted the commentary considered that the ADAR did not present sufficient evidence that clonoSEQ® would have superior effectiveness and non-inferior safety in patients with ALL compared to other molecular methods of MRD testing, to justify the

higher proposed fee over these other MRD options. ESC noted that clonoSEQ® is reported to be sensitive to 10^{-3} to 10^{-6} blasts, but that a threshold of 10^{-4} is required for blinatumomab access, and that the commentary stated any clinical utility benefit from a lower detection threshold was not assessed in the ADAR and may not be realised in clinical practice. ESC considered that patients would likely have variable rates of progression from low to high levels of their dominant leukaemic clone, and presumed that the benefit of increased sensitivity would be lead time improvement, though noted the assessment had not demonstrated a health outcome improvement from using clonoSEQ® over other methods based on the improved sensitivity.

ESC noted the applicant had provided a disaggregation of the costs of using clonoSEQ®, however considered that it was unclear why the labour costs were low and reagent costs were high – though accepted that the stated costs probably reflect the cost of using clonoSEQ® overseas. ESC considered that it was unclear why the ADAR commented that testing using clonoSEQ® was less costly than the other methods proposed in application 1703, as the proposed fee is much higher, and the ADAR reported the cost-effectiveness of clonoSEQ® to be similar to that of ASO-qPCR. ESC considered that it was not clear how much patients currently pay out-of-pocket to access clonoSEQ® testing, and how this compares to the price of clonoSEQ® in the United States.

ESC noted that although mpFC was part of the proposed intervention for 1707, PASC had advised that the test options proposed by both 1703 and 1707 should be compared with each other as well as with the comparator, as this was needed to justify the proposed different costs of testing per patient. ESC considered that the ADAR had not conducted all comparisons as requested by PASC, and the evidence provided did not sufficiently justify the higher cost of clonoSEQ® testing compared to the generic methods proposed in 1703 – in particular, ESC considered that ASO-qPCR should be considered in parallel to mpFC and clonoSEQ® testing. However, ESC considered that some patients' biomarkers (the applicant stated 10% of patients, which ESC considered reasonable) will not be detectable with one method, and so considered that while molecular techniques are superior to mpFC, the multiple methods proposed to detect MRD are complementary.

ESC noted that the ADAR stated that, because the same type of sample (bone marrow biopsy) was used for the proposed intervention and the comparator test, the use of clonoSEQ® was not expected to introduce any additional direct safety concerns for patients with ALL.

ESC noted the clinical management algorithm showed the MRD assay was performed at the same time as the bone marrow test for morphological assessment, on the basis if MRD was detected earlier the patient could get earlier and more appropriate treatment.

ESC noted that the applicant stated that the research assay (immunoSEQ) and clinical assay (clonoSEQ®) were the same with respect to primers and computational algorithm, and as new versions of the assay were introduced, comparability studies were performed and routinely showed high concordance at the population level. ESC noted that in the pre-ESC response the applicant provided an unpublished clinical validation report for the clonoSEQ® assay, which found that the correlation coefficient between the laboratory-developed test (immunoSEQ) and clonoSEQ® was 91.80% (95% confidence interval [CI]: 89.66% to 93.51%). ESC considered that the concordance between immunoSEQ and clonoSEQ® was uncertain, as high-quality evidence had not been provided.

ESC noted that diagnostic accuracy was applied to the adult model as discordance between mpFC and clonoSEQ®; however, ESC considered the discordance to be uncertain, noting it was

based on a single study¹⁶ with small sample size (n=21), and the commentary observed that calculating using the correct denominator gives a 24% (rather than 42%) discordant rate.

ESC noted the economic analysis had used a cost-utility assessment (CUA) and considered this was appropriate. ESC noted the CUA had three steps: step 1, trial-based analysis over a 5-year time horizon representing the results of the BLAST trial; step 2 Markov cohort modelled analysis presented as cost per LY gained over a 30-year time horizon extrapolating from the trial data; step 3 (base case) is a Markov cohort modelled CUA presented as cost per QALY gained over a 30-year time horizon. ESC noted the ADAR reported incremental cost-effectiveness ratios (ICERs) of \$29,517/QALY in the paediatric population, and \$12,332/QALY in the adult population. ESC considered the decision tree incorporating Markov models to be reasonable, and that the transitions were appropriate, however it was concerned that some of the inputs were uncertain.

ESC noted that estimates of length of stay in hospital were sourced from personal communication (via the Health Quality Ontario 2016 report) in the Canadian healthcare setting. ESC considered that these costs constituted a significant proportion of overall costs, but that the estimates were uncertain as the clinical treatment pathway could have changed since 2016. Their applicability to the Australian context was also uncertain.

ESC considered the cost of blinatumomab over an episode had been costed incorrectly, as the approved ex-manufacturer price (AEMP) price of the drug was not used in the calculation of the ICER. ESC noted that correcting the economic model to incorporate the AEMP increased the ICER for the paediatric population to \$62,694/QALY and the adult population to \$42,189/QALY.

