



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1532 – Expansion of MBS item 73325 to include additional populations and mutations beyond those currently specified

Applicant: The Royal College of Pathologists of Australasia (RCPA)

Date of MSAC consideration: MSAC 75th Meeting, 28-29 March 2019

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

1. Purpose of application

A request to expand Medicare Benefits Schedule (MBS) item 73325 to (a) include the characterisation of mutations in the calreticulin (*CALR*) gene testing in polycythaemia vera (PV) and essential thrombocythaemia (ET), and (b) provide molecular testing for *JAK2*, *MPL* and *CALR* mutations in primary myelofibrosis (PMF), was referred to MSAC from the Genetics Working Group of the Pathology Clinical Committee of the MBS Review Taskforce.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC deferred its advice regarding public funding for expansion of MBS item 73325 (mutation testing for *JAK2* and *MPL* in myeloproliferative diseases [MPD]) to include additional populations and mutations beyond those currently specified, to seek further information regarding:

- consultation with haematologists and pathology laboratories to ascertain the appropriate clinical algorithm, including the nature and order of testing if a simultaneous panel test or next generation sequencing (NGS) is not considered optimal
- the consequential proposed item descriptor(s)
- whether any triage testing arrangement should include any pathologist-determinable reflex tests or be separated into steps requiring further requests by the treating clinician
- the cost of testing, to justify the appropriate fee(s)
- a simplified linked analysis summarising the prognostic variation discerned by testing these three genes across the three types of MPD (for example, as used to justify their inclusion in the World Health Organization [WHO] 2016 diagnostic guidelines), and

thus the usefulness of this testing for subsequent clinical management decisions and provision of healthcare resources.

MSAC also requested further analysis of the current utilisation estimates and budget implications, given that data indicate an ongoing increase in testing that appears to outweigh the estimated number of patients requiring diagnosis of MPD.

MSAC advised that this further information would need to be considered via ESC.

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

MSAC noted that the current MBS item 72235 funds mutation testing for *JAK2* and/or *MPL* genes in patients with two variants of MPD – polycythaemia vera (PV) and essential thrombocythaemia (ET), with a fee of \$74.50. The current application requests addition of a third type of myeloproliferative disease (MPD), primary myelofibrosis (PMF), and a third relevant gene for mutation assessment, calreticulin (*CALR*), and proposes an increase in the fee to \$100.

MSAC noted that addition of *CALR* testing and of the PMF population is in line with current WHO diagnostic guidelines (2016). As mutations in the identified genes are usually mutually exclusive, current clinical/laboratory practice is to test for *JAK2* +/- *MPL* under item 72235 (possibly several iterations of the item), and then pursue (patient-funded) *CALR* testing if *JAK2* is negative. This raises equity of access issues for patients with suspected MPD who are *JAK2*-negative.

MSAC noted that mutation testing is used for risk stratification of patients with MPD – specific mutations result in different risk profiles for PV, ET and PMF patients. Classification of ET or PMF as high risk or low risk depends on *CALR* testing. MSAC noted the evidence that changes in risk stratification result in changes in clinical management (for example, use of anti-thrombotic therapy, rate of blood transfusion for anaemia, and likelihood of needing bone marrow transplantation).

MSAC considered that the structure of the proposed item (addition of *CALR* testing to the current population [PV and ET patients] and addition of PMF patients to testing for all three genes) needed more scrutiny. At presentation the subcategory of MPD maybe unclear. Adding *CALR* testing for patients with presumed ET should confirm the diagnosis in the subset of *JAK2/PML*-negative patients and help discriminate indolent (triple-negative) disease from disease with intermediate prognosis (*CALR*+), but *CALR* testing provides no additional benefit in patients with PV. Testing for all three genes in PMF patients allows confirmation of an MPD diagnosis and stratifies patients (particularly differentiating *CALR*+ PMF patients with a relatively good prognosis from triple-negative PMF patients who have the worst prognosis). MSAC considered it unlikely that patients with suspected PMF are currently not undergoing testing, given the often overlapping clinical presentations of MPD.

MSAC noted that the molecular assay for *CALR* is more complicated than testing for *JAK2* and *MPL* due to numerous potential mutations in *CALR* exon 9. MSAC noted that the 'most common' *JAK2* mutation (V617F; 95%) is assessed by a simple quantitative polymerase chain reaction (PCR) assay, whereas *CALR* usually requires PCR plus either fragment length analysis or sequencing; these are not necessarily run on the same platform or simultaneously. MSAC considered that a single item and fee to cover all three tests would only be practical if testing was triaged. MSAC noted that laboratories currently have in place triaging protocols, for example starting with *JAK2* V617F testing, and proceeding to testing for variant *JAK2* exon 12 mutation, *MPL* and (patient-funded) *CALR* testing if negative.

