Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1532 – Expansion of genetic testing for myeloproliferative neoplasms under MBS item 73325

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

Date of MSAC consideration: MSAC 80th Meeting, 26-27 November 2020

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

1. Purpose of application

An application requesting an expansion of MBS-funded genetic testing for myeloproliferative neoplasms 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 supported the creation of new Medicare Benefits Schedule (MBS) items for genetic testing for myeloproliferative neoplasms (MPNs), for both gene-specific and next generation sequencing (NGS) gene panel testing, following initial *JAK2* V617F triage testing. MSAC considered that the identification of specific genetic variants underlying MPNs has diagnostic and prognostic and/or predictive clinical utility. This expansion of testing is aligned with current World Health Organisation (WHO) clinical guidelines.

MSAC noted that not all laboratories have next generation sequencing (NGS) panel capability at present, though genetic testing will likely move in this direction in the future – therefore creating both gene-specific and NGS items will allow laboratories to transition to NGS tests over time. MSAC supported revising MBS item 73325 to test for *JAK2* V617F variant allele frequency, and supported simultaneous rather than sequential gene-specific testing. MSAC noted that a positive *JAK2* V617F test result should not exclude patients from NGS panel eligibility if further testing is clinically indicated. MSAC advised that the NGS panel item descriptors should specify a core set of genes that must be included, and a minimum number of genes, but should not exclude testing for other relevant genes.

Consumer summary
The Royal College of Pathologists of Australasia (RCPA) applied for public funding via the Medicare Benefits Schedule (MBS) to expand genetic testing for myeloproliferative neoplasms. Myeloproliferative neoplasms, also called myeloproliferative diseases, are a

Consumer summary

very rare group of blood cancers. Myeloproliferative neoplasms include primary myelofibrosis, polycythaemia vera and essential thrombocythaemia.

One specific genetic variant (V617F) in the *JAK2* gene is found in more than half of people with myeloproliferative neoplasms, which is why it should be tested for first. However, there are several other genes and genetic variants involved in these diseases, such as *JAK2* exon 12, MPL and CALR. People with variants in these genes have different treatment options and health outcomes, so it is important for doctors to know which genetic variants a person has.

The Medical Services Advisory Committee (MSAC) recommended that genetic testing be done using multiple testing methods for people with myeloproliferative neoplasms. The genetic testing must be done in a particular order, with the next test based on the results of the genetic test before it.

MSAC's advice to the Commonwealth Minister for Health

MSAC recommended that additional genes be tested for after *JAK2* V617F in people with myeloproliferative disease, because such testing is valuable for doctors and patients to plan the best treatment. This testing is also in line with current guidelines from the World Health Organisation.

The changes to existing MBS item 73325 and new item descriptors supported by MSAC are provided below.

Revised item descriptor for MBS item 73325 for initial JAK2 V617F testing

Category 6 - PATHOLOGY SERVICE	Group P7 - Genetics
Determination of *JAK2* V617F variant allele frequency in the diagnostic work-up by, or on behalf of, the specialist or consultant physician, of a patient with clinical and laboratory evidence of a myeloproliferative neoplasm.	
Fee: $90 Benefit: 75% = $67.50 85% = $76.50	

Item descriptor for JAK2 exon 12 testing in patients with PV

Category 6 - PATHOLOGY SERVICE	Group P7 - Genetics
Characterisation of variants in *JAK2* exon 12 in the diagnostic work-up by a specialist or consultant physician of a patient with clinical and laboratory evidence of polycythaemia vera.	
Fee: $90 Benefit: 85% = $76.50 75%= $67.50	

Item descriptor for CALR and MPL testing in patients with ET and PMF (simultaneous testing)

Category 6 - PATHOLOGY SERVICE	Group P7 – Genetics
Characterisation of variants in the *CALR* and *MPL* genes in the diagnostic work-up by a specialist or consultant physician of a patient with clinical and laboratory evidence of essential thrombocythaemia or primary myelofibrosis. 1 test	
Fee: $200 Benefit: 85% = $170 75% = $150	

Item descriptor for NGS myeloproliferative panel for patients with PV and ET

Category 6 - PATHOLOGY SERVICE	Group P7 - Genetics
Characterisation of variants in at least 8 genes, including the following genes, in the diagnostic work-up by the specialist or consultant physician, of a patient with clinical and laboratory evidence of polycythaemia vera or essential thrombocythaemia: (a) *JAK2* gene (including exons 12, 14); and (b) the *CALR* gene; and (c) the *MPL* gene. 1 test per diagnostic episode	
Fee: $420 Benefit: 85% = $357 75%= 315	

Item descriptor for NGS myeloid panel for patients with PMF

Category 6 - PATHOLOGY SERVICE	Group P7 - Genetics
Characterisation of variants in at least 20 genes, including the following genes, in the diagnostic work-up by the specialist or consultant physician, of a stem cell transplant-eligible patient with clinical and laboratory evidence of primary myelofibrosis: (a) *JAK2* gene (including exons 12,14); and (b) the *CALR* gene; and (c) the *MPL* gene. 1 test per diagnostic episode	
Fee: $700 Benefit: 85% = 595 75%= $525	

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

MSAC noted that Application 1532 was a deferred application (from March 2019) for the expansion of MBS item 73325 (mutation testing in *JAK2* and *MPL* genes in myeloproliferative neoplasms [MPNs]) to include additional populations and mutations:

- patients with a third type of Philadelphia-negative classical MPN, primary myelofibrosis (PMF)
- a third relevant gene, calreticulin (*CALR*).

Current MBS item 73325 funds testing for *JAK2* and/or *MPL* genetic variants in patients with two MPNs, polycythaemia vera (PV) and essential thrombocythaemia (ET).

MSAC noted the reasons for deferral of the application at its March 2019 meeting:

- *CALR* variant testing is not needed in patients with PV; lack of clarity in the testing algorithm for MPNs and the need for multiple iterations of the item to cover real testing costs. With respect to the testing costs, it was noted that all three genes cannot be assessed for $100. This was because *CALR* mutations are very heterogeneous and analysis of this gene requires different methodology than testing for the common *JAK2* V617F mutation.
- Failure to recognise the clinical utility of testing to determine subtypes of MPD and the potential impact on prognosis and treatment.

