



**Australian Government**  
**Department of Health**

## **MSAC Application 1703**

**Detection of measurable residual disease in  
patients with acute lymphoblastic leukaemia**

# **Ratified PICO Confirmation**

Summary of PPICO criteria to define questions to be addressed in the Assessment Reports to the Medical Services Advisory Committee (MSAC).

**Table 1 PPICO for MRD in patients with ALL**

Component	Assessment 1703	Assessment 1707
<b>Population</b>	ALL	ALL
<b>Prior tests</b>	Tests to diagnose ALL	
<b>Intervention</b>	Detection of MRD in bone marrow BM by: 1. mpFC of leukaemia-associated immunophenotypes 2. molecular methods including real-time qPCR or NGS + morphological assessment ± cytogenetic analysis for assessing morphological remission	Detection of MRD in BM by: 1. mpFC of leukaemia-associated immunophenotypes 2. NGS-based MRD test using the clonoSEQ® assay + morphological assessment ± cytogenetic analysis for assessing morphological remission
<b>Comparators</b>	Morphological assessment ± cytogenetic analysis for assessing morphological remission	<i>Primary comparator:</i> Morphological assessment ± cytogenetic analysis for assessing morphological remission <i>Secondary comparator:</i> Other molecular methods including qPCR and other NGS methods
<b>Reference standard</b>	Prognostic and predictive reference standards: health outcomes (e.g. overall survival, event-free survival, recurrence rate)	
<b>Outcomes</b>	<p><u>Test outcomes</u>            Longitudinal accuracy for determining prognosis            Longitudinal accuracy for predicting response to treatment (e.g blinatumomab, CAR-T, HSCT)            Accuracy of monitoring to detect responsiveness to treatment (relative to background random variation, i.e. signal to noise ratio)            Detectability of long-term change relative to background random variation (to justify frequency of monitoring)            Safety of testing            Turnaround time            Test availability            Rate of rebiopsy/reaspiration</p> <p><u>Change in management</u>            Changes to treatment strategies based on test results            Proportion of tested patients whose MRD-directed treatment differs from standard treatment (number needed to test to alter treatment)</p> <p><u>Clinical utility</u>            Changes in health outcomes due to testing strategy and changes in management (e.g. survival, quality of life, rate of remission)            Safety of changes in management (such as reduced adverse events due to those with good prognosis avoiding intensive treatment)</p> <p><u>Economic evaluation</u>            Cost of test and financial implications to Medicare Benefits Schedule and healthcare system            Cost-effectiveness</p>	

Component	Description 1703	Description 1707
<b>Assessment questions</b>	<p>1a. What is the safety, effectiveness and cost-effectiveness of MRD testing (mpFC or molecular methods) in addition to assessment of morphological remission, compared to assessment of morphological remission alone, in patients with ALL?</p> <p>2a. What is the incremental prognostic benefit of using MRD testing in addition to assessment of morphological remission, compared to assessment of morphological remission alone, in patients with ALL?</p> <p>3a. What is the incremental predictive benefit of using MRD testing in addition to assessment of morphological remission, compared to predicting treatment benefit with assessment of morphological remission alone, in patients with ALL?</p> <p>4a. How accurate is MRD testing (mpFC or molecular methods) for monitoring (distinguishing between response to treatment and random variation) compared to assessment of morphological remission alone, in patients with ALL?</p> <p>5a. Does MRD testing (mpFC or molecular methods) alter management compared to assessment of morphological assessment alone, in patients with ALL?</p> <p>6a. How safe and effective are the alterations in management (found in response to question 5a)?</p>	<p>1b. What is the safety, effectiveness and cost-effectiveness of MRD testing (mpFC or using the clonoSEQ® assay) in addition to assessment of morphological remission, compared to assessment of morphological remission alone, in patients with ALL?</p> <p>2b. What is the incremental prognostic benefit of using MRD testing (mpFC or using the clonoSEQ® assay) in addition to assessment of morphological remission, compared to assessment of morphological remission alone, in patients with ALL?</p> <p>3b. What is the incremental predictive benefit of using MRD testing (mpFC or using the clonoSEQ® assay) in addition to assessment of morphological remission, compared to predicting treatment benefit with assessment of morphological remission alone, in patients with ALL?</p> <p>4b. How accurate is MRD testing (mpFC or using the clonoSEQ® assay) for monitoring (distinguishing between response to treatment and random variation) compared to assessment of morphological remission alone, in patients with ALL?</p> <p>5b. Does MRD testing (mpFC or using the clonoSEQ® assay) alter management compared to assessment of morphological assessment alone, in patients with ALL?</p> <p>6b. How safe and effective are the alterations in management (found in response to question 5b)?</p> <p>1c. What is the safety, effectiveness and cost-effectiveness of using the clonoSEQ® assay for MRD testing vs other molecular methods in patients with ALL?</p> <p>2c. What is the accuracy of the clonoSEQ® MRD assay for determining prognosis vs other molecular methods in patients with ALL?</p> <p>3c. What is the accuracy of the clonoSEQ® MRD assay for predicting response to treatment vs other molecular methods in patients with ALL?</p> <p>4c. How accurate is the clonoSEQ® assay for monitoring (distinguishing between response to treatment and random variation) vs other molecular methods in patients with ALL?</p> <p>5c. Does use of the clonoSEQ® assay alter management compared to other molecular methods in patients with ALL?</p> <p>6c. How safe and effective are the alterations in management (found in response to question 5c)?</p>

ALL = acute lymphoblastic leukaemia; BM = bone marrow; CAR-T = chimeric antigen receptor T cell treatment; HSCT = hematopoietic stem-cell transplantation; mpFC = multiparametric flow cytometry; MRD = measurable residual disease; NGS = next generation sequencing; qPCR = quantitative polymerase chain reaction

## Purpose of application

Two applications requesting Medicare Benefits Schedule (MBS) listing for tests to detect measurable residual disease (MRD) (previously termed “minimal residual disease”) in patients with acute lymphoblastic leukaemia (ALL) were received from the Royal College of Pathologists of Australasia (RCPA; application 1703) and from Adaptive Biotechnologies™ (application 1707) by the Department of Health.

In application 1703, the RCPA requested two Medicare Benefits Schedule (MBS) items for methods of MRD measurement:

- Multiparametric flow cytometry (mpFC); and
- Molecular methods (method-agnostic, so would include both allele-specific oligonucleotide real time quantitative polymerase chain reaction (ASO RT-qPCR) tests and next generation sequencing (NGS) methods such as, but not limited to, the use of the clonoSEQ® assay).

In application 1707 and after further consultation with the Department of Health, Adaptive Biotechnologies™ have requested two MBS items for methods of MRD measurement:

- mpFC; and
- NGS, with an item descriptor that reflects and supports use of the clonoSEQ® assay.

The RCPA claim that measuring MRD is superior to bone marrow morphological assessment, as it allows more appropriate treatment allocation:

- Resulting in more intensive treatment in those with poor prognosis, improving survival, and reducing the risk of recurrence (superior effectiveness, non-inferior safety), and
- and allowing less intensive treatment in those with a good prognosis, reducing adverse events (non-inferior effectiveness, superior safety).

Adaptive Biotechnologies™ claim that the clonoSEQ® assay and mpFC are superior in effectiveness to morphological assessment alone (with non-inferior safety), and the clonoSEQ® assay is superior to other molecular methods of testing MRD (with non-inferior safety).

## PICO criteria

### **Population**

The target population are people diagnosed with acute lymphoblastic leukaemia (ALL), or suffering relapse with this disease. ALL is a malignancy that affects immature blood white cells (or blasts). Abnormal blast cells are called leukaemic cells, which multiply quickly but do not mature into normal cells, or fulfil the infection-fighting role of white blood cells. When leukaemic cells build up in bone marrow, the number of red blood cells and platelets drop, which causes fatigue, bleeding problems and other health problems (Cancer Council NSW 2020). Without treatment, the leukaemic cells spread from the bone marrow into the bloodstream, and can spread to lymph nodes and some organs (Cancer Council NSW 2020). The particular types of immature white blood cells affected are lymphoblasts, which normally develop into lymphocytes, or T cells and B cells.

The World Health Organization (WHO) has classified ALL into several groups: B-cell ALL with genetic abnormalities (gene or chromosome changes), B-cell ALL not otherwise specified, and T-cell ALL.

The precursor B-cell ALL is the most common subtype, and a common genetic abnormality associated with adult B-ALL is the Philadelphia chromosome (Ph-positive ALL). Other common genetic changes in ALL are hyperdiploidy and *ETV6-RUNX1* translocation. The different germline and somatic genetic alterations associated with ALL influence its prognosis and treatment strategy (together with the patient's age, performance status, comorbidities and end-organ function (Brown, PA, Ji, et al. 2021)).