MSAC was therefore concerned that the appropriate pathway to making a differential diagnosis within MPD has not been articulated in the application. It was not clear whether up-front testing of all suspected MPD patients for all three genes is appropriate, given that *CALR* variants will not be identified in patients with PV. It was also unclear whether testing might be also used in disease monitoring; in affected patients, not all cells contain the mutation and the 'level' of mutation might be clinically relevant in some circumstances (although literature suggests the percentage of mutant cells does not necessarily correlate with symptoms or prognosis). MSAC also considered that the sensitivity of the assay is important (it should be able to detect 1% mutant cells to have 90% confidence in the result), but the potential for a false negative result has not been discussed in the application.

MSAC noted data from the Department of Human Services showing that about 7% of patients had multiple tests billed against MBS item 73325. MSAC considered that this implies the test is either being used to monitor disease, or (more likely) it is being used multiple times to achieve a differential diagnosis within MPD (i.e. *JAK2* V617F screening followed by variant exon 12 *JAK2* testing and *MPL* testing as appropriate). Testing (and the requested increased fee of \$100) may therefore be used a fourth time to examine *CALR* unless some restriction is in place or another clinical algorithm is proposed. MSAC considered that *CALR* testing will have a higher detection rate than *MPL* testing.

MSAC noted that there were no particular safety issues identified. Testing would be done on a blood or marrow sample that would be taken for other investigations.

MSAC noted that there were no data presented on clinical effectiveness. Despite this, MSAC acknowledged that identifying specific mutations and thus underlying variants of MPD has prognostic value (clinical validity) and expected clinical utility in terms of influencing the subsequent choice of therapeutic options, including differences in the use of anti-thrombotic therapy, differences in the rate of blood transfusion for anaemia, and the likelihood of needing a bone marrow transplant. MSAC considered that a key issue is whether *CALR* testing in patients with ET or PMF facilitates accurate assignment of risk category and appropriate treatment. MSAC considered there would be little value in re-reviewing the entire literature related to clinical validity of testing since the requested testing is now required by the World Health Organisation (WHO) for MPD classification. Any future literature review should focus on the practical aspects of implementation adopting a linked analysis approach rather than searching for evidence of a direct change in clinical management consequent to testing. MSAC suggested that the impact of *CALR* testing in patients with ET and PMF could be determined by looking at the proportion of patients who were wrongly assigned to a risk group before the availability of testing, and the likely effects and costs of over- or under-treatment. Given that testing for *CALR* is now routine (albeit not funded via the MBS), historical data should be available for comparison.

MSAC noted that the application did not include an economic evaluation; there were no data on comparative test costs or true costs associated with the current testing approach, and there was no analysis of whether the proposed \$100 fee was appropriate. The impact on subsequent provision of other healthcare resources was also not estimated. MSAC advised that, as an alternative to the proposed simultaneous testing of all three genes, a triage approach should be further explored from a costing perspective (*JAK2* V617F screen, then additional testing if negative), including assessment of the costs associated with allowing multiple uses of the proposed combined MBS item to achieve a differential diagnosis within MPD. MSAC suggested seeking input from laboratories and haematologists about whether *CALR* testing after a negative *JAK2* test should be reflex or would need to be requested (and, if so, by whom), and what the costs would be from the laboratory and requester points of view. This

analysis would also require defining what the appropriate testing methodology for *CALR* would be and its associated cost.

If a triage approach is warranted, MSAC foreshadowed that a new MBS item might be to characterise mutations in the *CALR* gene in the diagnostic work-up of a patient with clinical and laboratory evidence of (a) essential thrombocythaemia or (b) primary myelofibrosis in patients who do not have a detectable *JAK2* or *MPL* mutation.

MSAC considered it likely that clinicians will instead increasingly choose to request an NGS panel to achieve ‘one-test’ diagnosis, but this would not be achievable at the current or proposed fee and so would necessarily introduce out-of-pocket expenses for patients. MSAC noted that at least one laboratory offers NGS for all three genes associated with MPD (plus several others), and charges patients a \$400 gap. A \$25 increase in the MBS fee would have minimal impact on this gap.

