



Australian Government

Department of Health

Application 1560:

17p Deletion Testing by FISH for Access to Ibrutinib in Patients with Previously Untreated Chronic Lymphoid Leukaemia or Small Lymphocytic Lymphoma

Ratified PICO Confirmation

(To guide a new application to MSAC)

(Version 1.0)

Summary of PICO/PPICO criteria to define the question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC) and the Pharmaceutical Benefits Advisory Committee (PBAC)

Table 1: PICO summary for 17p deletion testing by FISH

Component	Description
Patients	<p>People with untreated chronic lymphocytic leukaemia or small lymphocytic lymphoma.</p> <p>Patients must be symptomatic or display active disease characterised by at least one iwCLL criterion, indicating that treatment needs to commence.¹</p>
Prior tests (for investigative medical services only)	<p>Essential tests to confirm the diagnosis of chronic lymphocytic leukaemia or small lymphocytic lymphoma include a full blood count and serum electrolytes, urea & creatinine, liver enzymes, protein and albumin.</p> <p>Additional laboratory tests (excluding 17p deletion testing) may be requested at the time of initial presentation, prior to staging.</p> <p>Staging confirms the signs of active disease as per the iwCLL criteria. If treatment is indicated, FISH testing for 17p deletion should be performed at this point to determine which treatment algorithm is used.</p>
Intervention	17p deletion (not <i>TP53</i> mutation) testing by fluorescence <i>in situ</i> hybridisation (FISH) to determine eligibility to access ibrutinib if it is listed on PBS.
Comparator	No genetic testing (prior test alone)
Outcomes	<p>Biomarker</p> <ul style="list-style-type: none"> ◦ Prognostic effect of 17p deletion status in untreated patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma <p>Test</p> <p><u>Safety:</u></p> <ul style="list-style-type: none"> ◦ Psychological and physical harms from testing (including rates of re-biopsy and re-testing). <p><u>Effectiveness:</u></p> <ul style="list-style-type: none"> ◦ Clinical validity²: clinical sensitivity and specificity, positive and negative predictive values (comparative performance of FISH test with karyotyping and genome-wide microarray test) ◦ Clinical utility: outcomes for treatment with or without 17p deletion testing, relative to standard of care ◦ Change of management: whether knowledge of the test result will cause a change in the management of the patient by the treating clinician.

iwCLL = International Workshop on Chronic Lymphocytic Leukemia

¹ See Appendix for full detail of the iwCLL guidelines active disease criteria to initiate therapy.

² Clinical validity: measures the test's ability to predict the presence or absence of disease, that is, the sensitivity, specificity and positive and negative predictive values, in this case, to accurately predict the risk of distant recurrence.

Table 2: PICO summary for treatment with ibrutinib and co-dependent technologies

Component	Description
Patients	People with untreated chronic lymphocytic leukaemia or small lymphocytic lymphoma AND re symptomatic or displaying active disease (characterised by at least one iwCLL criterion, indicating treatment needs to commence ¹ 17p deletion positive using FISH testing.
Intervention	Treatment with Ibrutinib
Comparator	Treatment with current standard of care: <ul style="list-style-type: none"> • fludarabine, cyclophosphamide plus rituximab (if young and fit) and • if elderly/frail <ul style="list-style-type: none"> ○ rituximab + chemotherapy ○ obinutuzumab + chlorambucil ○ ofatumumab + chlorambucil
Outcomes	<p>Biomarker</p> <ul style="list-style-type: none"> ○ Ibrutinib treatment effect modification by 17p deletion status <p>Drug</p> <p><u>Safety:</u></p> <ul style="list-style-type: none"> ○ Adverse events and toxicity related to treatment; treatment interruptions; treatment discontinuation. <p><u>Effectiveness:</u></p> <ul style="list-style-type: none"> ○ Primary: overall survival; progression free survival; health-related quality of life ○ Secondary: overall response rate; rate of minimal residual disease negative responses <p>Co-dependent technologies</p> <ul style="list-style-type: none"> ○ Clinical utility: outcomes from treatment with and without FISH testing relative to standard of care. <p><u>Cost-effectiveness:</u></p> <ul style="list-style-type: none"> ○ FISH testing and ibrutinib treatment in patients who express 17p deletion compared to no FISH testing and standard of care treatment. <p><u>Healthcare system outcomes:</u></p> <ul style="list-style-type: none"> ○ Predicted use of the test and drug in clinical practice ○ Number of patients tested ○ Number of patients treated ○ Number of patients tested per 17p deletion positive result ○ Number of patients tested per 17p deletion positive result treated with ibrutinib ○ Financial implications for MBS ○ Financial implications for PBS ○ Financial implications for Australian Government

iwCLL = International Workshop on Chronic Lymphocytic Leukemia; FISH = fluorescence *in situ* hybridisation

¹ See Appendix for full detail of the iwCLL guidelines active disease criteria to initiate therapy.

² Clinical validity: measures the test's ability to predict the presence or absence of disease, that is, the sensitivity, specificity and positive and negative predictive values, in this case, to accurately predict the risk of distant recurrence.

PICO or PPICO rationale for therapeutic and investigative medical services only

Population

The proposed population for FISH testing is previously untreated patients with a confirmed diagnosis of Chronic Lymphocytic Leukaemia (CLL)/Small Lymphocytic Lymphoma (SLL). Patients should have documented evidence of active disease, characterised by at least one iwCLL criterion indicating the need to start a treatment (1).