To more accurately reflect the likely economic impact of blinatumomab access due to MRD testing, a sensitivity analysis using the effective price for blinatumomab was requested by ESC and conducted by the Department (Table 20). ESC noted that using the effective price reduced the ICER by ██████% (paediatric) and ██████% (adults).

Table 20 Sensitivity analysis using the blinatumomab effective price

Parameter tested	Incremental cost	Incremental QALYs	ICUR (\$/QALY gained)	% change ICUR
Paediatric				
Corrected base case (blinatumomab AEMP)	\$23,895	0.38	\$62,694	-
Blinatumomab effective price (weighted)	\$████	0.38	\$████	█████%
Adult				
Corrected base case (blinatumomab AEMP)	\$55,245	1.26	\$42,189	
Blinatumomab effective price (weighted)	\$████	1.26	\$████	█████%

Abbreviations: AEMP, average ex-manufacturer price; ICUR, incremental cost-utility ratio; QALY, quality-adjusted life year.

Correction to the ADAR's model was only to incorporate the price of blinatumomab into the model. Weighting based on PBS utilisation data (2021-22).

Source: Post-ESC analyses conducted by the Department.

ESC noted that the average age used in the base case adult model was 23 years based on the average age of the overall population, rather than the average age of the adult population, which was 45–50 years. ESC noted the commentary's sensitivity analysis showed this had minimal effect on the ICER.

¹⁶ Sala Torra, O., M. Othus, D. W. Williamson, B. et al. (2017). Next-Generation Sequencing in Adult B Cell Acute Lymphoblastic Leukemia Patients. *Biology of Blood and Marrow Transplantation*, 23(4): 691-696.

ESC noted the ADAR used bone marrow morphology as the comparator, rather than bone marrow morphology ±cytogenetics as per the PICO, and that the commentary considered this would have over-estimated the cost-effectiveness.

ESC noted the ADAR used an epidemiological approach to estimate utilisation. ESC considered that the estimated utilisation of clonoSEQ® was potentially underestimated as an expected utilisation of 10-50% was used over 6 years, however the ADAR stated that up to 85% of patients with B-ALL could be eligible for clonoSEQ®. ESC considered that an analysis of an 85% uptake of clonoSEQ® and 15% mpFC would align with the ADAR's claims, but noted this had not been conducted. ESC considered that an assumption inherent in the ADAR's analyses was that other methods besides mpFC and clonoSEQ® will not be used at all in MRD testing, which it considered unreasonable.

ESC noted that the ADAR's financial analyses showed listing clonoSEQ® and mpFC on the MBS for the paediatric and adult populations would result in a net cost to the MBS of \$1,445,057 in 2022, increasing to \$3,600,347 in 2027, and totalling \$15,798,380 over 6 years. ESC noted that no other services were proposed to change in utilisation as a result of listing this testing on the MBS, which it considered appropriate as MRD testing is already fully disseminated as standard of care in Australia.

ESC agreed that the ADAR had double counted the proportion of patients that relapse, and noted that the commentary's analysis to correct this showed a \$2,137,270 reduction in the net cost to the MBS over 6 years compared to the base case.

ESC noted the higher relapse rate of 50% for the paediatric population aged <12 months at diagnosis was described in the PICO but not addressed in the ADAR's economic modelling. ESC noted the majority of paediatric patients with ALL were aged between 0-4 years old (54% of the paediatric population aged 0-14 years in 2017 as per the ACIM data). As such, to avoid an underestimation of the proportion of paediatric patients eligible for MRD testing, ESC considered the relapse rate stated in the PICO for the paediatric population aged 0-12 months old (50%) should have been used in the financial model. ESC noted the commentary added a sensitivity analysis of the financial impact, which showed increasing the paediatric relapse rate to 50% would double the paediatric population's cost of MRD testing to the MBS.

ESC noted that a 3% annual growth rate of the incidence of patients with haematological malignancies was used in the financial model; however, Australian Institute of Health and Welfare (AIHW) data for ALL-specific incidence were available (approximately 1.9%), and ESC considered it was more appropriate to use these data in the financial analysis. ESC noted that the commentary's sensitivity analysis using the AIHW ALL-specific growth rate reduced the net cost to the MBS over 6 years by \$1,304,504.

ESC noted that the combined sensitivity an analysis altering the relapse rate to correct double-counting and using the ALL-specific growth rate resulted in a \$3,167,063 reduction in the net cost to the MBS over 6 years.

17. Applicant comments on MSAC's Public Summary Document

Adaptive Biotechnologies is pleased that MSAC has recognised the high clinical utility of MRD testing in patients with ALL and welcomes MSAC's support of listing MRD testing using NGS methods including clonoSEQ® on the MBS. Adaptive Biotechnologies wishes to reiterate the importance of a sensitive, standardised, and consistent disease monitoring approach given the need for MRD measurement throughout treatment. Adaptive Biotechnologies is committed to working with the Department of Health and Aged Care to continue substantiating the value of clonoSEQ® across lymphoid malignancies and sample types (blood, bone marrow, plasma) to further improve access to MRD testing using clonoSEQ® for Australian patients.

18. Further information on MSAC

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