MSAC considered that increasing the fee to \$100 would not be justified for the majority of *JAK2*-positive patients, but may also be insufficient to cover the true cost of additional testing in *JAK2*-negative patients and the revised MBS item is therefore likely to be used and billed multiple times.

MSAC noted that, using an annual incidence of PMF of <1/100,000 (Leukaemia Foundation), adding patients with PMF to the testing population would increase test numbers by about 250 per year (assuming stability in utilisation of testing in existing populations). In 2014–15, MBS item 73325 was billed 9170 times. Assuming stability in utilisation, increasing the fee from \$75 to \$100 was estimated to result in an overall cost to the MBS of \$810,129 for current patients, plus \$25,000 for the additional 250 PMF patients. However, MSAC noted that 15,247 tests were done in 2017–18, so the cost for the current number of patients (at 85% of \$100) would be \$1,352,246.

However, based on claims history data, assuming stability in utilisation may not be valid. MSAC noted MBS data on the claims history for the current MBS item 73325 showing a steady increase in the rate of claims between 2012–13 (6604) and 2017–18 (15,247); usage of the item has almost doubled since 2013–14 (7933). MSAC also noted that a disproportionate share of total claims in 2017–18 were in Queensland. MSAC therefore advised that the impact of a linearly increasing testing rate requires more detailed assessment. Extrapolating from current test usage to 2022–23 suggests around 21,500 tests might be performed, thus the expected cost (at 85% of \$100) would be in the order of \$1,827,500. The reason for the increasing rate of testing is unknown.

MSAC noted that the annual incidence of new diagnoses of MPD in Australia is 6/100,000 population (equating to <1500 patients per year), but more than 13 times more MBS-billed tests are being done. MSAC considered that it appears the test is being performed to ‘exclude’ rather than ‘confirm’ suspected MPD (i.e. a low testing threshold), particularly in the context of managing thrombosis.

4. Background

MBS 73325 is currently funded for *JAK2* and *MPL* gene testing in patients with PV or ET. This was based on the MSAC assessment of Application 1125 Part A (Molecular testing for myeloproliferative disease Part A (PV, ET and PMF)), which MSAC agreed that for a proportion of patients with suspected PV or ET (but not PMF) molecular testing may remove the need for cost of a bone marrow biopsy and may improve diagnostic certainty [Public Summary Document (PSD) 1125 Part A 2009, p4].

In 2016, the WHO diagnostic criteria for myeloproliferative neoplasms was extended to include *CALR* mutation. This was based on preliminary data which suggested that *CALR* mutations had prognostic significance, particularly with respect to thrombosis, and cardiovascular events.

In 2017, the Medicare Benefits Schedule (MBS) Review Taskforce Genetics Working Group (GWG) of the Pathology Clinical Committee (PCC) requested advice from the MSAC Executive on the pathway for expansion of MBS item 73325 to include additional populations and mutations beyond those currently specified.

In July 2017, the Department sought MSAC Executive’s agreement that an MSAC review of the proposed extension of 73325 was necessary, and that the appropriate assessment pathway was to be assessed by all MSAC committees.

The MSAC Executive agreed that MSAC consideration was appropriate. However, the MSAC Executive considered that the PICO was well defined with sufficient evidence of clinical utility, and that there was no requirement for consideration by PASC.

The proposed expansion of MBS item 73325 seeks to align MBS arrangements with WHO recommendations for the diagnosis of myeloproliferative neoplasms.

5. Prerequisites to implementation of any funding advice

This was not provided in the contracted assessment (CA), or the Critique.

6. Proposal for public funding

The CA’s proposed revised MBS item descriptor for item 73325 is summarised in **Table 1**.

Table 1 Proposed revised MBS item descriptor (proposed changes highlighted in yellow)

Category 6 - PATHOLOGY SERVICE	Group P7 - Genetics
Characterisation of mutations in:	
(a) the JAK2 gene; or	
(b) the MPL gene; or	
(c) the CALR gene; or	
(d) up to all three genes;	
in the diagnostic work-up of a patient with clinical and laboratory evidence of:	
(a) polycythaemia vera; or	
(b) essential thrombocythaemia; or	
(c) primary myelofibrosis,	
1 or more tests	
Fee: \$100	

Source: Department of Health MSAC Executive Teleconference, 9 June 2017

Abbreviations: CALR, Calreticulin; JAK2, Janus kinase 2; MPL, Myeloproliferative Leukemia; PMF, Primary Myelofibrosis

The CA stated that it was unclear why the Schedule fee of \$100 had been chosen (compared with \$74.50 currently for item 73325). In addition, the CA stated the proposed item descriptor subsequently also changed the wording relating to who can request item number 73325 from ‘the specialist or consultant physician, of a patient ...’ in the existing item descriptor to become ‘the treating specialist or pathologist’.