- No economic analysis was presented. MSAC had advised exploring a triage strategy from a financial impact and costing perspective.

Since the initial submission, additional clinically or prognostically significant genes have been identified in patients with MPNs (particularly in patients with PMF), leading to different options being proposed for MSAC's consideration, including single-gene testing and inclusion of NGS panels.

MSAC considered that *CALR* testing was appropriate for patients with ET and PMF, but not those with PV. Detecting *CALR* variant status allows for a more precise diagnosis, prognosis and treatment pathway for patients with ET and PMF. MSAC noted that the proposed expansion of genetic testing to include not only *CALR*, *MPL* and *JAK2* but also additional genes with diagnostic and prognostic and/or predictive clinical utility, reflects the WHO's diagnostic criteria for MPN classification[1].

MSAC acknowledged that characterising additional genetic variants in patients with PMF would provide significant additional prognostic information and, together with other clinicopathological factors, now forms the basis of risk stratification and treatment decision-making.

MSAC noted the three proposed options for testing:

- option 1A: step 1 *JAK2* V617F test, then step 2 sequential, reflex *CALR*/*MPL* (non-NGS) for ET/PMF, plus *JAK2* exon 12 for PV
- option 1B: step 1 *JAK2* V617F test, then step 2 simultaneous *CALR*/*MPL* (non-NGS) for ET/PMF, plus *JAK2* exon 12 for PV
- option 2: step 1 *JAK2* V617F test, then step 2 a NGS MPN gene panel for ET/PV and NGS myeloid gene panel for PMF.

MSAC considered the stepwise testing algorithm (i.e. initial *JAK2* V617F triage testing) to be appropriate, and supported options 1B and 2. MSAC advised that MBS item 73325 should be modified (to restrict it to *JAK2* V617F testing) and additional items should be created:

- *JAK2* exon12 testing in patients with suspected PV
- combined (simultaneous) *MPL* and *CALR* testing in patients with suspected ET and PMF (option 1B)
- small NGS myeloproliferative panel for patients with suspected ET and PV
- larger NGS myeloid panel for patients with suspected PMF.

MSAC considered that a third option proposed by the applicant of upfront NGS panel testing was not appropriate, as *JAK2* V617F comprises more than 50% of the pathogenic variants in these patients, and performing NGS panels upfront would lead to excessive and unnecessary NGS panel utilisation at an increased cost. In addition, many laboratories do not yet have the capability to perform NGS panel tests. Thus, MSAC considered that it is currently necessary to have items for gene-specific testing in addition to NGS panels during a transition period. MSAC acknowledged that the knowledge base around genomic profiling is rapidly evolving and, over time, an upfront NGS panel that permits all relevant genes to be tested for may be appropriate. When this occurs, amendment of the item descriptors would be required.

[1] Arber D, et al The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukaemia *Blood* (2016) 127 (20): 2391–2405.

MSAC advised that the second test should be a reflex test, automatically done if the first test returns a negative result.

MSAC considered that the requirement for a "negative or uninformative *JAK2* V617F test result" should be removed from the new item descriptors for subsequent testing after *JAK2* V617F testing, since these tests may be used to seek further diagnostic or prognostic information in cases that returned a positive *JAK2* V617F result. However, MSAC advised that any requests for additional testing after a positive *JAK2* V617F test should only be from specialist haematologists/physicians.

MSAC advised that the item descriptor wording should be altered to specify a minimum set of genes that should be interrogated. For the myeloproliferative panel item, the descriptor should specify that at least "eight genes be tested", as per the recommendation of the National Pathology Accreditation Advisory Council (NPAAC) recommendation, rather than "up to 12 genes". For the myeloid panel item, the descriptor should state "at least 20 genes". Both descriptors should then list the minimum gene set to be tested. MSAC considered that the minimum gene sets for each panel should be finalised out-of-session.

MSAC considered that in the future additional genes could be added to the core set required for NGS panels, if necessary. If enough genes are added to these lists and the item numbers require a higher fee, then a separate application should be made with a request to increase the fee.

MSAC noted that there are no safety issues associated with this type of genetic testing in comparison to no genetic testing.

MSAC noted that the number of patients with MPNs is small and there is little risk of leakage. MSAC considered that using the item number for monitoring disease progression is inappropriate. However, MSAC noted that some clinicians use *JAK2* V617F testing to monitor residual disease after a bone marrow transplant, which it considered to be reasonable as there is a low risk of leakage. MSAC considered that this may explain the current higher utilisation of MBS item 73325 in Queensland, and recommended the Department explore further the difference in requests for testing between jurisdictions.

MSAC noted that ESC had recommended early auditing of use, especially if no limit on testing is set. MSAC advised that appropriateness of test utilisation should be audited early on after implementation, and should include examining whether NGS items are being used more than once per patient.

MSAC noted that the focused Department-contracted assessment report (DCAR) did not present an economic evaluation, and presented a financial analysis of different testing options. MSAC noted that the applicant advised it did not have any further comments beyond its pre-ESC response, and thus no pre-MSAC response.

4. Background

In 2009, MSAC supported genetic testing for some MPNs (application 1125), in line with the addition of genetic testing to WHO diagnostic criteria for MPNs in 2008. MBS item 73325 was created for the genetic testing of *JAK2* and *MPL* variants in patients with PV or ET. MSAC opted not to include PMF patients as it would neither remove the need for bone

marrow biopsy nor improve diagnostic certainty in these patients[2]. Patients must currently pay for *CALR* mutation testing themselves at a cost of approximately $85.

In 2016, the WHO diagnostic criteria for MPNs were extended to include *CALR* variant testing in patients suspected of having ET, and pathogenic variants in *JAK2/CALR/MPL* were introduced as diagnostic criteria for PMF[3]. The focused DCAR stated that in the absence of *JAK2/CALR/MPL* variants, the presence of clonal marker variants in a set of other genes was also added as a major criterion in pre-PMF or overt PMF, and as a minor criterion for ET.

In 2017, the MBS Review Taskforce Genetics Working Group of the Pathology Clinical Committee 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, specifically *CALR* and patients with PMF. The RCPA agreed to act as the applicant.