ALL is the most common cancer in childhood, with 243 cases per 100,000 aged 0 to 19 years estimated to be diagnosed in Australia in 2021 (AIHW 2021). It may also be diagnosed in adults, with bi-modal peaks of incidence between 2 and 5 years, and after 50 years of age (Della Starza et al. 2019). All age groups would therefore be considered eligible for the proposed tests (paediatric, adolescent, young adult and adult). Data from the Australian Institute for Health and Welfare (AIHW) indicate that the incidence of haematological malignancies is increasing at an average of 3.1% per year, so the expected number of newly diagnosed patients in 2022 is 460 (adults and children combined).

Treatment options have improved for patients with ALL over time, resulting in the 5 year survival rate in children having increased from 57% to 92% (Della Starza et al. 2019). In adults, those who are diagnosed with ALL are more likely to have high-risk leukaemia, with a relapse rate of 40-50%, likely due to the combination of having a higher incidence of high-risk variants, and also due to the fact that older adults are less able to tolerate intensive treatments (Della Starza et al. 2019). Between 2013 and 2017, the 5-year survival rate for children aged 14 and under was 94.0%, whereas for people aged 15 to 39, 5-year survival was 81.0%, and for those aged 40 and over, 5-year survival was 37.3% (AIHW 2021).

The RCPA provided data on an Australian cohort of children and teenagers (aged  $\geq 12$  months – 18 years) treated for ALL between 1998 and 2013, that demonstrated a relapse rate of 10%. The RCPA also advised the relapse rate is 50% in infants aged  $\leq 12$  months.

Assumptions used to project the uptake of MRD testing include:

- 3.1% growth in incidence of ALL per year (based on AIHW data that haematological malignancies are increasing at 3.1% per year)

- Uptake of 100% of paediatric cases (aged 0 to 14) and 90% of adults aged 15+ (to allow for some patients being unsuitable for testing)
- 57.4% of incident cases being aged 0 to 19 years and 42.6% of cases being aged ≥20 years (based on AIHW data from 2013 - 2017)
- Relapse rates:
  - 50% in infants aged ≤12 months
  - 10% in children aged 12 months to 18 years (based on in press data provided by the RCPA)
  - 50% in adults

**Table 2 Projected number of incident ALL cases, and patients eligible for MRD testing**

	2022	2023	2024	2025	2026	2027
Projected new cases <sup>s</sup>	460	474	489	504	520	536
Projected new cases who may uptake MRD testing <sup>b</sup>	436 (221 + 0.9*239)	449 (227 + 0.9*247)	463 (235 + 0.9*254)	478 (242 + 0.9*262)	493 (249 + 0.9*270)	535 (257 + 0.9*278)
Projected relapsed cases <sup>c</sup>	124 (14+ 21 + 89)	127 (15+ 21 + 91)	133 (15 + 22 + 95)	137 (16 + 23 + 98)	141(16 + 24 + 101)	146 (17 + 25 + 104)
Projected total cases <sup>d</sup>	560	576	596	615	634	681

<sup>s</sup> (based on AIHW projections for 2021 and assumption of 3.1% growth)

<sup>b</sup> (based on 100% of 0-14 years olds, and 90% of 15+ year olds)

<sup>c</sup> (based on 50% relapse in those aged ≤12 months, 10% relapse in 1-18 year olds, and 50% of 19+ year olds from incident cases 3 years prior)

<sup>d</sup> Sum of new cases who uptake MRD testing and relapsed cases

## **Interventions**

### **The proposed intervention for application 1703 is MRD testing, using mpFC, or molecular methods.**

MRD testing detects the presence of, and quantifies, malignant (precursor) B- or T-cells in a patient's body. This information is used to determine the person's prognosis, predict how beneficial treatment is likely to be, and monitor response to treatment. All of these factors are used to inform treatment decisions across the treatment pathway.

Although not currently MBS-listed, MRD testing has been standard practice for children with ALL in Australia for more than 10 years (RCPA 2022). MRD testing is performed in addition to morphological assessment ± cytogenetic analysis, which is performed in order to determine whether the patient has achieved morphological remission. Given that MRD testing is proposed to only be used at times when bone marrow morphological assessment is also performed, the MRD testing is proposed to be performed on bone marrow samples rather than blood samples.

*PASC discussed whether the intervention should also include analysis on peripheral blood. Clinical advice suggested that although testing on peripheral blood may be performed in the future, it is not done currently in Australia. It was decided that the current assessments and proposed items should be limited to MRD testing on bone marrow tissue, and that a future application may request expansion of MRD testing to include peripheral blood samples. If the item descriptors do not further specify then this would include*

*both aspirate and biopsy bone marrow samples: the assessment report should examine whether there is sufficient confidence that all options within scope perform sufficiently similarly to allow them to be interchanged, or justify any proposed selection, preferably in terms of consequences for the patients tested. All item descriptors should be consistent with respect to aspirate, biopsy, or both.*

Multi-parametric flow cytometry (mpFC) detects malignant cells through detection of leukaemia-associated immunophenotypes. It can be successfully used in >90% of cases to a sensitivity of  $10^{-3}$  to  $10^{-4}$  (one leukaemic cell out of 1000-10,000 cells). Flow cytometry is the fastest of MRD methods, with a turnaround time of a few hours. However, the samples must be analysed within a short time period of sample collection (to avoid cell death), which limits the ability of samples to be sent to a central laboratory for analysis (Della Starza et al. 2019). There can also be some false-positive results due to post-induction regeneration of normal lymphoid cells co-expressing some ALL-type antigens, or due to the bone marrow sample hypocellularity or phenotypic shift (Della Starza et al. 2019).

Molecular methods of MRD testing use leukaemia-specific fusion gene transcripts or patient-specific (immunoglobulin/T-cell receptor gene rearrangements and microdeletions) molecular markers (Della Starza et al. 2019). The most common molecular methods are real time quantitative polymerase chain reaction (qPCR) or NGS. Molecular methods are more robust than flow cytometry when the sample is being sent to a central laboratory, so are less time-critical. The RCPA comment that where it is difficult to obtain bone marrow by aspiration, allele-specific oligonucleotide (ASO) qPCR can be performed on bone marrow biopsy (trephine samples).

The RCPA suggest that flow cytometry and molecular methods are complementary, as MRD is easier to measure in some individuals using flow cytometry, whereas in other individuals, molecular methods are easier. Flow cytometry is helpful when there is a large proportion of leukaemic cells in the sample (such as early in the treatment pathway), as in these situations the lower sensitivity is not a concern, and the results may be returned quickly. However, there are times when the flow cytometry result is hard to interpret, or patients in whom appropriate markers are not identified, and who must be tested with molecular methods in order to determine MRD. Similarly, not all patients have molecular markers, and for such patients flow cytometry may be the only option for MRD testing. Different treatment centres have preferences for one method over the other. Once a marker has been identified using one method, then patients are likely to continue to have their MRD tested using that method. The RCPA therefore considered it important to have flexibility of methods.

*PASC noted that ASO qPCR methods for MRD testing are currently being assessed by the National Association of Testing Authorities (NATA).*

**The proposed intervention for application 1707 is MRD testing, using mpFC, or the clonoSEQ® Next Generation Sequencing (NGS)-based assay.** The clonoSEQ® assay uses a proprietary multiplex polymerase chain reaction (PCR) and NGS platform to identify specific sequences within a malignant lymphocyte in a given patient sample. The assay identifies and quantifies DNA sequences associated with ALL: rearranged IgH (VDJ), IgH (DJ), IgK and IgL receptor gene sequences. Adaptive Biotechnologies™ submitted an application to the Therapeutic Goods Administration for registering of the clonoSEQ® assay in December 2021, and feedback is expected in March or April 2022.

The clonoSEQ® is proposed as an alternative to flow cytometry and other forms of molecular MRD testing (RT-qPCR and other forms of NGS). Though as discussed above, there will be a small proportion of patients without molecular variants identifiable by the clonoSEQ® assay or other molecular methods. The

clonoSEQ® therefore cannot completely replace use of flow cytometry (hence also proposing mpFC as an additional intervention).

Each person diagnosed and being treated for ALL would be tested for MRD at multiple timepoints. Initially, they would have MRD testing performed on a bone marrow aspirate sample prior to induction therapy to establish a baseline assessment. Subsequent to induction therapy, additional MRD assessments would occur on bone marrow aspirates or peripheral blood samples, to assess and monitor treatment effectiveness. More discussion of the number of tests is provided under 'Proposal for public funding'.

The assessment of MRD testing will need to separate the clinical evidence into the different time points when MRD testing is performed (i.e. demonstrating the value of testing after induction therapy, separate from testing after consolidation therapy, separate from testing before high-intensity protocols etc.).