7. Summary of Public Consultation Feedback/Consumer Issues

There was no public consultation details provided by the applicant, however peak organisations were consulted as part of the MBS Review process.

8. Proposed intervention's place in clinical management

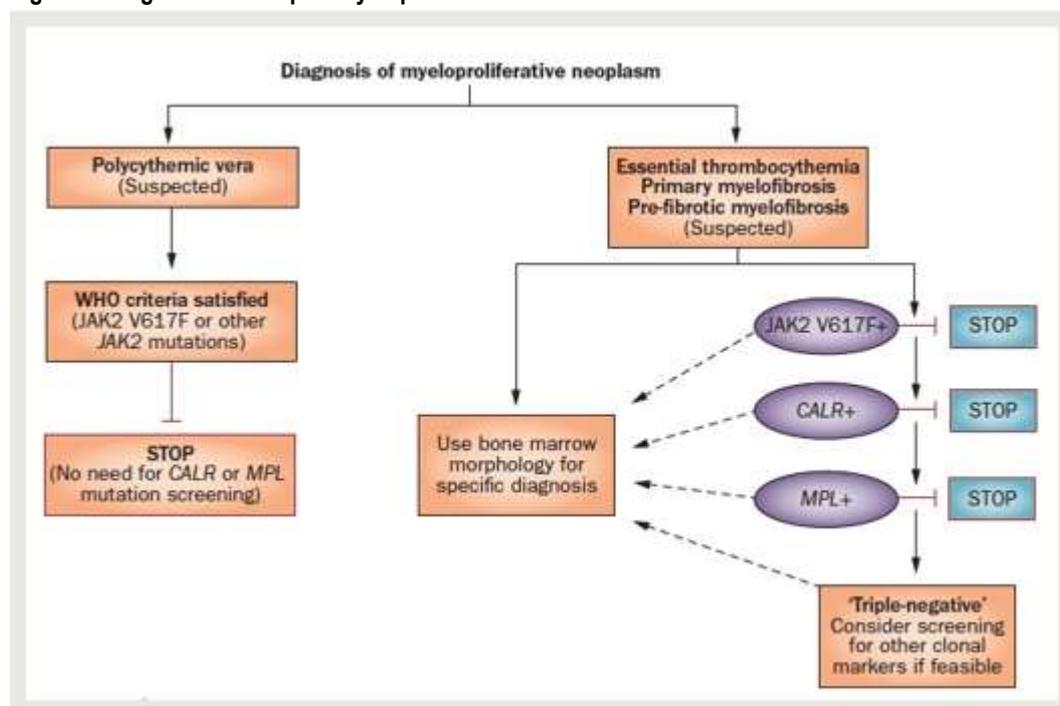
The CA stated that molecular testing of *JAK2*, *MPL* and *CALR* are useful in the diagnostic work up of patients with myeloproliferative disorders. While no direct evidence was identified in the CA showing that additional testing of *CALR* results in a direct or immediate change in patient management, it does have prognostic significance, particularly with respect to thrombosis events, cardiovascular events, splenomegaly and survival.

The CA stated that the proposed clinical management algorithm would be for patients to undergo testing for all three genes (*JAK2*, *MPL* and *CALR*) simultaneously, which would allow for appropriate diagnosis and classification, and also allow appropriate treatment according to the current clinical guidelines both nationally and internationally.

The CA stated that currently patients undergo testing for two genes (*JAK2* and *MPL*) simultaneously, although some patients will undergo testing for *CALR* and are charged the cost of testing.

The current and proposed clinical algorithms were not provided schematically by the CA (or the Critique). However, the CA presented a diagnostic workup of myeloproliferative disorders (Figure 1).

Figure 1 Diagnostic workup of myeloproliferative disorders



Source: Contracted Assessment for MSAC Application 1532. Figure A6.1 p, 14.

The CA stated that treatment for PV, ET and PMF is based upon the patient's risk. In ET, patients aged over 60 years with *JAK2* mutations are considered at high risk, and are recommended for treatment with cytoreductive therapy if response to aspirin, hydroxyurea, interferons or anagrelide is inadequate.