At its March 2019 meeting, MSAC considered the first DCAR for application 1532 and deferred its advice to seek further information regarding[4]:

- 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 NGS is considered optimal clinical practice
- 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 myeloproliferative disease (MPD) (for example, as used to justify their inclusion in the WHO 2016 diagnostic guidelines), and thus the usefulness of this testing for subsequent clinical management decisions and provision of healthcare resources.

The public summary document (PSD) noted a number of concerns with the analysis provided in the first DCAR, and the Department proposed actions for the focused DCAR on each (Table 1).

[2] MSAC Application 1125, PSD – Part A
[3] Arber D, et al The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukaemia *Blood* (2016) 127 (20): 2391–2405.
[4] MSAC Application 1532, PSD for consideration of first DCAR

Table 1: Matters of MSAC concern from 1532 PSD, and actions arising for focused DCAR

Component	Matter of concern from PSD	Action for focused DCAR
Clinical algorithm	Seek further information and targeted consultation from haematologists and pathology laboratories to ascertain clinical algorithm [p1, PSD]	Review and incorporate targeted consultation with haematologists and pathology; and identify if further consultation is needed, noting: – Initial consultation feedback has been requested for the algorithms (see Figures 1-3) from HSANZ by Dr Neil Everest. Response was requested by end of May 2020 – Upon receipt of this information, the Department (Pathology Policy) plan to consult the relevant groups from the pathology sector
Intervention: Item descriptor(s)	– Consequential item descriptor [PSD, p1] – Triage testing arrangement include any pathologist-determinable reflex tests or be separated into steps requiring further requests by the treating clinician [PSD, p1, p3] – Cost of testing, to justify proposed fee [PSD, p1] – Appropriate test methodology? *CALR* molecular assay more complicated than *JAK2* and *MPL*, and not necessarily run on same platform or simultaneously [PSD, p2]	DCAR to confirm the appropriate test methodology/ies in consultation with haematologists and pathology. This can then be used to inform the appropriate alternative MBS item descriptors and their proposed fees to align with contemporary Australian practice. The item descriptors can then be used to inform the required estimation of the financial implications and an economic evaluation (if considered necessary), see below.
Comparator	Use historical data (before availability of *CALR* testing) for comparison with *CALR* testing [PSD, p3]	Appropriate comparator for DCAR: If assessment of comparative effectiveness and safety is required, using a linked analysis: – For safety, effectiveness: clinical diagnosis (without genetic testing) e.g. historical data on prognosis without further differential diagnosis by biomarker – For financial implications: genetic testing with current MBS item 73325.
Clinical effectiveness	– No data. MSAC accepted that identifying specific mutations and thus underlying variants of MPD has prognostic value (clinical validity) and expected clinical utility [PSD, p3] – No need to do full literature review as 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 [PSD, p3] – Key issue: assessing whether *CALR* testing in patients with ET or PMF facilitates accurate assignment of risk category and appropriate treatment [PSD, p3] – Impact of *CALR* testing in ET and PMF, which could be determined by looking at proportion of patients who were wrongly assigned to a risk group before the availability of testing [PSD, p3]	DCAR to address MSAC concerns as necessary, noting the precedent subsequently set for MSAC application 1526, 1527 and 1528 (see below).
Economic evaluation	– Likely effects and costs of over- or under-treatment [PSD, p3] – The impact on subsequent provision of other healthcare resources was also not estimated [PSD, p3 – Investigate costs using simultaneous approach or MSAC suggested-triage approach, and confirm costs with appropriate test methodology from laboratory and requestor [PSD, p4]	DCAR to use targeted consultation to resolve these issues, and use the targeted consultation data to inform any relevant analysis. DCAR, to decide (in consultation with the Department) if an economic evaluation would be required; and if so, to undertake the economic evaluation, for example to help determine the optimal implementation of the MSAC-suggested triage approach to testing.
Utilisation	– Current data indicates ongoing increase in testing that appears to outweigh the estimated number of patients requiring diagnosis of MPD [PSD, p2] – Based on recent utilisation, assuming stability in utilisation was not a valid approach, [PSD, p4]	DCAR to provide updated financial analyses, which address MSAC previous concerns, and matching the different MBS items for any alternative options for the MSAC-suggested triage approach to testing.

Source: Compiled by Department from 1532 PSD

Abbreviations: CALR = calreticulin; ET = essential thrombocythaemia; DCAR = department contracted assessment report; HSANZ = Haematology Society of Australia and New Zealand; JAK2 = Janus kinase 2; MPD = myeloproliferative disorders; MPL = myeloproliferative leukaemia; PMF = primary myelofibrosis; PSD = Public Summary Document

Precedent for claims based on WHO guidelines

At its August 2019 meeting, MSAC supported genetic tumour testing applications 1526, 1527 and 1528. The PSDs for these applications note that by virtue of their place in the WHO guidelines, the proposed genetic tests have documented clinical utility in these diseases[5]. MSAC confirmed that it accepts the entry of each test into the WHO guidelines as sufficient demonstration of its diagnostic performance, clinical validity (prognostic value), and clinical utility (resulting in changes to subsequent clinical management)[6], therefore the precedent has already been established for MSAC accepting such claims based on WHO guidelines.

Note that this application was renamed in August 2020 from "Expansion of MBS item 73325 to include additional populations and mutations beyond those currently specified (for the characterisation of *JAK2* or *MPL* genes)" to "Expansion of genetic testing for myeloproliferative neoplasms under MBS item 73325", in order to better reflect the purpose of the application.

5. Prerequisites to implementation of any funding advice

The NPAAC advised MSAC that regarding quality framework for testing, there are no issues if the Application is restricted to three tests (*JAK2* exon 12, *CALR*, and *MPL*) as in options 1A and 1B. These tests are currently performed in Australian laboratories and there is an external quality assurance (EQA) program available. There are questions to be answered about a quality framework however, if testing utilises NGS for multiple genes (as in option 2). This testing strategy is only used in one or two Australian laboratories, it involves complex testing of a large number of genes and requires validation of an in-house assay, and there is no EQA program in place.

The NPAAC also notes that implementation issues will depend on the technology to be used. There is an existing quality framework for the single gene tests, however if the descriptor specifies NGS, then setting a minimum list of genes should be considered, and a sample exchange program would need to be established between laboratories in the absence of an external QA program.