### **Comparators**

**The comparator for application 1703, and the primary comparator for application 1707, is proposed to be morphological assessment ± cytogenetic analysis performed on bone marrow samples.** After the sample has been obtained, a slide is prepared and stained with Giemsa before its morphology is examined with a microscope. Morphology tends to only be able to detect leukaemic cells if there are more than five per 100 white cells (i.e. 5% blast cells), and the definition of complete morphologic remission is a blast count <5%. Although this may be useful to diagnose ALL (when ≥20% of cells are leukaemic), it is too insensitive to detect whether the patient has gone into remission after treatment (RCPA 2022), and cannot be used to assess treatment response once the blast percentage is <5%. Bone marrow examination is used after initial treatment (induction and consolidation) to confirm that a patient has achieved morphological remission. After achieving morphologic remission, the major clinical purpose of additional bone marrow examinations is to measure MRD and confirm ongoing morphologic remission. Bone marrow biopsies are performed for morphological assessment, and the RCPA considered that if the sample is sufficient for morphological assessment, it would usually be sufficient for MRD testing as well. The RCPA commented that rebiopsies occur in very rare circumstances, and could occur for MRD testing alone: all paediatric and adolescent ALL protocols have treatment stratified by MRD response. If there is an inadequate sample for MRD at a stratifying timepoint then there would be a recollection to repeat the MRD analysis, particularly if the MRD result is used to stratify high risk treatment (i.e. to identify patients who would benefit from blinatumomab, as per the PBS indication, CAR-T cells or stem cell transplantation).

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. It is carried out on a cell-by-cell basis and can detect large scale abnormalities. Where there is an identified translocation (such as *KMT2A* or *BCR-ABL*), cytogenetic analysis could be done using existing MBS items (73314 and 73315). It may be used to detect leukaemic cell burden if at least five per 100 white cells are affected. However, it does rely on a clonal cytogenetic marker to be identified (so is only suitable for those with chromosomal abnormalities).

*PASC affirmed that the comparator was morphological assessment ± cytogenetic analysis performed on bone marrow samples (ie without the addition of the proposed interventions), and that morphological assessment ± cytogenetic analysis performed on bone marrow samples would continue to be performed with the addition of the proposed interventions.*

*PASC advised that the test options proposed by both 1703 and 1707 should be compared with each other as well as compared with morphological assessment ± cytogenetic analysis performed on bone marrow*



*samples alone. This is needed to justify the different costs per patient of these different proposed test options.*

MBS items relevant to morphological assessment and cytogenetic analysis are described in Table 3. These items are nonspecific to ALL, so MBS statistics are unable to provide data on the number of services performed per year for ALL.

**Table 3 MBS items for morphological assessment and cytogenetic analysis**

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

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

**The secondary comparator for application 1707 is proposed to be other molecular methods of MRD testing.** This involves any molecular methods of MRD testing likely to be used in Australia under the MBS item proposed by the RCPA in application 1703, such as ASO-qPCR, or other NGS assays. This comparison is necessary due to the higher fee proposed in application 1707 for use of the clonoSEQ® assay, than proposed in application 1703 for a method-agnostic item for molecular methods of MRD testing.

### **Reference standard**

The prognostic and predictive test performance of MRD will be assessed using health outcomes as the reference standard (e.g. overall survival, disease-free survival).

The analyses for prognostic and predictive accuracy will need to be grouped by time of testing, and by the treatment received subsequent to testing (e.g. accuracy of MRD prognostic estimates after induction therapy presented separately from accuracy of MRD prognostic estimates after consolidation therapy; and accuracy of MRD to predict response to CAR-T separate from from accuracy of MRD to predict response to treatment with HSCT).

### **Clinical utility standard (for codependent investigative technologies only)**

Although assessment of MRD testing is not considered to be an integrated codependent assessment, it is used to determine treatment allocation, including for PBS-listed blinatumomab.

*PASC noted that the proposed service would allow earlier access to blinatumomab if a lower limit of MRD detection was used, but would not increase the number of patients being treated with the drug as (non-MBS funded) testing is performed in accordance with the PBS restriction.*

The key trial for the blinatumomab PBAC submission was the BLAST trial, which selected patients using qPCR of clonally rearranged immunoglobulin and/or T-cell receptor genes or using flow cytometry. The PBS listing for blinatumomab (code 11867N) allows access to patients with pre-B-cell-ALL and MRD defined at least  $10^{-4}$  (0.01%) blasts measured in bone marrow, and measured using PCR or flow cytometry ([PBS Online](#)). As the restriction does not mention the method of PCR, it could either be real-time PCR or NGS PCR, making the proposed interventions for application 1703 and 1707 both suitable.

## Outcomes

### Test performance

Prognostic ability (to predict health outcomes, e.g. hazard ratios for different MRD-categorised groups)

Predictive accuracy (predicting response to treatment, such as blinatumomab, HSCT, CAR-T)

Responsiveness to treatment (relative to background random variation, i.e. signal to noise ratio)

Detectability of long-term change relative to background random variation (to justify frequency of monitoring)

Test turnaround time and availability of test (equity of access)

Rate of rebiopsy/reaspiration

*PASC agreed to additional outcomes of “test turnaround time”, “cost of test”, and “availability of test”.*

*PASC noted that some public consultation responses suggested that the proposed intervention may result in an increase in bone marrow biopsies. The applicants for 1703 and 1707 had both reported that this would not occur (as MRD testing would only occur simultaneously with bone marrow biopsies for morphological assessment). PASC agreed the proposed intervention would not result in an increase in bone marrow biopsies. However, if any evidence becomes available during the assessment phase on the rate of rebiopsy, this should be included.*

### Change in management

Proportion of tests where the resulting MRD-directed treatment would differ from standard treatment (i.e. number needed to test to alter treatment)

Evidence that test results (at different points in the treatment pathway) are used to change management

### Clinical utility

Health outcomes as a result of using MRD-directed treatment versus standard treatment, e.g. survival, quality of life, rate of remission

Safety of using MRD vs morphological assessment ± cytogenetic analysis to guide treatment decisions (adverse events related to treatments chosen).

### Economic evaluation

Cost of test and financial implications to Medicare Benefits Schedule and healthcare system

Cost-effectiveness

## Assessment framework

Application 1703 identified two studies that provide direct from test to health outcomes evidence for MRD testing.

The key evidence in de novo ALL patients comes from two randomised trials in one (UKALL2003). In those with low risk (determined by MRD), patients were randomised to receive standard treatment (equivalent to what they would have received in the absence of MRD testing), or reduced treatment (qPCR MRD-

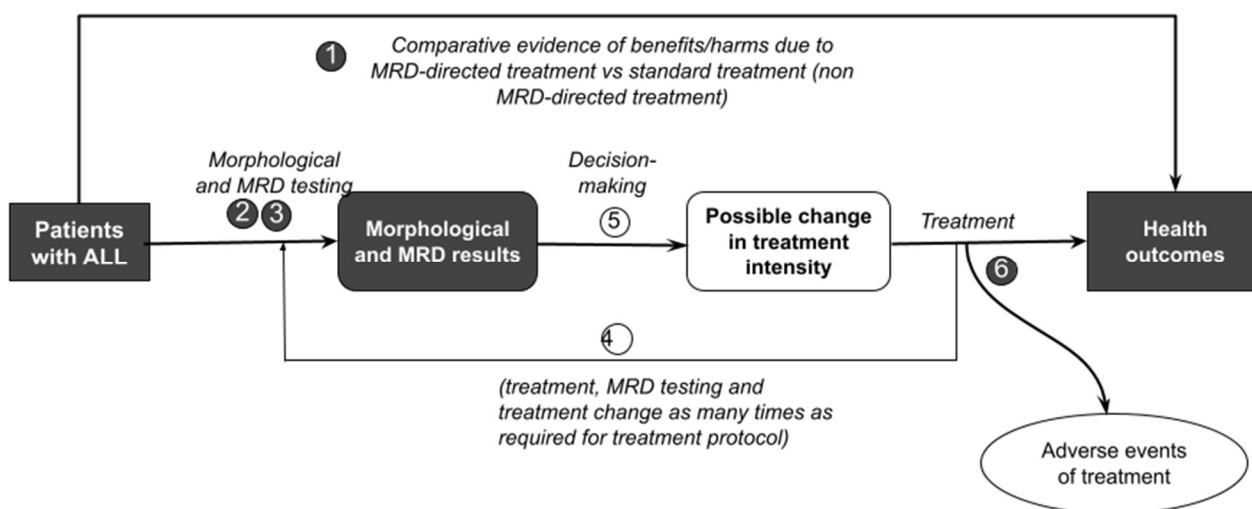
directed treatment), and had equivalent health outcomes (i.e. no loss of effectiveness, but reduced risk of adverse events).