9. Comparator

The CA provided the comparators as per the proposed revisions to MBS item 73325:

Adding CALR to the intervention for the current population (PV and ET)

The nominated comparator for this population is the current MBS listed indication (i.e. present management with less genetic testing). MBS item 73325 (listed on 1 July 2011) includes characterisation of *JAK2* gene ± *MPL* gene in patients with clinical and laboratory evidence of PV or ET.

Testing (JAK2 V617F, MPL and CALR) for the PMF population

The nominated comparator for this population is clinical diagnosis using bone marrow biopsy, assessment of anaemia, leucocytosis, splenomegaly, lactate dehydrogenase (LDH) and leukoerythroblasts (i.e. present management without genetic testing).

Background

Previously for application 1125 Part A (Molecular testing for myeloproliferative disease Part A (PV, ET and PMF)), MSAC agreed that the comparator of ‘present management without genetic testing’ (which may involve bone marrow examination and (for PV) red cell mass measurement which is not available at all centres) was appropriate, noting that molecular testing for myeloproliferative disorders has been adopted by the WHO in its diagnostic criteria for these conditions [PSD Application 1125 Part A 2009, p2].

10. Comparative safety

The CA included 77 studies from literature review, the majority of which provided low level evidence. Most studies were likely influenced by selection bias. In addition, the CA stated that, without a comparison to a reference standard or comparator test strategies, the value of information provided by level IV diagnostic evidence is limited.

No studies were identified that provided direct evidence of a change in patient health outcomes as a result of molecular testing in the diagnosis of PV, ET and PMF. Therefore, a linked evidence approach was used in the assessment, which considered the diagnostic accuracy, change in management and change in patient outcomes following a change in management, as per the previous assessment report (i.e. Application 1125).

Within the systematic literature review, no studies were identified that reported safety outcomes specifically related to bone marrow aspirate or biopsy for molecular testing for the diagnosis of PV, ET or PMF. Hence, no studies were identified that could inform an assessment of the safety of molecular testing in the diagnosis of PV, ET or PMF.

11. Comparative effectiveness

Given clinical features, and presence of *JAK2* V617F mutations, are diagnostic for PV, and it was assumed that *JAK2* mutation testing is conducted first, the effectiveness of *CALR* testing in PV was not further assessed.

CALR testing in ET

The Critique summarised the results for benefits and harms in patients with ET (Table 2).

Table 2 Summary of CA's findings for the diagnostic accuracy and health outcomes of CALR testing in ET

Outcomes	Studies	Quality of evidence (GRADE)	Estimate (95% CI)
Diagnostic accuracy - sensitivity	4	⊕⊕⊕⊖	Range 89.3% to 100%
Diagnostic accuracy – specificity	4	⊕⊕⊕⊖	Range 90.9% to 100%
Diagnostic yield	12	⊕⊕⊕⊖	26% (95% CI: 24% to 28%)
Mortality	4	⊕⊕⊕⊖	OR 0.55 (95% CI: 0.23 to 1.29) favouring <i>CALR</i> mutated
Thrombotic events	8	⊕⊕⊕⊖	OR 0.64 (95% CI: 0.46 to 0.89) favouring <i>CALR</i> mutated
Splenomegaly	3	⊕⊕⊕⊖	OR 1.54 (95% CI: 0.79 to 2.99) favouring <i>CALR</i> non-mutated

Source: Contracted Assessment for MSAC Application 1532. Table B6.1 p 61

Abbreviations: *CALR*, calreticulin; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; OR, odds ratio; **bold** = statistically significant

^a GRADE Working Group grades of evidence (Guyatt et al., 2013).

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.

⊕⊕⊕⊖ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

⊕⊕⊖⊖ **Low quality:** Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate.

⊕⊖⊖⊖ **Very low quality:** Very little confidence in the effect estimate: The true effect is likely to be substantially different from estimate.

JAK2 *V617F*, MPL and CALR testing in PMF

The Critique summarised the results for benefits and harms in patients with PMF (Table 3).

Table 3 Summary of CA's findings for the diagnostic accuracy and health outcomes of JAK2, MPL and CALR testing in PMF