6. Proposal for public funding

The focused DCAR stated that the proposed interventions would be used predominantly, but not exclusively, in the outpatient setting for the diagnosis and management of classical Philadelphia-negative MPNs.

The focused DCAR proposed two options for expanding genetic testing for MPNs, whereby option 1 includes expansion to only *JAK2*, *CALR* and *MPL* testing, and option 2 is more comprehensive and based on NGS panels. Option 1 also has sub-options for sequential/reflex versus simultaneous testing:

- Option 1A: Step 1 *JAK2* V617F test, then step 2 sequential, reflex *CALR/MPL* (non-NGS) for ET/PMF, plus *JAK2* Exon 12 for PV
- Option 1B: Step 1 *JAK2* V617F test, then step 2 simultaneous *CALR/MPL* (non-NGS) for ET/PMF, plus *JAK2* Exon 12 for PV
- Option 2: Step 1 *JAK2* V617F test, then step 2 NGS Myeloproliferative gene panel for ET/PV and NGS Myeloid gene panel for PMF

[5] MSAC Application 1527, PSD p7
[6] MSAC Application 1528, PSD p9

Option 1A – sequential JAK2 exon 12/CALR/MPL testing

Step 1: *JAK2* V617F testing

All options presented by the focused DCAR utilise quantitative *JAK2* V617F testing as the initial investigation. The focused DCAR proposes revising the existing MPN genetic testing MBS item 73325 to address this initial test, as in Table 2.

Table 2: Proposed revised MBS item descriptor Item 73325 for initial JAK2 V617F testing

Category 6 - PATHOLOGY SERVICE	Group P7 - Genetics
Determination of *JAK2* V617F variant allele frequency in the diagnostic work-up by, or on behalf of, the specialist or consultant physician, of a patient with clinical and laboratory evidence of a myeloproliferative neoplasm.	
Fee: $90 Benefit: 75% = $67.50 85% = $76.50	

Abbreviations: *JAK2*, Janus kinase 2 gene
Source: Focused DCAR, Table 8

The focused DCAR justified proposing an initial *JAK2* V617F screen on the basis that identification of a *JAK2* V617F variant establishes clonality in 95% of patients with PV, 50-60% with ET or with PMF and therefore makes a logical first step towards making a diagnosis of an MPN at an early stage in the clinical algorithm. When correlated with the other clinicopathological findings, a positive *JAK2* V617F (as opposed to negative or uninformative) result obviates the need for any further *JAK2/CALR/MPL* characterisation to establish a diagnosis, particularly in uncomplicated presentations. This is a critical juncture, requiring collation and interpretation of results from other clinical investigations by the haematologist or consultant physician. For the majority of patients referred, these will point to a non-neoplastic cause with no further genetic testing required; for other patients, these results may change the likelihood of one MPN over another (e.g. leukoerythroblastic film, low serum erythropoietin (EPO) – noting the latter, a WHO Minor Criterion for PV, is also not currently funded).

The focused DCAR noted that MSAC may wish to consider specifying the methodology as a quantitative allele-specific PCR to ensure sufficient sensitivity to detect mutations occurring at a low allele frequency. The RCPA proposed a fee of $90 ($76.50 rebate) for digital droplet PCR (ddPCR) for quantitative *JAK2* V617F testing. The focused DCAR noted that this represents an increment of $15.50 above the current Item 73325 rebate, set at $74.50 ($63.35 rebate) for a *JAK2* test in 2013.

The focused DCAR recommended that the revised item 73325 descriptor also include the addition ‘by or on behalf of a haematologist or specialist’, and that requesters of testing beyond *JAK2* V617F be limited to haematologists or consultant physicians attending the patient. In the pre-ESC response the applicant put forward an argument to limit requesters to specialists to reduce the number of tests required to be performed, to which the HTA group responded in the rejoinder that this necessarily and problematically assumes 60% of current test requesters are non-specialists (without evidence of such), and removes a step in the current diagnostic/clinical algorithm by promoting testing of all three driver genes upfront. The HTA group also noted that it is not currently possible to identify what proportion of testing under item 73325 is ordered by specialists, but per consultation in the focused DCAR, it was estimated that 10% would be by non-specialists – thus, restriction to specialists only as an initial step would seem very unlikely to reduce the numbers of tests ordered to 40% (3,250 patients) as suggested by the applicant in the pre-ESC response.

In the pre-ESC response, the applicant expressed reservations about *JAK2* V617F testing as the initial triaging test, stating that the reliance on this initial test before NGS testing will result in *JAK2*-mutated MPNs (mainly in patients with PMF) receiving lower rates of NGS

testing (including of genes with established utility for prognostication) than *CALR/MPL*-mutated cases, as this second test would not be eligible for an MBS rebate. This would result in inequity being generated based on driver mutation status, as patients would only be able to access additional testing by out-of-pocket payments.

The RCPA previously proposed using a 7-9 gene NGS panel as an upfront test. Based on a cost of $295, (based on the $250 current cost adjusted for Medicare 85% reimbursement), this would have an annual estimated cost far greater than the other options ($4,054,628 per annum). The option for upfront testing with an NGS panel was therefore not subsequently retained for consideration, and is not included in any proposed options.

Step 2: subsequent testing for *JAK2* exon 12/*CALR*/*MPL*

Where initial *JAK2* V617F testing is negative or uninformative, option 1 proposes further testing limited to *JAK2* exon 12/*CALR/MPL*. Patients with suspected PV would proceed to *JAK2* exon 12 testing (Table 3), while patients with suspected ET or PMF would proceed to *CALR* and/or *MPL* testing, under a reflex testing strategy (option 1A, Table 4).

Table 3: Options 1A & 1B Proposed item descriptor for characterisation of JAK2 Exon 12 in PV

Category 6 - PATHOLOGY SERVICE	Group P7 - Genetics
Characterisation of variants in *JAK2* Exon 12 in the diagnostic work-up by a specialist or consultant physician of a patient with clinical and laboratory evidence of polycythaemia vera, and who has previously had a negative or uninformative *JAK2* V617F test result (item 73325).	
Fee: $90 Benefit: 85% = $76.50 75%= $67.50	

Abbreviations: *JAK2*, Janus kinase 2
Source: Focused DCAR, Table 13

The focused DCAR estimated the cost of non-NGS *JAK2* exon 12 testing at $90.