The outcome of this test will determine whether patients with CLL/SLL harbouring 17p deletion are eligible for subsequent treatment with ibrutinib in the first-line setting. PASC accepted that the population is patients with untreated CLL or SLL, for whom active treatment is being considered. PASC noted that most patients can receive other care (even watchful waiting), but once the disease progresses to more severe or has relapsed, or treatment has failed, more aggressive treatment is needed.

The applicant has indicated they wish to submit a streamlined co-dependent MSAC/PBAC submission after the applicant has received advice from PASC and the Department.

Background

CLL is a life-threatening lymphoproliferative B-cell malignancy characterised by a progressive accumulation of monoclonal B lymphocytes in the blood, bone marrow, lymph nodes, or other lymphoid tissue. SLL, another type of B-cell malignancy, is recognized as the same pathological entity as CLL, with a different clinical presentation; CLL presents with peripheral-blood involvement and SLL presents with lymph tissue involvement. The prognosis of CLL and SLL are similar and therefore the existing approaches to management, as well as treatment considerations are consistent with one another. The treatment and outlook of CLL and SLL are identical and, according to the WHO classification, they are the same entity (2).

The application form indicated that, while the incidence of CLL/SLL is low in Australia, the burden of disease is high. Leukaemia was ranked seventh in terms of the Australian Institute of Health and Welfare's (AIHW) leading cancer causes of burden of disease in Australia in 2012. The rate of diagnosis is approximately 4.8 cases per 100,000 persons. In 2013, there were an estimated 1,259 new patients diagnosed in Australia with CLL and an estimated 313 deaths (3). The incidence of SLL is much lower than CLL and there are limited epidemiological data available for this disease. In 2012, an estimated 190 patients were diagnosed with SLL in Australia (4).

CLL is an incurable disease with conventional therapies, with a natural history of repeated relapse. CLL is life-threatening due to development of immune cytopenia and impaired production of normal immunoglobulin (5, 6). Patients with CLL have a high risk of morbidity and mortality from disease-related infections, which are commonly due to bacteria and influenced by the degree of hypogammaglobulinemia. In more advanced stages of disease, neutropenia due to bone marrow infiltration and/or cytotoxic therapy may also contribute to the increased risk of infection-related morbidity and mortality (7).

The clinical sequelae of CLL/SLL can have substantial negative impacts on patients' quality-of-life because of disease-related symptoms (such as fatigue, recurrent infections, and anaemia); treatment-related adverse events (AEs); and the psychological, socioeconomic, and functional effects of living with the disease. There have been several publications studying the quality of life impacts of CLL/SLL (8-

11), which demonstrated that various domains of quality of life are negatively impacted due to both the disease itself and the agents used to treat the disease.

CLL/SLL is most commonly a disease of the elderly and many patients with CLL/SLL will have major and/or multiple comorbidities; it has been estimated that approximately half of patients > 65 years of age with CLL have ≥ 1 major comorbidity (e.g. coronary heart disease, peripheral vascular disease, diabetes, pulmonary disease, etc.) (12, 13).

The clinical course of CLL/SLL is extremely variable, with a significant proportion of patients requiring no treatment for decades, whilst more urgent intervention is indicated in others, particularly those with progressive, clinically symptomatic disease. CLL is pathologically, clinically and genetically heterogeneous, resulting in many patient subgroups responding markedly less favourably to currently available treatment strategies, independent of age and comorbidity.

17p chromosomal deletion in CLL/SLL

The applicant stated that one feature which has consistently been associated with the worst overall prognosis is deletion of the short arm of chromosome 17 (17p deletion). The 17p chromosomal deletion abnormality occurs in approximately 5-9% of CLL cases at diagnosis (14-17). The application form claimed that chromosome 17p deletion is the pre-eminent adverse prognostic parameter, with most patients belonging to an “ultra-high-risk” group characterised by the worst possible overall outcome (16, 18). The applicant submitted two clinical studies as an evidence to support the prognostic effect of 17p deletion on outcomes among patient with CLL (16, 19). The applicant indicated that in a prospective study, patients with 17p deletion had the shortest median treatment-free interval (9 months) and median survival (32 months), which may be indicative of poor prognosis (16).

The applicant stated that MSAC has previously acknowledged the importance of identifying genetic markers for informing prognosis, and accepted the inferior prognosis of CLL patients with 17p deletion: *“MSAC noted that CLL is the most common form of leukaemia and, although considered to be a slowly progressing cancer, genetic markers can be used to provide useful prognostic information. MSAC highlighted that one such marker is the presence of a 17p deletion, which affects 5-8% of CLL patients who are chemotherapy naïve and 30-37% of patients with disease progression after first-line treatment. MSAC noted that, according to the applicant, patients with a 17p deletion have substantially inferior prognosis, with a shorter survival period and marked resistance to first-line chemotherapy. Of patients with a confirmed 17p deletion, more than 80% also exhibit mutations in the TP53 allele, which may also be indicative of poor prognosis.”* (MSAC Public Summary Document - Application 1456, MSAC 69th Meeting, 6-7 April 2017, p2)

Current international guidelines from the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) (1), National Comprehensive Cancer Network (20), and European Society for Medical oncology (21), recommend testing for 17p deletion before treatment is commenced, to determine the most appropriate management strategy. The clinical guidelines emphasise that a patient is only eligible for FISH testing if there is documented evidence of active disease, characterised by at least one iwCLL criterion. The presence of 17p deletion without any signs of active disease is not an indication for treatment (1, 20, 21).