In those deemed intermediate risk by morphological assessment, but high risk by qPCR MRD testing, patients were randomised to either standard treatment (equivalent to what they would have received in the absence of MRD testing) or augmented treatment (qPCR MRD-directed treatment). Event-free survival and risk of relapse were significantly better in those with MRD-directed treatment, and the hazard ratio for overall survival looked clinically important, although there were too few events for it to be statistically significant.

An additional historical control study (ALL-REZ BFM 2002 for qPCR MRD-directed treatment, and ALL-REZ BFM P95/96 for standard treatment) provides direct from test to health outcomes evidence, in children with relapsed ALL. In the prospective cohort component, those low risk by MRD testing proceeded without HSCT, and those deemed high risk received HSCT. Health outcomes were compared to those in a historical control group who had MRD testing performed as part of a prognostic study (without MRD-directed treatment).

As these direct evidence studies do not cover all uses of MRD testing, and only cover qPCR methods (not mpFC), the assessment will also need to include additional prognostic and predictive evidence to demonstrate the benefit of testing at other time points, and other methods, and seek any further evidence on how it impacts on the management of patients.

References provided in application 1703 suggests that the assessment framework will be able to include the evidence components in the dark boxes and circles in Figure 1. (Please note, a comprehensive search will only be performed during the assessment stage, and some forms of evidence may have been missed in the scoping search).



**Figure 1 Assessment framework for assessment 1703 showing direct from test to health outcomes evidence and linked evidence from test to health outcomes for assessment**

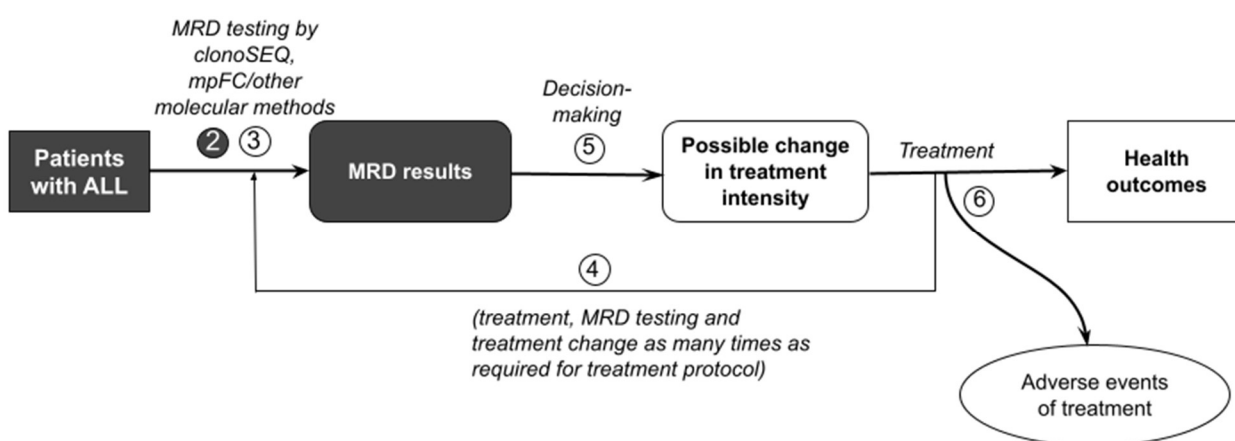
Figure notes: 1: direct from test to health outcomes evidence (safety and effectiveness); 2: prognostic accuracy; 3: predictive accuracy; 4: monitoring accuracy; 5: change in treatment/management; 6: influence of the change in management on health outcomes (safety and effectiveness), which do not meet the criteria to be direct from test to health outcomes evidence

The questions to be addressed in the assessment report (relating to components of the framework above) for 1703 are:

- 1a. What is the safety, effectiveness and cost-effectiveness of MRD testing (mpFC or molecular methods) in addition to assessment of morphological remission, compared to assessment of morphological remission alone, in patients with ALL?
- 2a. What is the incremental prognostic benefit of using MRD testing in addition to assessment of morphological remission, compared to assessment of morphological remission alone, in patients with ALL?
- 3a. What is the incremental predictive benefit of using MRD testing in addition to assessment of morphological remission, compared to predicting treatment benefit with assessment of morphological remission alone, in patients with ALL?
- 4a. How accurate is MRD testing (mpFC or molecular methods) for monitoring (distinguishing between response to treatment and random variation) compared to assessment of morphological remission alone, in patients with ALL?
- 5a. Does MRD testing (mpFC or molecular methods) alter management compared to assessment of morphological assessment alone, in patients with ALL?
- 6a. How safe and effective are the alterations in management (found in 5a)?

No direct from test to health outcomes evidence was identified from scoping searches on either mpFC or the clonoSEQ<sup>®</sup> assay. A linked evidence approach will therefore likely be required, linking together evidence regarding the accuracy of mpFC and clonoSEQ<sup>®</sup> (for determining prognosis, predicting treatment response, and monitoring), compared to no MRD testing, and MRD testing by other molecular methods, combined with evidence that MRD is used to alter treatment, and evidence that these treatment alterations are likely to benefit the health of patients (note, in the absence of direct from test to health outcome evidence, the evidence of MRD-guided treatment altering health outcomes may come from studies using other methods of MRD testing, such as qPCR).

The assessment framework expected to be used for assessment 1707 is shown in Figure 2. The dark boxes and circles are the components of the assessment framework for which evidence is known from the scoping searches to be available (i.e. evidence of superior prognostic accuracy of clonoSEQ<sup>®</sup> versus other molecular methods, superior prognostic accuracy of clonoSEQ<sup>®</sup> versus mpFC, and superior prognostic accuracy of mpFC vs no MRD testing). (Note that a full systematic review is yet to be performed and the scoping searches do not represent all available information).



**Figure 2 Assessment framework for assessment 1707 showing linked evidence from test to health outcomes for assessment**

Figure notes: 2: prognostic accuracy; 3: monitoring accuracy; 4: change in treatment/management; 5: influence of the change in management on health outcomes (safety and effectiveness), which do not meet the criteria to be direct from test to health outcomes evidence

The questions to be addressed in the assessment report (relating to components of the framework above) for 1707 are:

Research questions for the primary comparison:

- 1b. What is the safety, effectiveness and cost-effectiveness of MRD testing (mpFC or using the clonoSEQ<sup>®</sup> assay) in addition to assessment of morphological remission, compared to assessment of morphological remission alone, in patients with ALL?
- 2b. What is the incremental prognostic benefit of using MRD testing (mpFC or using the clonoSEQ<sup>®</sup> assay) in addition to assessment of morphological remission, compared to assessment of morphological remission alone, in patients with ALL?
- 3b. What is the incremental predictive benefit of using MRD testing (mpFC or using the clonoSEQ<sup>®</sup> assay) in addition to assessment of morphological remission, compared to predicting treatment benefit with assessment of morphological remission alone, in patients with ALL?
- 4b. How accurate is MRD testing (mpFC or using the clonoSEQ<sup>®</sup> assay) for monitoring (distinguishing between response to treatment and random variation) compared to assessment of morphological remission alone, in patients with ALL?
- 5b. Does MRD testing (mpFC or using the clonoSEQ<sup>®</sup> assay) alter management compared to assessment of morphological assessment alone, in patients with ALL?
- 6b. How safe and effective are the alterations in management (found in response to question 5b)?

Research questions for the secondary comparison:

- 1c. What is the safety, effectiveness and cost-effectiveness of using the clonoSEQ<sup>®</sup> assay for MRD testing vs other molecular methods in patients with ALL?
- 2c. What is the accuracy of the clonoSEQ<sup>®</sup> MRD assay for determining prognosis vs other molecular methods in patients with ALL?
- 3c. What is the accuracy of the clonoSEQ<sup>®</sup> MRD assay for predicting response to treatment vs other molecular methods in patients with ALL?
- 4c. How accurate is the clonoSEQ<sup>®</sup> assay for monitoring (distinguishing between response to treatment and random variation) vs other molecular methods in patients with ALL?
- 5c. Does use of the clonoSEQ<sup>®</sup> assay alter management compared to other molecular methods in patients with ALL?
- 6c. How safe and effective are the alterations in management (found in response to question 5c)?

## Clinical management algorithms

The clinical management algorithm provided in application 1703 for the scenario in the absence of MRD testing is shown in [Figure 3](#). The tests are shown in blue. These algorithms are based on the ALL06 treatment protocol, which has been found to be effective in children, and is now also being used in adults. The treatment protocol is provided in more detail in Appendix A (explaining what the treatment elements are in each phase).

*PASC noted that after patients have relapsed, they are considered to have high risk of recurrence. However, instead of starting a new treatment phase which includes the Protocol I induction and consolidation, they would receive the treatments suitable for those with no morphological remission (i.e. CAR-T, inotuzumab ozogamicin or blinatumomab). They may also be considered for new anti-cancer therapies (including*

cytotoxic drugs and clinical trials). The algorithm should also include an option for clinical remission, and surveillance.