Table 4: Option 1A Proposed item descriptor for CALR and MPL in ET and PMF using reflex testing strategy

Category 6 - PATHOLOGY SERVICE	Group P7 – Genetics
Characterisation of variants in one of the following genes, with reflex testing determinable by the pathologist or specialist to the next test only if the previous result is negative or uninformative: 1. *CALR* 2. *MPL* in the diagnostic work-up by a specialist or consultant physician of a patient with clinical and laboratory evidence of: (a) essential thrombocythaemia; or (b) pre-fibrotic or primary myelofibrosis. and who has previously had a negative or uninformative *JAK2* V617F test result (item 73325). 1 or more tests	
Fee: $100 (per test); Benefit: 85% = $85 75% = $75	

Abbreviations: *CALR*, Calreticulin; *JAK2*, Janus kinase 2; *MPL*, myeloproliferative leukaemia
Source: Focused DCAR, Table 14

The cost of testing *CALR* and *MPL* (Table 4) was suggested in the first DCAR to be $100, which is the figure used in modelling by the focused DCAR while also noting that this does not cover the anticipated costs of the complex testing required for *CALR*, which would potentially result in a fee being charged to the patient, or a cheaper, perhaps less sensitive or specific and/or less comprehensive methodology being employed.

In the pre-ESC response, the applicant commented that serial testing in any form (as in reflex testing option 1A) is highly inefficient and has the potential for suboptimal diagnostic accuracy in patients with MPN. Serial testing will inevitably delay patient management planning and treatment, and may lead to repeated billings of the same MBS item number (73325) by different laboratories (because many laboratories cannot perform both tests in-house and so would need to send all negative *JAK2* cases out for *CALR* testing elsewhere), or to out-of-pocket expense to patients when *JAK2/CALR/MPL* are requested simultaneously. The applicant also noted that reflex testing of either *JAK2* exon 12 (for PV) or *CALR* followed by *MPL* (for ET/PMF) as described in options 1A and 1B, has the significant disadvantage of not providing any of the 'incidental' prognostic value offered by a small NGS panel (unless individual laboratories choose to perform these tests by NGS, as is sometimes the case).

In the pre-ESC response, the applicant also commented that if option 1A were supported, then it would be necessary to provide single item numbers for *CALR* and *MPL* testing so that both tests could be reimbursed from the same blood draw. It was suggested that separate item numbers should be considered for the testing of each of *JAK2*, *CALR*, and *MPL*, to permit single gene tests for laboratories that do not perform all three gene tests.

Option 1B – simultaneous JAK2 exon 12/CALR/MPL testing

Option 1B starts with initial testing for *JAK2* V617F (Table 2), as described above. Where initial *JAK2* V617F testing is negative or uninformative, option 1 proposes further testing limited to *JAK2* exon 12*/CALR/MPL*. Patients with suspected PV would proceed to *JAK2* exon 12 testing (Table 3) the same as in option 1A, while patients with suspected ET or PMF would proceed to *CALR* and/or *MPL* testing, under a simultaneous testing strategy (option 1B, Table 5).

Table 5: Option 1B Proposed item descriptor for CALR and MPL in ET and PMF using simultaneous testing strategy

Category 6 - PATHOLOGY SERVICE	Group P7 – Genetics
Characterisation of variants in the *CALR* and *MPL* genes in the diagnostic work-up by a specialist or consultant physician of a patient with clinical and laboratory evidence of essential thrombocythaemia or primary myelofibrosis, and who has previously had a negative or uninformative *JAK2* V617F test result (item 73325). 1 test	
Fee: $200 Benefit: 85% = $170 75% = $150	

Abbreviations: *CALR*, Calreticulin; *JAK2*, Janus kinase 2; *MPL*, myeloproliferative leukaemia
Source: Focused DCAR, Table 15

The cost of separately testing for each of *CALR* and *MPL* was suggested in the first DCAR to be $100 (Table 4), and the focused DCAR doubles this to obtain the $200 fee for simultaneous testing (Table 5). However, the focused DCAR also noted that this does not cover the anticipated costs of the complex testing required for *CALR*, which would potentially result in a fee being charged to the patient, or a cheaper, perhaps less sensitive or specific and/or less comprehensive methodology being employed.

The focused DCAR favoured simultaneous (option 1B) over reflex testing, as reflex testing appears to offer a minimal saving over non-NGS combined testing for *CALR/MPL* but has potential for inconvenience to the patients, clinicians and pathology services of a potentially fragmented service. Simultaneous testing is also noted by the focused DCAR to be more pragmatic and simpler. This is supported by the applicant's comments indicating a strong preference for simultaneous over sequential testing, as outlined above for option 1A.

Option 2 – subsequent testing using an NGS panel

The focused DCAR stated that three-gene testing does not complete the molecular testing incorporated into the 2016 WHO Diagnostic criteria for ET and PMF nor support current contemporary clinical practice, and therefore proposes the alternative option 2, in which patients with a negative or uninformative *JAK2* V617F test result would instead proceed to testing using an NGS panel. Clonality, supportive of a diagnosis, may be missed on the basis of 'other' gene mutations that are required to meet the Major Diagnostic Criterion for PMF, and the Minor Diagnostic Criterion for ET if *JAK2/CALR/MPL* testing is not informative. Comprehensive testing ends the diagnostic odyssey (given the alternative in both conditions requires extensive investigations to exclude other potential causes), and also provides prognostic information to guide life planning and treatment interventions, particularly in PMF.

The focused DCAR noted the RCPA recommendation for a 12-gene panel incorporating genes with diagnostic and prognostic utility in the management of PV and ET, at minimum including *JAK2* exon 12, *CALR* and *MPL*. A smaller 7-9 gene 'myeloproliferative panel' is currently available in Australia, and is proposed by the focused DCAR for PV and ET patients (Table 6), with a more complex 26-31 gene 'myeloid gene panel' proposed for patients with PMF (Table 7). The 85% rebates for the myeloproliferative and myeloid panel items were estimated at $357 and $595 respectively, based on prices for these services as currently provided in Australia.