Estimates of size of the testing population

The proposed eligible patients for FISH testing would include those patients who are untreated and deemed suitable to start first-line therapy (based on iwCLL criteria). The details of the estimated incidence and prevalent population eligible for FISH testing is given below.

Table 3: Estimated eligible patients for FISH testing (incident patients)

	Estimate	Year 2020	Calculation/Source
A	Patients newly diagnosed with CLL/SLL	1,776	Extrapolation by applicant using the age-specific incident rates from AIHW (2008-12) and Australian Bureau of Statistics population projection
B	Proportion of newly diagnosed patients requiring the treatment who will be eligible for FISH test	REDACTED	Applicant's assumption considering DUSC comment in company's PBAC submission in November 2017 and internal market research report
C	New patients eligible for FISH testing	REDACTED	A x B

AIHW = Australian Institute of Health and Welfare; CLL = chronic lymphocytic leukaemia; DUSC = drug utilisation sub-committee; FISH = fluorescence in situ hybridisation; PBAC = Pharmaceutical Benefits Advisory Committee; SLL = small lymphocytic lymphoma

The applicant indicated that the assumption of REDACTED 'incident' patients (eligible for FISH testing) was based on DUSC's comment in the company's Pharmaceutical Benefits Advisory Committee (PBAC) November 2017 submission (for ibrutinib in previously untreated CLL/SLL). However, in a more recent PBAC resubmission, it was noted that the proportion (REDACTED) was based on data from the Leukaemia Foundation (Ibrutinib PBAC minutes - March 2018, p20). PASC noted there are about REDACTED pre-existing (prevalent) cases that may need to be considered in Year 1, if funding is approved.

Table 4: Estimated eligible patients for FISH testing (prevalent patients)

	Estimate	Year 2020	Calculation/Source
E	Patients living with CLL/SLL	10,337	AIHW 2017 (3)
F	Proportion of existing patients requiring the treatment who will be eligible for FISH test	REDACTED	Applicant's assumption considering DUSC comment in company's PBAC submission in November 2017 and internal market research report
G	New patients eligible for FISH testing	REDACTED	E x F
H	Total population eligible for FISH testing	REDACTED	C + G

AIHW = Australian Institute of Health and Welfare; CLL = chronic lymphocytic leukaemia; DUSC = drug utilisation sub-committee; FISH = fluorescence *in situ* hybridisation; PBAC = Pharmaceutical Benefits Advisory Committee; SLL = small lymphocytic lymphoma

Prevalent patients were included, based on a 31-year prevalence from the Australian Institute of Health and Welfare's 'Cancer in Australia' report (10,337 patients) (3). The applicant argued that if ibrutinib is PBS listed in the first-line setting, then there would be an increase in the proportion of CLL/SLL patients who are ever treated from REDACTED% (based on REDACTED market research) to REDACTED%, that's a REDACTED% increase (REDACTED% less REDACTED%). This REDACTED% is applied to the prevalent pool, but it didn't account for the prevalent pool of people that are affected

and not showing signs but would develop signs of active disease later, *this may lead to an underestimation of the population.*

The projected use of 17p deletion FISH testing after the first year of introduction would align with the incident patients requiring first-line of treatment.

Rationale

The applicant has requested that FISH testing for detection of 17p deletion (not *TP53* mutation) to be conducted at the time of initiating the first line of treatment, in order to determine if the patient fulfils the requirements for PBS-listed ibrutinib (assuming it is recommended by the PBAC). PASC noted that the PBAC has considered similar applications twice before but has not recommended public funding because there was no urgent clinical need. PASC noted that this application is for patients with a high clinical need.

Population diagnosed with CLL

Patients with CLL/SLL can present with lymphadenopathy, systemic symptoms such as life-disrupting tiredness, fever, night sweats and weight loss, or the symptoms of anaemia or infection. However, approximately 80% are asymptomatic at presentation and are therefore diagnosed incidentally (*i.e.* routine blood samples at check-up, or comorbidities).

Patients are initially diagnosed with CLL by a specialist or consultant physician (haematologist or oncologist). To confirm a diagnosis of CLL, it is necessary to evaluate their full blood count (FBC), blood smear, as well as establishing immunophenotype of peripheral blood lymphocytes. Some patients may also undergo a bone marrow biopsy if there are symptoms suggestive of bone marrow infiltration. Patients are staged for the severity of their disease as per either the Rai or Binet staging system for CLL. The median age of diagnosis of CLL is approximately 69 years of age, and approximately 33% of patients diagnosed in Australia were aged < 65 years (4).

Current approach in clinical practice

The applicant indicated that, in Australia, a proportion of newly diagnosed patients will not require treatment straight away and will only require regular monitoring (watch and wait) (22). Treatment is only initiated in patients who have significant constitutional symptoms (weight loss, fatigue, fever and night sweats in the absence of infection), bulky disease, progressive lymphocytosis, autoimmune anaemia or thrombocytopenia, recurrent infections or Richter transformation (22).

Before treatment is commenced with symptomatic patients, a patient would generally undergo prognostic/predictive tests that could provide guidance with treatment choices. This is the point at which the proposed medical service (detection of 17p deletion by FISH) would be carried out. Testing for 17p deletion at this time will determine a patient's eligibility for treatment with first-line ibrutinib. As FISH testing for 17p deletion is not currently reimbursed for first-line treatment in Australia, the cost of the test is either covered by the hospital (if public) or by the patient (if private), or the test is not conducted at all.