PASC queried whether patients with low to moderate risk of relapse (including children and adolescents) would be monitored using MRD testing after completion of therapy. Expert advice suggested that MRD after completion of therapy is not a standard used internationally, and not proposed. The exception is for those at high risk of recurrence, who have undergone HSCT or treatment with blinatumomab.

PASC queried whether there should be separate clinical management algorithms for children and adults. However, expert advice suggested that there are many different protocols for treating patients with ALL, and it would be impossible to capture all the different treatment pathways. PASC therefore did not see a benefit in creating additional clinical management algorithms.

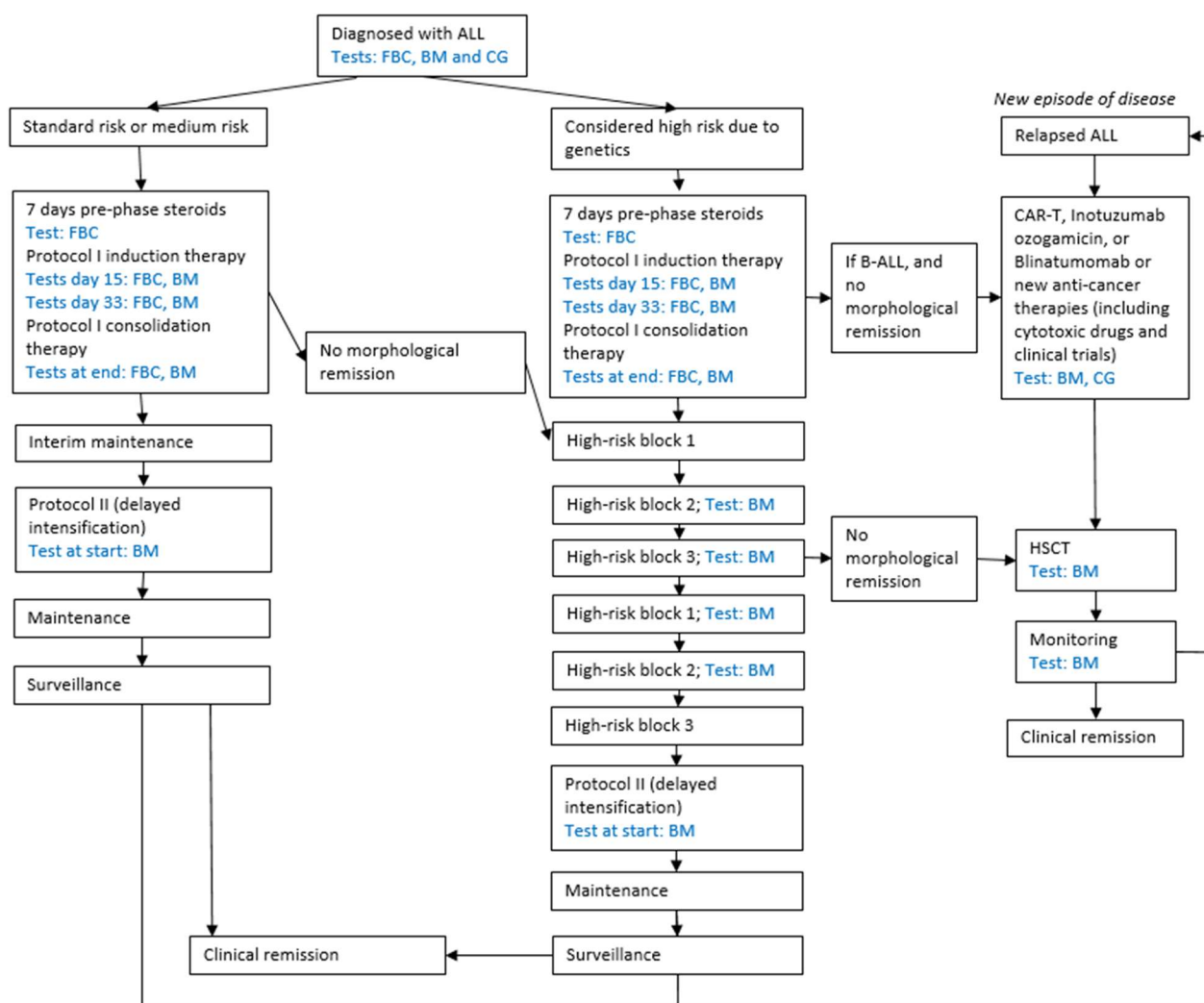
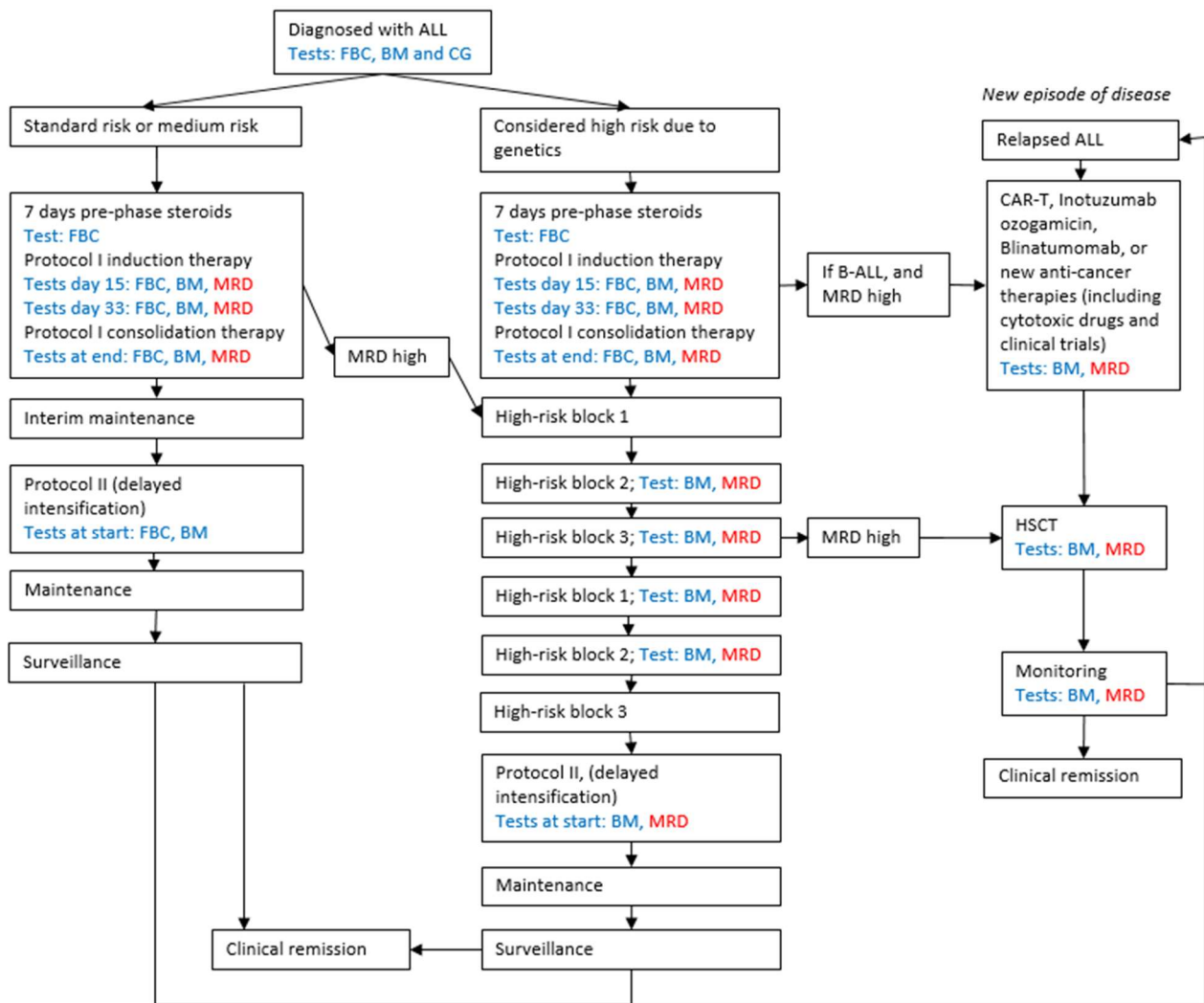


Figure 3 Clinical management algorithm for patients with ALL in absence of MRD (current)

ALL = acute lymphoblastic leukaemia; B-ALL = B cell ALL; BM = bone marrow morphological assessment; CAR-T = chimeric antigen receptor T cell treatment; CG = cytogenetic analysis; FBC = full blood count; HSCT = hematopoietic stem-cell transplantation; MRD = measurable residual disease

The clinical management algorithm showing the addition of MRD testing (in red) is provided in Figure 4. MRD testing influences the proportion of patients who receive different treatments, and is also used to determine access to blinatumomab, hematopoietic stem-cell transplantation (HSCT) and chimeric antigen receptor T cell treatment (CAR-T).