Table 6: Option 2 Proposed item descriptor including genes for 'Myeloproliferative gene panel' for PV and ET

Category 6 - PATHOLOGY SERVICE	Group P7 - Genetics
Characterisation of variants in up to 12 genes, including the following genes, in the diagnostic work-up by the specialist or consultant physician, of a patient with clinical and laboratory evidence of polycythaemia vera or essential thrombocythaemia, and who has previously had a negative or uninformative *JAK2* V617F test result (item 73325): (a) *JAK2* gene (including Exons 12, 14); (b) the *CALR* gene (c) the *MPL* gene; 1 test	
Fee: $420 Benefit: 85% = $357 75%= 315	

Abbreviations: *CALR*, Calreticulin; *JAK2*, Janus kinase 2; *MPL*, myeloproliferative leukaemia
Source: Focused DCAR, Table 19

Table 7: Option 2 Proposed item descriptor including genes for 'Myeloid gene panel' for PMF

Category 6 - PATHOLOGY SERVICE	Group P7 - Genetics
Characterisation of variants in up to 31 genes, including the following genes, in the diagnostic work-up by the specialist or consultant physician, of a patient with clinical and laboratory evidence of primary myelofibrosis, and who has previously had a negative or uninformative *JAK2* V617F test result (item 73325): (a) *JAK2* gene (including Exon 12,14); and (b) the *CALR* gene; and (c) the *MPL* gene; and 1 test	
Fee: $700 Benefit: 85% = 595 75%= $525	

Abbreviations: *CALR*, Calreticulin; *JAK2*, Janus kinase 2; *MPL*, myeloproliferative leukaemia
Source: Focused DCAR, Table 20

In the pre-ESC response, the applicant recommended removal of a specified number of genes in a panel, as in the myeloproliferative and myeloid gene panel item descriptors proposed in the focused DCAR (Table 6, Table 7). In the rejoinder, the HTA group responded that the number of genes was included to allow some flexibility in the panel-testing approach and as a placeholder for MSAC to consider whether or which genes should be nominated if a panel approach is accepted. A recommendation had been made to consider the RCPA's initially proposed 12-gene panel, but it is not clear why expanded gene testing is no longer favoured by the applicant. Noting a risk of fewer genes being tested for the same rebate, the HTA group recommends that MSAC considers nominating exemplar genes. In addition to *JAK2*, *CALR* and *MPL*, these could include the following with established clinical utility in all three MPNs as described in the focused DCAR: *ASXL1*, *SRSF2*, *EZH2*, *IDH1*, *IDH2*, *TP53*, *SH2B3* and *SF3B1*. The HTA group suggests that whether other genes should be included to allow the diagnosis/exclusion of other MPNs (as per the Applicant's 1 July 2020 advice) could be considered. The HTA group favoured a whole-of-disease approach facilitating not only diagnosis of the individual MPNs presenting with an overlapping phenotypes and which are otherwise diagnoses of exclusion, but also genetic characterisation to support optimal management, life and treatment decisions.

In the rejoinder, the HTA group noted that the proposed myeloproliferative gene panel item (Table 6; incorporated in response to the initial RCPA advice) may also diagnose/distinguish patients presenting with overlapping phenotypes who have one of the less common MPNs, rather than solely for diagnosing PV, ET or PMF.

7. Summary of public consultation feedback/consumer Issues

The first DCAR for application 1532 noted that there was no public consultation details provided by the applicant, however peak organisations were consulted as part of the MBS review process.

The focused DCAR stated that the Department sought external consultation from two professional clinical organisations. The HTA group sought the advice of a clinical haematologist and bone marrow transplant physician regarding the clinical algorithm and to provide background on use of the different tests available in contemporary Australian clinical practice.

Following MSAC's decision to defer its advice to seek further information, targeted feedback questions were developed by the Department to seek additional information on matters not addressed in the first DCAR, to inform the development of the focused DCAR. Responses from the two organisations are synthesised below.

Both professional organisations supported updating the current MBS item. One stated that the current MBS item is outdated, and the arbitrary exclusion of patients with PMF is not appropriate from a clinical perspective. The other stated that there is clearly significant need for subsidised panel testing of a more substantial gene set (greater than the three driver genes alone) of relevance across a spectrum of myeloid malignancies. The WHO diagnostic criteria for PMF include other clonal markers (in addition to *JAK2*, *CALR* and *MPL*) in triple negative cases. If the scope of testing extends beyond diagnostic workup to prognostication, then these additional genes would be valuable and would require simultaneous testing.

Regarding the optimal position of *CALR* testing in the pathway, feedback stated that *CALR* testing is not required in PV, and in ET and PMF, *CALR* testing should be in addition to both *JAK2* and *MPL* testing. Other feedback stated that *CALR* testing is predicted to have the highest yield in patients who have suspected MPN but are negative for *JAK2* V617F. The

proposed raise of the rebate to $100 per test will be insufficient to cover tests for all three genes, which will likely result in pathology companies requiring a negative *JAK2* V617F result before *CALR/MPL* testing, which may in turn result in additional delays to diagnosis and additional phlebotomy tests. A more appropriate reimbursement would be $100 for *JAK2* V617F if positive, and an additional $100 to test each of *CALR* and *MPL* on the same sample to be paid only if the *JAK2* V617F comes back negative. A compromise may be to reimburse $100 up front and then an additional $100 if *CALR* and *MPL* testing are required.

Feedback stated that the MPN pathways described may be appropriate in some patients, however there are some inaccuracies, for example there is no mention of the secondary causes that must be excluded. Hereditary causes of polycythaemia are not recognised and may include genetic variants in EPO-receptor or regulators of erythropoiesis.

Both professional organisations regarded the likelihood of unintended usage as low. One stated that unintended use seems unlikely as these tests are not yet mature enough for disease monitoring, though this may change in the future. This was supported by comment from the other organisation that serial monitoring is not the current standard of care, however introducing a limit on testing frequency is not recommended as re-testing after technical failure or an equivocal result may be required. Feedback also noted that highly active new drugs are now available that may have disease modifying activity, and can cause a reduction in molecular allelic burden. It is not a routine clinical requirement to monitor molecular tests to assess response to therapy, but this may become more important and more common with the advent of newer, highly active treatments.