Outcomes	Studies	Quality of evidence (GRADE)	Estimate (95% CI)
Diagnostic accuracy - <i>JAK2</i>	4	⊕⊕⊕⊖	Sensitivity 89% to 100% Specificity 82.6% to 100%
Diagnostic accuracy – <i>MPL</i>	3	⊕⊕⊕⊖	Sensitivity 89% to 100% Specificity 96% to 100%
Diagnostic accuracy – <i>CALR</i>	2	⊕⊖⊖⊖	Sensitivity 89% to 100% Specificity 96% to 100%
Diagnostic yield – <i>JAK2</i>	28	⊕⊕⊕⊖	58% (95% CI: 56% to 60%)
Diagnostic yield – <i>MPL</i>	5	⊕⊕⊕⊖	4% (95% CI: 3% to 5%)
Diagnostic yield - <i>CALR</i>	11	⊕⊕⊕⊖	24% (95% CI: 22% to 26%)
Thrombotic events	4	⊕⊕⊕⊖	Rare
Haemorrhage events	3	⊕⊕⊕⊖	Rare
Stroke events	1	⊕⊖⊖⊖	Rare
Splenomegaly	2	⊕⊖⊖⊖	OR 1.52 (95% CI: 0.82 to 2.80)

Source: Contracted Assessment for MSAC Application 1532. Table B6.2 p 61

Abbreviations: *CALR*, calreticulin; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; *JAK2*, janus kinase-2; *MPL*, myeloproliferative leukemia virus oncogene; OR, odds ratio

^a GRADE Working Group grades of evidence (Guyatt et al., 2013).

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.

⊕⊕⊕⊖ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

⊕⊕⊖⊖ **Low quality:** Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate.

⊕⊖⊖⊖ **Very low quality:** Very little confidence in the effect estimate: The true effect is likely to be substantially different from estimate.

Clinical claim

For both populations, the CA concluded that, on the basis of the benefits and harms reported in the evidence base (summarised above), the investigative intervention has uncertain safety and non-inferior effectiveness relative to the comparator. The Critique stated that safety should be non-inferior as no additional invasive testing is conducted on the patient as bone marrow aspirate is already required for diagnosis of myeloproliferative diseases.

12. Economic evaluation

The CA did not provide an economic evaluation on the purported basis that there was no difference in patient outcomes. The Critique stated this approach was not appropriate and an economic evaluation should have been conducted to estimate the impacts of a change in the number of patients diagnosed with ET and PMF (i.e. with addition of *CALR* testing), and on the risk stratification and treatment of PMF (i.e. with addition of *JAK2*, *MPL* and *CALR* testing).

Previously for MSAC Application 1125, insufficient evidence was available to undertake an economic evaluation. Instead a cost comparison of the test services was undertaken. Calculation of an incremental cost effectiveness ratio (ICER) was also not possible due to the lack of evidence of measurable health outcomes [PSD 1125 Part A 2009, p3].

13. Financial/budgetary impacts

The CA stated an epidemiological approach had been used to estimate the financial implications of a successful expansion of MBS item 73225 to include molecular testing of the *CALR* gene and the PMF population. The estimates were based on current utilisation of the existing item and expected utilisation by patients suspected of PMF.

The CA estimated the expansion of MBS item 73325 was expected to cost an additional \$0.43 million in Year 1, increasing to \$0.59 million by Year 5 (*similar to the Critique's corrected values in italics*; see Table 4).

Table 4 Total costs to the MBS associated with the expansion of MBS item 73325

	2019-2020	2020-2021	2021-2022	2022-2023	2023-2024
Current MBS listing					
Services (MBS 73325)	18,020	19,702	21,383	23,064	24,745
Cost per service (85%)	\$63.10	\$63.10	\$63.10	\$63.10	\$63.10
Sub-total cost	\$1,137,135	\$1,243,223	\$1,349,310	\$1,455,398	\$1,561,486
Proposed MBS listing					
Services (MBS 73325)	18,531 <i>18,546</i>	20,260 <i>20,276</i>	21,989 <i>22,006</i>	23,718 <i>23,737</i>	25,447 <i>25,467</i>
Cost per service (85%)	\$85	\$85	\$85	\$85	\$85
Sub-total cost	\$1,569,612 <i>\$1,570,874</i>	\$1,716,048 <i>\$1,717,427</i>	\$1,862,483 <i>\$1,863,980</i>	\$2,008,919 <i>\$2,010,534</i>	\$2,155,354 <i>\$2,157,087</i>
Total impact to MBS	\$432,478 <i>\$433,739</i>	\$472,825 <i>\$474,205</i>	\$513,173 <i>\$514,670</i>	\$553,520 <i>\$555,135</i>	\$593,868 <i>\$595,600</i>

Source: Contracted Assessment for MSAC Application 1532. Table E4.1, page 84. *Corrections in italics calculated by the Critique.*