**Figure 4 Clinical management algorithm for patients with ALL with MRD (proposed)**

ALL = acute lymphoblastic leukaemia; B-ALL = B cell ALL; BM = bone marrow morphological assessment; CAR-T = chimeric antigen receptor T cell treatment; CG = cytogenetic analysis; FBC = full blood count; HSCT = hematopoietic stem-cell transplantation; MRD = measurable residual disease

The algorithm in Figure 3 would also be relevant to the primary comparator scenario for assessment 1707. For the secondary comparison in assessment 1707, the clinical management algorithms for the intervention (clonoSEQ<sup>®</sup> assay) versus the comparator (other molecular methods of MRD testing) would be identical to each other (although the accuracy of the MRD method may alter the proportion of patients who receive different treatments). Figure 4 would therefore be relevant to both the intervention and comparator scenarios.

## Proposed economic evaluation

Application 1703 and 1707 both claim that MRD testing (by mpFC, clonoSEQ<sup>®</sup> assay or other molecular methods) has superior effectiveness and non-inferior safety to assessment of morphological remission alone (morphological assessment ± cytogenetic analysis).

Application 1707 further claims that clonoSEQ<sup>®</sup> has superior effectiveness to other molecular methods of MRD testing. *PASC emphasised that both assessments will require evidence of incremental benefits associated with the more expensive test options over the cheaper test options.*



The type of economic evaluations for these comparisons would be a cost-effectiveness or cost-utility analysis (Table 4).

A published economic analysis was identified for MRD testing by flow cytometry in childhood ALL vs no MRD testing (Health Quality Ontario & Toronto Health Economics and Technology Assessment Collaborative 2016). Testing with flow cytometry at the end of induction and consolidation (i.e. two tests per patient) was associated with improved survival in newly diagnosed patients with ALL, and an incremental cost of C\$43,613 per Quality Adjusted Life Year (QALY) (or C\$53,515/QALY after adjusting for parameter uncertainty).

**Table 4 Classification of comparative effectiveness and safety of the proposed intervention, compared with its main comparator, and guide to the suitable type of economic evaluation**

Comparative safety	Comparative effectiveness			
	Inferior	Uncertain <sup>a</sup>	Noninferior <sup>b</sup>	Superior
Inferior	Health forgone: need other supportive factors	Health forgone possible: need other supportive factors	Health forgone: need other supportive factors	? Likely CUA
Uncertain <sup>a</sup>	Health forgone possible: need other supportive factors	?	?	? Likely CEA/CUA
Noninferior <sup>b</sup>	Health forgone: need other supportive factors	?	CMA	CEA/CUA
Superior	? Likely CUA	? Likely CEA/CUA	CEA/CUA	CEA/CUA

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

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

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

<sup>b</sup> An adequate assessment of 'noninferiority' is the preferred basis for demonstrating equivalence

### **Financial analysis**

*While the applicants and PASC agreed the proposed interventions would not result in an increase in the number of bone marrow biopses, the financial analysis should incorporate any increase in the number of bone marrow aspirations/biopsies performed should evidence suggesting this become available during the assessment phase.*

*The RCPA explained that although MRD testing is routinely used in paediatric ALL, its use is currently funded by hospitals and oncology departments, usually using donated funds, or by patients paying out-of-pocket. MRD testing is therefore not paid for by the states/territories, and the implications of cost-shifting do not need to be assessed.*

*Some patients may be tested with different testing modalities or swap testing providers over the course of their disease. This may require archival tissue to be retrieved. The costs of archival tissue retrieval (MBS item 72860) should be incorporated into the assessment reports.*

## Proposal for public funding

Three MBS items were initially proposed across the two applications, for flow cytometry, molecular methods of MRD, and by NGS (with an item descriptor that reflects and supports the use of the clonoSEQ® assay).

Table 5 and Table 6 incorporate revisions made after PASC to include the following:

*The item should be amended for “a patient”, rather than “patients”. The item should also incorporate restrictions to limit requesting the item to haematologists or oncologists, for the purpose of guiding treatment decisions.*

*The RCPA clarified that proposed item AAAA should be in group P4 Immunology, and proposed item BBBB should be in group P7 Genetics.*

*PASC noted expert advice that qualitative methods are not used, and advised that item BBBB for molecular methods should specify “quantitative” molecular methods.*

*PASC noted that Adaptive Biotechnologies were satisfied to proceed with the item for flow cytology, as suggested by the RCPA, and amended by PASC.*

*At the meeting, the RCPA was willing for the proposed item BBBB (for molecular methods of MRD testing) to be split into 3 separate items, to be further developed by the policy area of the Department:*

- 1) *an item for NGS testing*
- 2) *an item for the development of the patient specific assay for qPCR and the first test using this assay*
- 3) *an item for subsequent testing using the patient specific assay for qPCR.*

*PASC noted post-PASC advice from the 1703 applicant that the assay would be developed using the sample at diagnosis and that the first use for MRD testing would take place weeks later on a follow-up bone marrow sample. PASC considered that for CCCC, the item descriptor should make clear that the rebate is for testing two separate samples taken at different time points: the diagnostic specimen and the first MRD specimen.*

*Having an item for assay development would be similar to the approach taken for pre-implantation genetic testing (MSAC Application 1165.1), implemented under MBS items 73384, 73385, 73386 and 73387.*

*PASC agreed that the restrictions on the number of tests able to be performed should incorporate all testing modalities. PASC noted there was no need to apply co-claiming restrictions across testing modalities, as it would be unlikely for a pathologist to use multiple modalities on the same occasion. PASC discussed how best to limit the use of MRD testing, as public consultation responses suggested that “per episode of disease” was difficult to define. Further discussion is required with the policy area on whether to restrict by time frame (e.g. 12 tests within 24 months of diagnosis or relapse), or by course of treatments before and after disease relapse (as currently worded).*

All steps associated with the MRD would be performed by trained and qualified scientists/laboratory technicians, under the direction of a pathologist, on the request of the treating clinician, with results provided back to the treating clinician to guide treatment selection.

The only laboratory in Australia that currently has the capacity and expertise to use the clonoSEQ® assay is the Molecular Haematology Laboratory, Peter MacCallum Cancer Centre in Melbourne. Additional sites may be included in the future to meet regional needs or as volume increases.

**Table 5 MBS items proposed in application 1703 for flow cytometry and molecular methods of MRD testing after amendments suggested by the Department of Health and PASC**

Category 6 – Pathology services	Group P4 Immunology
<p>MBS item AAAA</p> <p>Measurable residual disease testing by flow cytometry performed on bone marrow from a patient diagnosed with acute lymphoblastic leukaemia (ALL) treated with combination chemotherapy treatment or after salvage therapy, requested by a specialist or consultant physician practising as a haematologist or oncologist.</p> <p>Maximum of 12 per course of disease for AAAA, BBBB, CCCC, DDDD, 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 BBBB</p> <p>Measurable residual disease testing by a quantitative molecular methodology on bone marrow from a patient diagnosed with acute lymphoblastic leukaemia (ALL) treated with combination chemotherapy or after salvage therapy, requested by a specialist or consultant physician practising as a haematologist or oncologist other than a service to which item CCCC, DDDD or EEEE applies.</p> <p>Maximum of 12 per course of disease for AAAA, BBBB, CCCC, DDDD, and EEEE combined</p> <p>Fee: \$1,550.00 Benefit: 75% = \$1,162.50 85% = \$1,462.10*</p>	
<p>MBS item CCCC</p> <p>Development of a patient-specific quantitative assay for measurable residual disease (MRD) based on the diagnostic bone marrow specimen from a patient diagnosed with acute lymphoblastic leukaemia (ALL) treated with combination chemotherapy or after salvage therapy, requested by a specialist or consultant physician practising as a haematologist or oncologist, and use on the first MRD specimen for one test described in item DDDD.</p> <p>Applicable not more than once per patient per course of disease</p> <p>Maximum of 12 per course of disease for AAAA, BBBB, CCCC, DDDD, and EEEE combined</p> <p>Fee: \$3,000.00 Benefit: 75% = \$2,250.00 85% = \$2,912.10*</p>	
<p>MBS item DDDD</p> <p>Measurable residual disease testing by a quantitative patient-specific assay on bone marrow from a patient diagnosed with acute lymphoblastic leukaemia (ALL) treated with combination chemotherapy or after salvage therapy, requested by a specialist or consultant physician practising as a haematologist or oncologist.</p> <p>Maximum of 12 per course of disease for AAAA, BBBB, CCCC, DDDD, and EEEE combined</p> <p>Fee: \$780.00 Benefit: 75% = \$585.00 85% = \$692.10*</p>	

\* Updated to reflect Greatest Permissible Gap (GPG) as at 1 November 2021.