The applicant therefore proposed that 17p deletion (not TP53 mutation) testing by FISH is for a patient with a diagnosis of CLL, who meets iwCLL diagnostic criteria. The condition must be previously untreated. The patient must be symptomatic or display active disease, characterised by at least one

iwCLL criterion, indicating that treatment needs to commence. The full iwCLL criteria are provided in the Appendix.

The application form listed the iLLUMINATE trial as the supporting evidence. iLLUMINATE is an open label, comparative, randomised, phase 3 trial of ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab as first-line treatment of untreated CLL (23). All patients recruited in iLLUMINATE were aged at least 18 years, had untreated, active CLL/SLL requiring treatment per iwCLL criteria, and were considered unsuitable for fludarabine-based chemoimmunotherapy (because they were aged 65 years or older, or younger than 65 years) with at least one of the following coexisting conditions: cumulative illness rating scale score greater than 6; creatinine clearance of less than 70 mL/min; presence of 17p deletion confirmed by FISH (Vysis CLL FISH Probe Kit); or *TP53* mutation.

Additional eligibility criteria were Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, measurable lymph node disease (> 1.5 cm longest diameter) by CT scan, adequate haematological function (absolute neutrophil count $\geq 1 \times 10^9$ cells/L, platelet count $> 50 \times 10^9$ /L), adequate hepatic and renal function, and creatinine clearance of at least 30 mL/min. All patients were screened at baseline to examine pre-treatment prognostic factors, including 17p deletion. The prevalence of 17p deletion in iLLUMINATE study was 13.97% (32 out of total 229 patients). *The proposed population for the FISH test is consistent with the population enrolled in iLLUMINATE.*

Prior test

Routine tests to confirm the diagnosis of CLL/SLL include a full blood count and serum electrolytes, urea & creatinine, liver enzymes, protein and albumin. Also, additional laboratory tests may be requested at the time of initial presentation, prior to staging. Staging tests to confirm signs of active disease as per the iwCLL criteria, and need for treatment, must be carried out prior to 17p deletion testing by FISH.

Intervention

The applicant is seeking to have FISH listed on the MBS, as the diagnostic testing strategy for 17p deletion (not *TP53* mutation) to identify patients eligible for ibrutinib treatment. PASC confirmed that the intervention is 17p deletion testing by FISH to determine eligibility to access ibrutinib (if that drug is listed on the Pharmaceutical Benefits Scheme [PBS]).

FISH testing for detection of 17p deletion

The presence of 17p deletion can be clinically detected by FISH (fluorescent in situ hybridisation). FISH is a molecular cytogenetic technique used to test for the presence or absence of specific chromosome regions and is often used to detect chromosome deletions such as 17p deletion. This involves using a DNA probe which is highly specific for the chromosome 17p region. The probe is labelled with a fluorescent dye and is hybridised to the chromosomes on a microscope slide, so in a normal cell it will give two signals (one from each chromosome) and a cell with a deletion will give only one signal.

The application form did not indicate any cut-off percentage for abnormal cells with 17p deletion (which have a negative impact on clinical outcomes). The iwCLL and NCCN guidelines indicate that the presence of 17p deletion in 10% or more cells was the strongest predictor of poor outcomes (1, 20). During the PASC meeting, the applicant confirmed that a 10% threshold would be used for access to ibrutinib.

The applicant presented evidence to support the analytical specificity (percentage of signals that hybridise to the correct locus and no other location) and sensitivity (percentage of scoreable interphase nuclei with the expected normal region signal pattern) of 17p deletion testing using the Vysis CLL Probe Kit (Abbott Molecular) (24). The Vysis CLL FISH Probe Kit FDA documentation specifically details the sensitivity and specificity of the three probe targets, LSI *TP53*, LSI *ATM* and LSI *D13S319* in addition to the gain in *D12Z3* sequence probe target. The LSI *TP53* probe contains the tumour protein *TP53* (sometimes referred in the literature as *p53*), located on the chromosome 17p. The application form stated that the Vysis CLL probes used to assess patient 17p deletion status have very high specificity (100%) and sensitivity (> 97%) values for the LSI *TP53* Spectrum Orange Probe.

The pivotal clinical studies (presented by the applicant) carried out FISH testing among recruited patients, using the same Vysis CLL FISH Probe Kit manufactured by Abbott Molecular Inc (16, 23).

Delivery of the intervention

The applicant stated that testing for 17p deletion by FISH in CLL patients would be requested by a specialist or consultant physician (haematologist or oncologist). Patients who proceed with screening would sign a consent form. A peripheral blood or bone marrow sample is taken and sent to a National Association of Testing Authorities (NATA) accredited laboratory to undertake a FISH testing. A qualified pathologist in NATA accredited laboratory would be responsible for examining and interpreting the results of sample testing. Once the test results are available, they are sent back to the specialist or consultant physician who inform and counsel the patient about the best course of action to take and most appropriate therapies available based on the FISH test outcomes.

As noted in an earlier MSAC application (1456), the pathological laboratory should have a quality assurance program (QAP) specific to FISH testing for 17p deletion, recommended by the Royal College of Pathologists of Australasia (25). *Further detail on this would be useful for MSAC's consideration.*

Regulatory Information

The Vysis CLL Probe Kit (Abbott Molecular Inc) is currently TGA-approved and marketed in Australia, with the approved purpose outlined as being "For the determination of acquired genetic alterations in human clinical specimens" (ARTG inclusion number 196286).