One organisation noted that the presence of variants in *JAK2*, *CALR* or *MPL* are exclusion criteria for chronic myelomonocytic leukemia and atypical chronic myeloid leukemia.

The adoption of NGS-based panels was supported by both professional organisations. One organisation supported using NGS-based panels as it allows the detection of non-canonical variants. One organisation commented that NGS panels are optimised for MPN diagnosis, and provide excellent sensitivity and specificity for MPN driver genes, as well as for important disease modifying genes that have a substantial impact on response to treatment and prognosis. NGS panels are recommended for transplant-eligible patients with a diagnosis of myelofibrosis, to ensure that optimal treatment pathways can be identified early and the appropriate workup completed while patients are fit and suitable for allogeneic HSCT. Feedback also noted that a separate item to support an MPN gene panel would be highly desirable, however would need to be funded at an appropriate price point that reflects the cost of testing. Ordering such an item should be restricted to specialist haematologist physicians only.

Feedback stated that there are significant analytical and practical deficiencies of a sequential approach to MPN diagnosis and for this reason, whilst individual laboratories may choose to employ this strategy, the MBS item criteria should not be structured to actively prefer sequential testing using *JAK2* V617F as a triage screen.

- Sequential testing risks misclassifying patients with co-mutated MPNs.
- Sequential testing has increased time and resource costs, and in practical terms is difficult for laboratories to manage. Simultaneous testing is the most efficient and cost-effective workflow for laboratories.
- For PV patients only, it would be appropriate to consider a *JAK2* V617F screen followed by *JAK2* exon 12 sequencing if negative.

Consultation feedback stated that whether or not *CALR* testing after a negative *JAK2* test should be reflex depends on the turnaround time and where the test is conducted. Reflex test

options would be *JAK2* exon 12 in suspected PV, and *CALR* and *MPL* in suspected ET or PMF.

Regarding the proposed cost of testing, feedback noted the costs would be substantially higher if genes for diagnosis and prognosis were tested, and if reflex testing were applied. The cost for a panel will depend on the platform used and labour costs. Many labs would use an NGS panel-based approach.

No consumer feedback was received for this application.

8. Proposed intervention's place in clinical management

The current clinical management algorithm (Figure 1) and algorithm proposed by the focused DCAR (Figure 2) are included below.

All changes to genetic testing for MPNs (options 1A, 1B, and 2) proposed by the focused DCAR would replace existing testing.

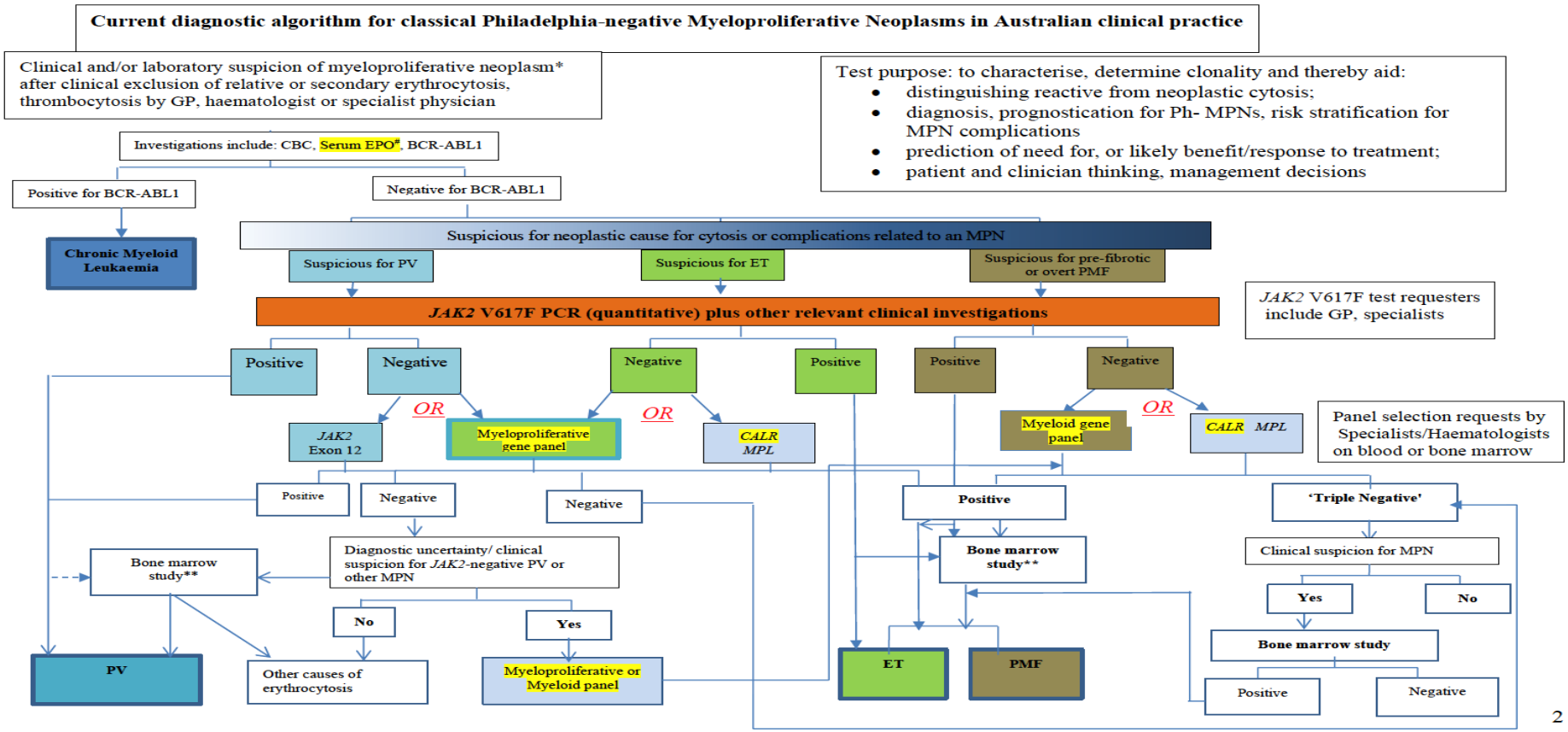

Figure 1: Diagnostic algorithm for MPNs incorporating 2016 WHO molecular diagnostic criteria, and molecular profiling as currently used in Australian clinical practice

Modified from the Mayo Clinic diagnostic approach to reflect Australian clinical practice (MPNs: a diagnostic approach to peripheral blood evaluation and MPNs: a diagnostic approach to bone marrow evaluation)

*Major criterion for PV: Increased Hb (>165g/L men; >160g/L women) **or**, Increased haematocrit (>49% in men; >48% in women) **or** Increased red cell mass (>25% above predicted); +/- thrombocytosis or neutrophilia; differential includes other non-classical Ph- MPN which per WHO criteria, require exclusion of PV, ET, PMF.