**Table 6 MBS item proposed in application 1707, reflecting use of the clonoSEQ® assay for MDR testing, after amendments suggested by the Department of Health and PASC**

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 of measurable 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 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 of disease for AAAA, BBBB, CCCC, DDDD, and EEEE combined.</p> <p>Fee: \$2,100.00 Benefit: 75% = \$1,575.00 85% = \$2,012.10*</p>	

\* Updated to reflect GPG as at 1 November 2021.

## Proposed fees

Application 1703 suggested that mpFC should have a fee of \$550. PASC noted that Adaptive Biotechnologies were satisfied to proceed with the item and fee for flow cytology, as suggested by the RCPA, and amended by PASC.

Application 1703 suggested that molecular methods should have a fee of \$1150, which is equivalent to what they suggested NGS methods would cost, lower than they suggested an initial allele-specific oligonucleotide (ASO)-qPCR would be, and higher than subsequent ASO-qPCR testing would be (after the patient-specific assay has been developed).

The fee proposed reflected maximal batching of samples in a large state-based reference laboratory, which smaller laboratories are unlikely to achieve. The revised fee for use of NGS methods is therefore \$1550.

The Department were concerned that the significant cost of developing the assay may be passed on to patients through out-of-pocket fees to patients, and asked PASC to consider if splitting of the item into three separate items may be more appropriate. At the meeting, the RCPA were willing for the proposed item BBBB to be split into 3 separate items, to be further developed by the policy area of the Department:

- 1) an item for NGS testing with a fee of \$1,550.00
- 2) an item for the development of the patient specific assay for qPCR and the first test using this assay with a fee of \$3,000.00
- 3) an item for subsequent testing using the patient specific assay for qPCR with a fee of \$780.00.

Application 1707 proposed that testing using the clonoSEQ<sup>®</sup> assay should have a fee of \$2100.

Both the RCPA and Adaptive Biotechnologies expect that if the proposed MBS items are listed with the suggested fees, there will be no out-of-pocket costs for patients.

**Table 7 Breakdown and overall cost of MDR methods**

Cost component	mpFC	ASO-qPCR development of patient-specific assay	ASO-qPCR Testing once patient-specific assay developed	NGS	clonoSEQ <sup>®</sup>
Cell Processing and data capture / sample processing	\$160			\$100	-
Reagents including Fluorochrome-labelled antibodies / other consumables	\$110	\$620	\$220	\$1,300	REDACTED
Scientific Labour cost	\$280	\$1,600	\$560	\$150	REDACTED
Instrument amortization	-	-	-	-	REDACTED
Total cost	\$550	\$2,220	\$780	\$1,550	\$2,100
MBS fee	\$550	\$3,000*	\$780	\$1,550	\$2,100
85% Benefit	\$467.50	\$2,912.10**	\$692.10**	\$1462.10**	\$2,012.10**
Difference between proposed MBS fee and 85% benefit	\$82.50	\$87.90	\$87.90	\$87.90	\$87.90

ASO-qPCR = allele-specific oligonucleotide quantitative polymerase chain reaction; MBS = Medicare Benefits Schedule; mpFC = multi-parametric flow cytometry; NGS = next generation sequencing

\* Reflects combined cost of development of patient-specific assay (\$2,220) and an initial test using patient specific assay (\$780)

\*\* Reflects Greatest Permissible Gap as at 1 November 2021.

### **The expected utilisation of the MBS items**

The RCPA estimated that patients would have a median of 4 to 6 MRD tests per course of disease. Those with standard or medium risk are expected to undergo 3 tests during the Protocol I induction and consolidation phase of treatment, while those considered to be at high risk are expected to have up to 8 tests per episode of disease (see Figure 4).

Application 1707 estimated that each new patient is expected to receive up to three (possibly four in a minority of cases who undergo HSCT or CAR-T therapy) MRD tests in total.

The approximate number of MRD tests to be performed each year is shown in Table 8. Each assessment should include the number of tests performed per person as a sensitivity analysis to incorporate the alternative estimate.

**Table 8 Projected number of MRD tests performed**

	2022	2023	2024	2025	2026	2027
De novo and relapsed cases potentially uptaking MRD testing (from Table 2)	560	576	596	615	634	681
Projected number of tests performed assuming mean of 5 tests per course of disease (as per 1703)	2,800	2,881	2,982	3,075	3,170	3,405
Projected number of tests performed assuming mean of 3 tests per course of disease (as per 1707)	1,680	1,729	1,789	1,845	1,902	2,043

## **Summary of public consultation input**

*PASC noted and welcomed consultation input from six [6] professional organisations, one (1) consumer organisations and one (1) health professional.*

The following organisations submitted input on application 1703:

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

The consultation feedback received was broadly supportive of public funding for MSAC application 1703. It was noted that MRD testing by flow cytometric and/or molecular methodology for patients with ALL is the current standard of care for risk stratification and to guide prognosis and treatment.

*PASC noted that both applicants were explicit that the proposed populations were patients with ALL, and not acute myeloid leukaemia (AML).*

### **Clinical need and public health significance**

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

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

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

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

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

The consultation feedback ranged from 'strongly agreeing' to 'agreeing' with the proposed population. The LF considered that patients with acute myeloid leukaemias (AML) would also benefit from the proposed service, but considered the evidence not quite as advanced as for ALL. LF noted that MSAC may wish to consider extending the patient population to 'acute leukaemias'.

The consultation feedback ranged from 'strongly agreeing' to 'agreeing' with the proposed comparators. All consultation feedback considered that the comparator, morphological assessment of the bone marrow, lacks sensitivity compared to MRD methods.

The consultation feedback strongly agreed with the clinical claim.

Consultation feedback considered the clinical evidence is supportive of the clinical benefit in identification of those patients with ALL who are MRD-positive after treatment. This would inform treatment, such as increased intensity of chemotherapy, use of blinatumomab therapy or reconsideration of allogeneic stem cell transplant. Similarly, patients who are MRD-negative may avoid higher-intensity treatment and/or stem cell transplantation.

### **Cost information for the proposed medical service**

The consultation feedback ranged from strongly agreeing' to 'agreeing' with the proposed service descriptor.

The consultation feedback broadly considered that the item descriptor captured current practice. Two organisations considered that the description '12 test per episode of disease' would need clarification, as there is a difference between re-emergence of molecular disease and overt relapse, and questions the limitation of the number of tests to twelve (12). Another organisation considered that it should be made clear whether a patient can have both flow cytometry and molecular testing performed on each occasion, or if testing is restricted to one modality per occasion. One organisation noted that where initial diagnostic sample was done through the molecular method ASO-qPCR the next few tests should be performed using the same technology platform, in order to realise the full potential of patient-specific PCR assays being developed for each case.

The consultation feedback ranged from strongly agreeing' to 'agreeing' with the proposed service fee. The consultation feedback generally considered the estimated costs reasonable. It was noted that ASO-qPCR is significantly more expensive upfront, given the development of patient-specific assay, though subsequent assays are cheaper than the NGS comparator.

### **Consumer Feedback**

One health professional provided consultation feedback who strongly supported the proposed service, noting that the proposed service is already the standard of care for patients with acute lymphoblastic leukaemia for the detection of MRD, risk stratification and appropriate treatment. Public funding would ensure equity of access for patients.