Frequency of FISH testing

The applicant indicated that the test will be performed once in their lifetime, they may need to be tested again at relapse, as 17p deletion status is known to change over time and following chemotherapy treatment (26, 27). Therefore, a clinician may request the patient be tested for 17p deletion a second time in order to determine if they fulfil the requirements to access PBS-reimbursed ibrutinib or idelalisib in the relapsed or refractory setting (current MBS Item 73343). Thus, it is possible that some patients will be tested twice, or more, for 17p deletion in their life time, although it is highly unlikely that this would occur more than once per year.

Similar MBS listing for FISH testing

- MBS Item 73343 subsidises the "*Detection of 17p chromosomal deletions by fluorescence in situ hybridisation, in a patient with relapsed or refractory chronic lymphocytic leukaemia or small lymphocytic lymphoma, on a peripheral blood or bone marrow sample, requested by a*

specialist or consultant physician, to determine if the requirements for access to idelalisib or ibrutinib on the Pharmaceutical Benefits Scheme are fulfilled.”

The application form indicates that uptake of FISH testing in the proposed population would be high (REDACTED%). Justification for this was that if iLLUMINATE (a phase 3 trial) indicates that among patients with 17p deletion, ibrutinib is superior to chemoimmunotherapy, then ibrutinib could replace chemoimmunotherapy as standard of care in untreated patients eligible for the first line of treatment. Uptake of testing is likely to depend on the comparative effectiveness and safety of ibrutinib to chemoimmunotherapy, in patients who express 17p deletion.

Comparator

Comparator for FISH testing

This application seeks to have 17p deletion testing (using the FISH technique) listed on the MBS. To date, clinical trials assessing the efficacy of ibrutinib have used the Vysis CLL Probe Kit, manufactured by Abbot Molecular Inc.

The applicant did not specifically nominate an alternative method of testing for 17p deletion as an evidentiary standard. The applicant provided supporting evidence, being three concordance studies, comparing the diagnostic accuracy of FISH with either G-banding or multiplex ligation-dependent probe amplification (MLPA) (24, 25, 28).

Comparators considered, but deemed inappropriate by PASC

Genome-wide microarray testing

Separate application 1544 (Genome-wide microarray testing for people with multiple myeloma and chronic lymphocytic leukaemia), currently progressing through the MSAC process, states that the FISH test only looks at a small number of chromosome changes. Application 1544 states that, given this limitation, FISH is often used in tandem with conventional karyotyping or with microarrays (29).

There is evidence to suggest discordance between results of FISH and genome-wide microarray (GWMA) testing, with confirmation that the rate of detection of 17p deletion using GWMA is approximately 11% (30-32). It was also noted in the application that GWMA will probably replace FISH testing in CLL. While PASC noted that FISH may be replaced by GWMA in the future, it confirmed that the intervention for application 1560 is 17p deletion testing by FISH to determine eligibility to access ibrutinib (if that drug is listed on the PBS).

PASC confirmed that GWMA testing should be excluded as a comparator, until there is evidence GWMA is an equivalent test to FISH.

Karyotyping

Karyotyping detects cytogenetic abnormalities in 20% to 30% of patients, being mainly numerical abnormalities (seen with chromosomes). Karyotyping is able to detect trisomy, monosomy, deletions, duplications, translocations and genetic rearrangement (33). With regard to access to 17p deletion testing through karyotyping testing (such as existing MBS item 73290), MSAC previously noted that karyotyping methods are unlikely to be as sensitive as FISH techniques, and

expressed concern about the potential for false negative results and consequential under-treatment (MSAC application 1456, 69th Meeting, 6-7th April 2017, p5). Application 1456 was for testing for 17p deletion to access a drug in the relapsed or refractory setting in CLL, while current application 1560 is for the newly diagnosed and untreated subgroup of patients.

Comparator for clinical practice

The applicant stated that patients with newly diagnosed CLL with 17p deletion are not currently being routinely identified unless they privately pay for FISH test or public hospitals provides coverage for it. Given that both 17p deletion abnormality and treatment with ibrutinib are novel interventions, the appropriate comparator for assessment is current clinical practice; *i.e.* standard care with no genetic testing. Standard care comprises of fludarabine + cyclophosphamide + rituximab (FCR) or chlorambucil in combination with either rituximab, obinutuzumab or ofatumumab who are unsuitable for FCR (refer “Current clinical management algorithm for identified population”).

Conclusion

PASC confirmed the comparator is ‘no genetic testing’ and treatment with current standard of care. Therefore, ‘no testing for 17p deletion (prior tests alone)’ would be replaced by the new medical service being proposed in this application.

Current standard of therapeutic care is:

- Where the patient is young and fit:
 - fludarabine, cyclophosphamide + rituximab
- Where the patient has CLL/SLL, but is not suitable for fludarabine, cyclophosphamide + rituximab (*e.g.* patient is elderly/frail):
 - obinutuzumab + chlorambucil (condition must be CD20 positive)
 - ofatumumab + chlorambucil (condition must be CD20 positive)
 - rituximab + chemotherapy (condition must be CD20 positive)

For information: PASC noted that bendamustine is not relevant to application 1560, because it is not currently PBS-listed for CLL/SLL.

Outcomes

Testing

- Psychological and physical harms from testing (including rates of re-biopsy and re-testing).

The applicant has stated that the proposed medical service (detection of 17p deletion by FISH) has been assessed by MSAC previously, when it was acknowledged to have an acceptable safety profile.