Abbreviations: MBS, Medicare Benefits Schedule

14. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Comparative safety	The intervention appears to be safe.
Comparative effectiveness	There is insufficient evidence to be certain of clinical effectiveness.
PASC	Including PASC in the assessment pathway would have better focused the contracted assessment (CA). Because there are likely to be more applications in future that are suitable to bypass PASC, MSAC may like to consider developing a pre-assessment proforma to ensure assessment groups have the information they require to assess clinical utility and perform an economic evaluation.
No economic evaluation	The lack of an economic evaluation makes it impossible to determine the cost-effectiveness of this expansion.
Financial impact	Impact is uncertain due to omission of the consequences that the changes would have on the number of patients diagnosed and treated. Bundling of the tests within the one MBS item with an increased fee of \$100 will increase the impact on the MBS, so it is important to ensure that the proposed fee is appropriate.

ESC discussion

MBS item 73325 is currently funded for Janus kinase (*JAK2*) and myeloproliferative leukaemia (*MPL*) gene testing in patients with polycythaemia vera (PV) or essential thrombocythaemia (ET). ESC noted that the proposed medical service being requested is the expansion of MBS item 73325 to allow testing for calreticulin (*CALR*) mutations in patients with PV or ET, and testing for *JAK2*, *MPL* and *CALR* in patients with primary myelofibrosis (PMF).

ESC noted that the Department originally sought MSAC Executive's agreement that consideration of the recommendation by all MSAC committees was appropriate. However, the Executive considered that the PICO was well defined and there was sufficient evidence of clinical utility, and therefore there was no requirement for consideration by PASC.

ESC considered that bypassing PASC created difficulties for both the Assessment Group and the Critique Group. ESC noted that, without PASC advice, the Assessment Group had to develop a PICO and diagnostic algorithm *de novo* based only on the MSAC Executive minutes.

ESC also noted that a revision to the proposed MBS item descriptor included the words 'by or on behalf of the treating specialist or pathologist' after PMF in the revised list of included patient groups. ESC considered this to be redundant as the revised descriptor already requires diagnostic work-up 'by, or on behalf of, the specialist or consultant physician'.

ESC noted that the revised item descriptor included an increased fee of \$100 (increased from \$74.50 in the current descriptor for MBS item 73325). However, the CA did not provide a breakdown of costs to justify the increased fee. ESC noted the Genetics Working Group's advice that the additional test to identify *CALR* mutations is significantly more expensive than the tests to identify *JAK2* or *MPL* mutations.

ESC noted that, because the different tests have different costs, and different populations require different combinations of tests, it may be more useful to have separate item numbers that specify costs appropriate for whatever combination is useful in a particular patient subset.

ESC noted that the 2016 WHO diagnostic criteria related to *JAK2*, *MPL* and *CALR* mutations are complicated and differ for PV, ET and PMF. Diagnosis of PV does not require *CALR* or *MPL* mutation testing. ESC noted that the proposed diagnostic algorithm provided in the CA suggested sequential testing of *JAK2*, *CALR* and *MPL* for the diagnosis of myeloproliferative neoplasm. However, ESC noted feedback from pathologists that normal practice is to do a panel of tests for all three genes.

ESC noted that clinicians see *CALR* testing as especially helpful for myelofibrosis patients, especially differentiating those who are ‘triple negative’ (for *JAK2*, *CALR* and *MPL* mutations) – and therefore have the worst prognosis – from those with a *CALR* gene mutation, who have a better prognosis. ESC considered that most of the changes arising from expansion of MBS item 73325 would be in this group.

ESC noted that the comparator used in the CA for the PMF population was a bone marrow morphology test which has potential limitations in terms of specificity. For example, an incorrect diagnosis using bone marrow morphology may result in inappropriate treatment with cytotoxic therapy or expensive PBS-funded drug therapy. ESC suggested that improved clinical utility arising from improved analytical validity and prognostic value should have been the clinical claim.

ESC considered the PICO proposed in the CA to be insufficiently comprehensive. Safety outcomes were limited to physical harms from testing but should have included other harms; effectiveness outcomes did not include diagnostic accuracy, clinical utility, uptake or changes in management; and clinical outcomes were insufficient. ESC noted that clarification of the comparator and the clinical and patient-relevant outcomes would have been useful for the Assessment Group, and input from content knowledge groups would have been informative.

ESC noted that the limited clinical evidence available is observational, involving relatively low patient numbers. No studies were identified that could inform an assessment of the safety or the clinical utility of molecular testing in the diagnosis of PV, ET or PMF. ESC considered from the limited evidence presented that there appear to be no safety issues, but there is not enough evidence to say that definitively.