## Next steps

*The applicant for application 1703 intend to proceed with a Department Contracted Assessment Report (DCAR).*

*The applicant for application 1707 intend to proceed with an Applicant Developed Assessment Report (ADAR).*

## Applicant comment on the ratified PICO Confirmation

### Interventions

*The applicant noted that where it is difficult to obtain bone marrow by aspiration, ASO qPCR can be performed on bone marrow biopsy (trephine samples).*

### Comparators

*The applicant noted the definition of a complete morphologic remission is a blast count <5% on morphology. They went on to state that morphology is an insensitive technique and cannot be used to assess treatment response once the blast percentage is <5%.*

*The applicant further stated that bone marrow examination is used after initial treatment (induction and consolidation) to confirm that patients achieve a morphologic remission. However, after achieving a morphologic remission the major clinical purpose of additional bone marrows has been to measure MRD and to confirm ongoing morphologic remission.*

*The applicant added that all paediatric and adolescent ALL protocols have treatment stratified by MRD response and that if there is an inadequate sample for MRD at a stratifying timepoint then there would be a recollection to repeat the MRD analysis particularly if the MRD result is used to stratify high risk treatment (ie identify patients who would benefit from blinatumomab, as per the PBS indication, CAR-T cells or stem cell transplantation). They stated that this does occur but it is rare.*

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## Appendix A ALL06 treatment protocol

Table 9 ALL06 Schema for treating ALL

<b>Protocol I induction (course duration:35 days); initial 7 days of prephase with prednisolone and intrathecal methotrexate included. Patients to receive: all risk groups</b>			
Prednisolone	PO	60 mg/m <sup>2</sup> /day	Day 1 to 28 then taper over 10 days and cease
Methotrexate <sup>a</sup>	IT	12 mg	Days 1, 15, 33
DAUNOrubicin	IV	30 mg/m <sup>2</sup>	Days 8, 16, 22, 29
vinCRISTine	IV	1.5 mg/m <sup>2</sup> (cap at 2 mg)	Days 8, 16, 22, 29
Pegaspargase	IM	1000 U/m <sup>2</sup>	Days 8, 22
<b>Protocol I consolidation: (course duration: 29 days); ideally day 1 of Protocol I consolidation commences on day 36 from the start of Protocol I induction). Patients to receive: all risk groups</b>			
CYCLOPHOSPHamide	IV	1000 mg/m <sup>2</sup>	Days 1 and 29
Mesna	IV	400 mg/m <sup>2</sup> at 0, 4 and 8 hours after cyclophosphamide dose	Days 1 and 29
Mercaptopurine	PO	60 mg/m <sup>2</sup> /day	Days 1 to 28
Cytarabine	SC	75 mg/m <sup>2</sup>	Days 1 to 4, 8 to 11, 15 to 18 and 22 to 25
Intrathecal methotrexate	IT	12 mg	Days 8 and 22
<b>Protocol maintenance (M): (course duration: 56 days); ideally day 1 of Protocol M commences on day 79 after the start of Protocol I induction (2 weeks after the last dose of cyclophosphamide in Protocol I consolidation). Patients to receive: standard risk and medium risk groups.</b>			
Mercaptopurine	PO	25 mg/m <sup>2</sup> /day	Days 1 to 56
Methotrexate	IV	500 mg/m <sup>2</sup>	Days 8, 22, 36, 50
Methotrexate	IV	4500 mg/m <sup>2</sup>	Days 8, 22, 36, 50
Methotrexate	IT	12 mg	Days 8, 22, 36, 50
Calcium folinate <sup>b</sup>	IV	15 mg/m <sup>2</sup> every 6 hours	Days 9, 23, 37, 51
<b>Protocol II: (course duration: 50 days), ideally day 1 of Protocol II commences 2 weeks after the end of Protocol M for standard risk and medium risk patients i.e. on day 70 after the start of Protocol M. For high risk patients (and very high risk not proceeding to transplantation) Protocol II begins 3 weeks after the end of the 6<sup>th</sup> high-risk block (i.e. Protocol II begins on day 57 after the start of HR block 6). Patients to receive: all risk groups.</b>			
Dexamethasone	PO	10 mg/m <sup>2</sup> /day	Days 1 to 21 then taper and cease
Pegaspargase	IM	1000 U/m <sup>2</sup>	Day 1
DOXOrubicin	IV	30 mg/m <sup>2</sup>	Days 3, 15, 22, 29
vinCRISTine	IV	1.5 mg/m <sup>2</sup> (cap at 2 mg)	Days 8, 15, 22, 29
Thioguanine	PO	60 mg/m <sup>2</sup> /day	Days 36 to 49
CYCLOPHOSPHamide	IV	1000 mg/m <sup>2</sup>	Day 36
Mesna	IV	400 mg/m <sup>2</sup> at 0, 4 and 8 hours after cyclophosphamide dose	Day 36
Cytarabine	SC	75 mg/m <sup>2</sup>	Days 36 to 39 and 43 to 46
Methotrexate <sup>c</sup>	IT	12 mg	Days 36 and 43

<sup>a</sup>Patients with CNS involvement receive additional methotrexate therapy on day 18 and 27 i.e. total of 5 intrathecal doses; <sup>b</sup>Commence 36 hours after start of methotrexate infusion, continue until methotrexate level is less than 0.05 micromol/L; <sup>c</sup>Patients with CNS involvement at diagnosis receive additional intracathal therapy on day 1 and 18 i.e. total of 4 intracathal doses. NOTE: Cranial irradiation should be considered for patients with initial CNS involvement; as prophylaxis treatment for all high risk and very-high risk patients not undergoing allogeneic stem cell transplant; and in T-ALL patients (other than low risk patients) especially those with initial WCC > 100 x 10<sup>9</sup>/L. Cranial irradiation is usually administered on day 38 of Protocol II depending on patient's clinical condition.

IT = PO = per oral;

High risk blocks 1 to 3 are administered to medium high risk, high risk and very high risk groups only. Commence high risk block 1 after completion of Protocol I consolidation.

Patients receive the sequence of HR1, HR2, HR3, HR1, HR2, HR3, except in patients who proceed to allogeneic stem cell transplantation after the first HR2 or HR3. Patients who are transplanted complete all of the high risk blocks and then commence Protocol II followed by cranial irradiation. Each high risk block should be given at 4 – 5 week intervals, not less.

<b>High risk block 1 (HR1)</b>			
Dexamethasone	PO	20 mg/m <sup>2</sup> /day	Days 1 to 5
vinCRISTine	IV	1.5 mg/m <sup>2</sup> (cap at 2 mg)	Days 1 and 6
Methotrexate	IV	500 mg/m <sup>2</sup>	Day 1
Methotrexate	IV	4500 mg/m <sup>2</sup>	Day 1
Methotrexate	IT	12 mg	Day 1
Cytarabine	IT	30 mg	Day 1
Hydrocortisone	IT	50 mg	Day 1
Calcium folinate <sup>d</sup>	IV	15 mg/m <sup>2</sup> every 6 hours	Day 2
CYCLOPHOSPHamide	IV	200 mg/m <sup>2</sup> every 12 hours (total 5 doses)	Days 2 to 4
Mesna	IV	70 mg/m <sup>2</sup> at 0, 4 and 8 hours after cyclophosphamide dose	Days 2 to 4
Cytarabine	IV	2000 mg/m <sup>2</sup> every 12 hours (total of 2 doses)	Day 5
Pegaspargase	IM	1000 U/m <sup>2</sup>	Day 6
Filgrastim	SC	5 microg/kg	Day 7 until neutrophil recovery
<b>High risk block 2 (HR2)</b>			
Dexamethasone	PO	20 mg/m <sup>2</sup> /day	Days 1 to 5
vinCRISTine	IV	1.5 mg/m <sup>2</sup> (cap at 2 mg)	Days 1 and 6
Methotrexate	IV	500 mg/m <sup>2</sup>	Day 1
Methotrexate	IV	4500 mg/m <sup>2</sup>	Day 1
Methotrexate	IT	12 mg	Day 1
Cytarabine	IT	30 mg	Day 1
Hydrocortisone	IT	50 mg	Day 1
Calcium folinate <sup>d</sup>	IV	15 mg/m <sup>2</sup> every 6 hours	Day 2
IFOSFamide	IV	800 mg/m <sup>2</sup> every 12 hours (total 5 doses)	Days 2 to 4
Mesna	IV	300 mg/m <sup>2</sup> at 0, 4 and 8 hours after cyclophosphamide dose	Days 2 to 4
DAUNOrubicin	IV	30 mg/m <sup>2</sup>	Day 5
Pegaspargase	IM	1000 U/m <sup>2</sup>	Day 6
Filgrastim	SC	5 microg/kg	Day 7 until neutrophil recovery
<b>High risk block 3 (HR3)</b>			
Dexamethasone	PO	20 mg/m <sup>2</sup> /day	Days 1 to 5
Cytarabine	IT	2000 mg/m <sup>2</sup> every 12 hours (total 4 doses)	Days 1 and 2
Etoposide	IV	100 mg/m <sup>2</sup> every 12 hours (total 5 doses)	Days 3 to 5
Methotrexate	IT	12 mg	Day 5
Cytarabine	IT	30 mg	Day 5
Hydrocortisone	IT	50 mg	Day 5
Pegaspargase	IM	1000 U/m <sup>2</sup>	Day 6
Filgrastim	SC	5 microg/kg	Day 7 until neutrophil recovery

<b>Maintenance phase: (course duration: 24 months calculated from the start of Protocol I); commence 2 weeks after the end of Protocol II depending on bone marrow recovery. Patients to receive: All risk groups (not transplanted)</b>			
Mercaptopurine	PO	50 mg/m <sup>2</sup> /day titrated according to WCC	Continuous
Methotrexate	PO	20 mg/m <sup>2</sup> titrated according to WCC	Once weekly

<sup>d</sup>Commence 36 hours after start of methotrexate infusion, continue until methotrexate level is less than 0.05 micromol/L