Treatment

The applicant has nominated the following efficacy and safety outcomes related to ibrutinib treatment:

Efficacy outcomes:

- Progression-free survival
- Overall survival

- Overall response rate
- Rate of minimal residual disease negative responses
- Health-related quality of life.

The applicant indicated that the health outcomes listed above relate to 17p deletion subgroup analysis of the iLLUMINATE study (23). Based on the iLLUMINATE study, ibrutinib was granted supplemental indication (ibrutinib plus obinutuzumab as First Non-Chemotherapy Combination Regimen for Treatment-Naïve Patients with Chronic Lymphocytic Leukemia) by the USFDA in January 2019, but is yet to be approved by the TGA (34).

Safety outcomes:

- Adverse events (AEs) and toxicity related to treatment
- Treatment interruptions
- Treatment discontinuation

The assessment of outcomes regarding the treatment with ibrutinib is the remit of PBAC.

Healthcare system

Cost-effectiveness

- FISH testing and ibrutinib treatment in patients who express 17p deletion compared to no FISH testing (i.e. prior test alone) and standard of care treatment (as appropriate): cost per quality-adjusted life year (QALY) gained; cost per life year gained; cost of testing per 17p deletion positive case detected; cost of testing per 17p deletion positive case detected and treated with ibrutinib.

Predicted use of the test and drug in clinical practice

- Number of patients tested
- Number of patients treated
- Number of patients tested per 17p deletion positive result
- Number of patients tested per 17p deletion positive result treated with ibrutinib
- Financial implications for MBS
- Financial implications for PBS

Rationale

Co-dependent submission should explicitly demonstrate the relationship between the test for the biomarker and the drug, such that it is clear whether treatment effect modification and/or a prognostic effect is operating in the relationship. The approach to presenting in a co-dependent submission may differ according to the available evidence (*i.e.* direct evidence or linked evidence).

The following outcomes could also be included:

Biomarker

- The prognostic effect of 17p deletion in patients with CLL/SLL irrespective of the clinical management provided

Testing

- Clinical validity¹ in terms of sensitivity, specificity, negative predictive value and positive predictive value.
- Clinical utility: outcomes for treatment with or without 17p deletion testing, relative to standard of care
- Change of management: whether knowledge of the test result will cause a change in the management of the patient by the treating clinician.

Current clinical management algorithm for identified population

Currently, for patients who are symptomatic or showing active disease, no FISH testing is performed before starting the first-line treatment. Patients receive their first line of therapy, most likely chemoimmunotherapy. The applicant noted that some patients may opt for FISH test privately or covered by public hospitals.

The current clinical management algorithm is shown below.

¹ Clinical validity: measures the test's ability to predict the presence or absence of disease, that is, the sensitivity, specificity and positive and negative predictive values, in this case, to accurately predict the risk of distant recurrence.