ESC noted that the evidence base for both diagnostic performance and health outcomes of the diagnostic tests had a high risk of bias, so diagnostic accuracy is likely to be overestimated. The Critique claimed that more than a third of the 77 articles in the CA should have been excluded. ESC noted the Critique’s finding that almost all analyses included transcription errors, and inappropriate inclusion or exclusion of studies. As a result, ESC considered that the effect of molecular testing on patient management and subsequently on quality of life is uncertain, and there is insufficient evidence to provide informed advice.

ESC noted that neither the CA nor the Critique included an economic evaluation. The CA claimed that, because there would be no difference in patient outcomes, a cost-effectiveness study could not be undertaken. However, the major claim of molecular testing of *CALR* in PV and ET patients and *JAK2*, *MPL* and *CALR* in PMF patients is that it provides information on prognosis including risk of disease-related complications. ESC noted that, given the proposed changes may have an impact on the number of patients diagnosed with ET and PMF (i.e. with addition of *CALR* testing), and on the risk stratification and treatment of patients with PMF

(i.e. with addition of *JAK2*, *MPL* and *CALR* testing), an economic evaluation should have been presented. ESC further noted that the economic evaluation should have explored changes in management due to changes in mutation status (i.e. prognostic information), changes in disease-related complications (i.e. thrombotic events) and changes in provision of healthcare resources.

ESC noted that the Critique presented methods for conducting cost-effectiveness analyses (CEA) for *CALR* testing in ET, and for *JAK2*, *MPL* and *CALR* testing in PMF. The Critique proposed using different models for each population (PV, ET and PMF), considering the impacts on diagnosis, and risk stratification and treatment separately. However, ESC noted that, because *CALR* testing is not required for diagnosis of PV, analysis was only required for ET and PMF populations.

ESC noted the Critique's conclusion that a linked evidence approach should be provided to assess the diagnostic accuracy of testing for the relevant mutations; the diagnostic accuracy of WHO 2016 diagnostic criteria with and without molecular testing; the stratification of patients to treatment; and subsequent costs and health outcomes.

ESC noted that an epidemiological approach was used to estimate the financial implications of expanding MBS item 73225. The estimates were based on current utilisation of the existing item and expected utilisation by patients suspected of having PMF. ESC considered this approach to be reasonable, the CA estimating an additional cost to the MBS of \$0.43 million in year 1, rising to \$0.59 million in year 5. ESC noted that the expansion of MBS item 73325 to include PMF is anticipated to generate low volumes of additional testing; however, considered that the bundling of the tests within the one MBS item with an increased fee of \$100 would have a more considerable impact on the MBS. ESC also queried whether the \$100 fee would be sufficient to avoid out-of-pocket costs for patients and whether there would be any other flow-on costs.

ESC noted the claim in the CA that expanding MBS item 73325 would not affect other MBS listed items. However, ESC agreed with the Critique that there is potential for the net cost per year to the MBS to be more or less than the CA's estimate because the proposed expansion would lead to changes in the number of patients diagnosed with ET or PMF, and the number of patients stratified to different risk categories.

ESC noted the claim in the CA that expanding MBS item 73325 would not change clinical treatment. However, because the proposed expansion may change the number of patients diagnosed with ET or PMF, and the number of patients stratified to each PMF risk category, there may also be changes in pharmaceutical and hospital use related to treatment of ET and PMF patients. ESC noted that, because neither the change in the number of patients diagnosed with ET or PMF nor any changes to the risk stratification of patients with PMF were calculated in the CA, impacts to the PBS and hospital system were not estimated.

ESC proposed that MSAC may consider further assessment with a specific request for what is needed regarding assessment of clinical utility and the economic evaluation in order to fully consider the application.

ESC noted that for similar applications in future – that is, those that are considered suitable for bypassing PASC – an alternative 'pseudo PASC' process or proforma is required to ensure that the PICO, clinical management algorithms and clinical utility are sufficiently clarified for assessment groups, so that information presented to ESC is sufficient to allow formulation of ESC advice. This could potentially include a pilot project in which providers and requesters of the proposed test/technology come together to clarify the purpose of the test

in terms of not only proven health outcomes or changes in management, but also factors such as the value of ‘knowing’, reducing the ‘diagnostic odyssey’ and future treatment for conditions diagnosed now. This would help to frame the clinical utility and clinical claims for these types of applications.

15. Other significant factors

Nil.

16. Applicant’s comments on MSAC’s Public Summary Document

The applicant had no comment.

17. Further information on MSAC

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