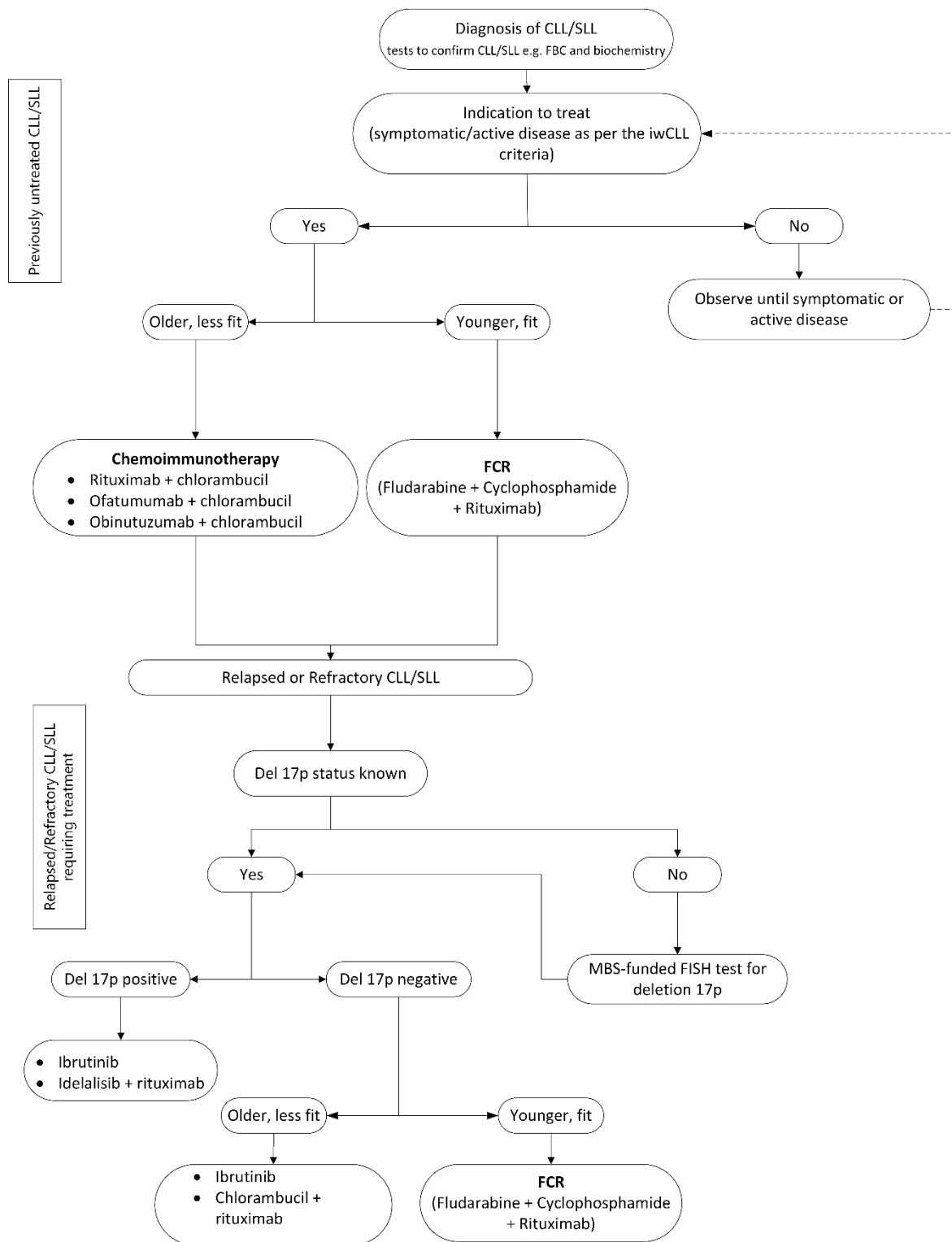


Figure 1: Current clinical management algorithm

CLL = chronic lymphocytic leukaemia; ESC = economics sub-committee; FBC = full blood count; FISH = fluorescence *in situ* hybridisation; MBS = Medicare Benefits Schedule; SLL = small lymphocytic lymphoma

* The ESC advised that in academic centres obinutuzumab plus chlorambucil is now the preferred option, as the most effective subsidised therapy (Ibrutinib, Paragraph 5.1, November 2017).

Proposed clinical management algorithm for identified population

Reimbursement of FISH testing for detection of 17p deletion in previously untreated CLL/SLL patients (and parallel PBS listing of ibrutinib for treatment of previously untreated patients who are found to harbour 17p deletion) will change the clinical management algorithm. The change will mean that all patients who receive a diagnosis of CLL, and are indicated for treatment (by iWCLL), will be screened for 17p deletion. Furthermore, PBS-listed ibrutinib will replace chemotherapy and chemoimmunotherapy in the first-line setting for patients with 17p deletion, as treatment with chemotherapy and chemoimmunotherapy is not suitable for this subgroup of patients. Therefore, this is an additional service which would alter clinical management and treatment of previously untreated CLL patients. Patients would normally receive testing for diagnosis and staging of CLL/SLL. If 17p deletion testing by FISH is listed, these tests will still occur, prior to FISH, as they are required to confirm diagnosis, assess if treatment is warranted (by iWCLL), and hence assess if the patient is appropriate for 17p deletion testing.

The proposed clinical management algorithm is shown below.

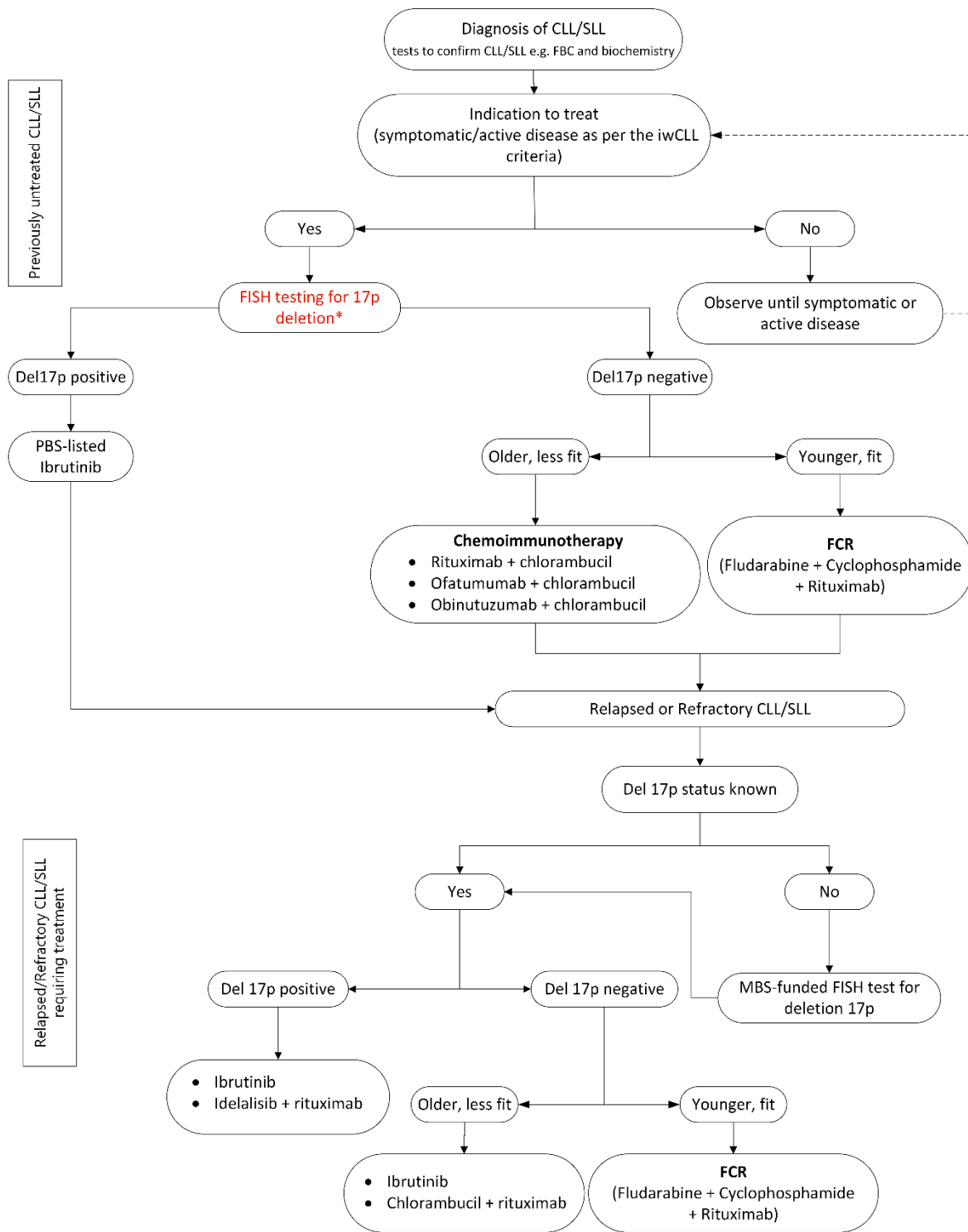


Figure 2: Proposed clinical management algorithm

CLL = chronic lymphocytic leukaemia; FBC = full blood count; FISH = fluorescence in situ hybridisation; PBS = Pharmaceutical Benefits Scheme; SLL = small lymphocytic lymphoma

*17p deletion (not TP53 mutation) testing by FISH to determine eligibility to access ibrutinib if it is listed on PBS.

Proposed economic evaluation

PASC noted that 17p deletion testing by FISH is well established, listed for other conditions and used to gain access to other drugs. Thus, PASC queried the usefulness of a full economic evaluation, concluding that a fast-tracked application (through MSAC Executive) may be suitable.

Proposed new and amended existing item descriptor

The applicant proposed the following MBS item descriptor, based on the proposed testing algorithm for 17p deletion FISH testing (in which patients have a peripheral blood or bone marrow sample taken, followed by confirmatory FISH testing). Bone marrow sample collection is included in MBS items 30081, 30084 and 30087. PASC noted this application is for a new MBS item, but MBS item 73343 could be extended to include previously untreated CLL and SLL patients.

The proposed fee for the proposed MBS service is the same as the fee for existing MBS item 73343 (for detection of 17p chromosomal deletions by FISH in patients with relapsed or refractory CLL/SLL).

PASC noted that, currently, the cost of the proposed test is covered by patients or the hospital, or testing is not done at all.

Category 6 – PATHOLOGY SERVICES
<p>Proposed <u>new</u> item descriptor:</p> <p>Detection of 17p chromosomal deletions by fluorescence <i>in situ</i> hybridisation, in a patient with previously untreated chronic lymphocytic leukaemia or small lymphocytic lymphoma, where active treatment is required, and testing is via a peripheral blood, bone marrow or lymph node tissue sample, requested by a specialist or consultant physician, to determine if requirements for access to ibrutinib on the Pharmaceutical Benefits Scheme are fulfilled.</p> <p>Proposed MBS Fee: \$230.95 Benefit: 75% = \$173.25 85% = \$196.35</p>

Category 6 – PATHOLOGY SERVICES
<p>Proposed <u>amendment to existing</u> MBS item 73343:</p> <p>Detection of 17p chromosomal deletions by fluorescence in situ hybridisation, in a patient with relapsed or refractory chronic lymphocytic leukaemia or small lymphocytic lymphoma, where active treatment is required, and testing is via on a peripheral blood, or bone marrow, or lymph node tissue sample requested by a specialist or consultant physician, to determine if requirements for access to idelalisib, ibrutinib, or venetoclax on the Pharmaceutical Benefits Scheme are fulfilled.</p> <p>MBS Fee: \$230.95 Benefit: 75% = \$173.25 85% = \$196.35</p>

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Appendix

Active disease criteria to initiate therapy. At least 1 of the following criteria should be met as per the iwCLL guidelines (Ref: Blood 131.25 (2018): 2745-60):

1. Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia and/or thrombocytopenia. Cut-off levels of Hb < 10 g/dL or platelet counts < 100 x 10⁹/L are generally regarded as indication for treatment. However, in some patients, platelet counts < 100 x 10⁹/L may remain stable over a long period; this situation does not automatically require therapeutic intervention.
2. Massive (*i.e.* ≥ 6cm below the left costal margin) or progressive or symptomatic splenomegaly.
3. Massive nodes (*i.e.* ≥ 10cm in longest diameter) or progressive or symptomatic lymphadenopathy.
4. Progressive lymphocytosis with an increase of ≥ 50% over a 2-month period, or lymphocyte doubling time (LDT) < 6 months. LDT can be obtained by linear regression extrapolation of absolute lymphocyte counts obtained at intervals of 2 weeks over an observation period of 2 to 3 months; patients with initial blood lymphocyte counts < 30 x 10⁹/L may require a longer observation period to determine the LDT. Factors contributing to lymphocytosis other than CLL (*e.g.* infections, steroid administration) should be excluded.
5. Autoimmune complications including anemia or thrombocytopenia poorly responsive to corticosteroids.
6. Symptomatic or functional extranodal involvement (*e.g.* skin, kidney, lung, spine).
7. Disease-related symptoms as defined by any of the following:
 - a. Unintentional weight loss ≥ 10% within the previous 6 months.
 - b. Significant fatigue (*i.e.* ECOG performance scale 2 or worse; cannot work or unable to perform usual activities).
 - c. Fevers ≥ 100.5°F or 38.0°C for 2 or more weeks without evidence of infection.
 - d. Night sweats for ≥ 1 month without evidence of infection.