If PV suspected, WHO Minor diagnostic criterion for PV (in conjunction with 2 major criteria) – not funded in Australia – may be used to differentiate *JAK2* unmutated.

PV from other causes of erythrocytosis and reduces false positive rate as 85% of patients with PV have subnormal serum EPO.

** Undertaken for diagnostic, prognostic information but not always done in Australian clinical practice (not routine for uncomplicated PV in British Society of Haematology Guideline (McMullin et al (2018)) for PV, ET unless diagnostic uncertainty, clinical concern - can meet WHO diagnostic criteria for PV with other criteria (but NB serum EPO not currently funded); for MF, always perform bone marrow if leukoerythroblastic blood film or suspect transformation from PV/ET; for MF, bone marrow sample may be used for molecular testing.

If *JAK2* V617F variant testing uninformative (low positive (0.06%-0.6%) or negative), then proceed to targeted gene or panel test as per specialist/haematologist.

Positive or negative is taken to mean pathogenic variant detected, or the result is uninformative.

Yellow highlight indicates test not currently MBS-listed in Australia.

Source: Focused DCAR, Figure 6.

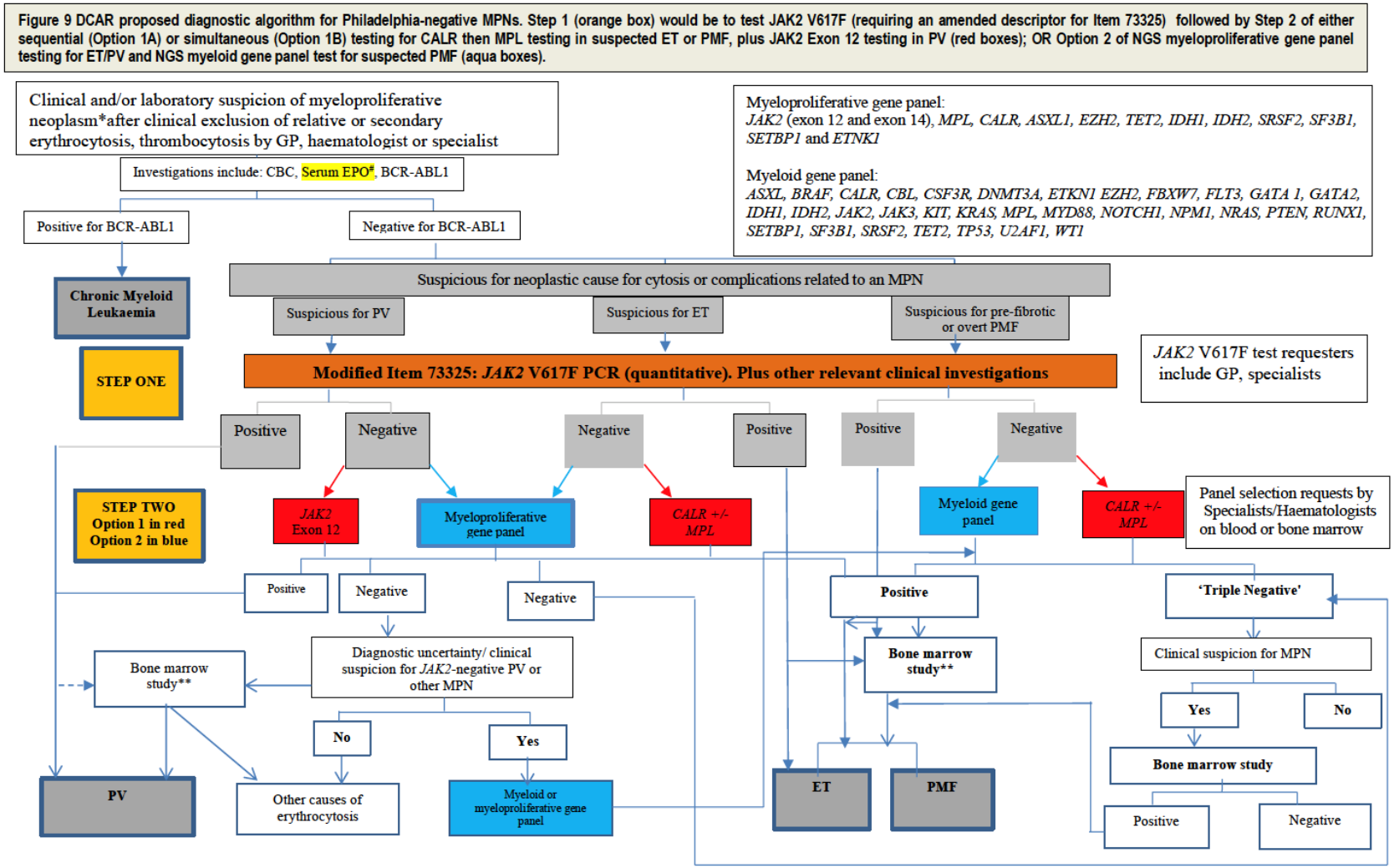

Figure 2: Focused DCAR's proposed diagnostic algorithm for MPNs, including Option 1 (red boxes) and Option 2 (blue boxes).
Source: Focused DCAR, Figure 9.

Description of Proposed Intervention
The focused DCAR proposed expansion of MPN genetic testing under MBS item 73325 to align MBS funding with the additional evidence that has accumulated since the WHO recommendations for the diagnosis of MPNs were updated in 2016[7], and since the referral from the Genetics Working Group of the Pathology Clinical Committee of the MBS Review in 2017.

While the original Application 1532 considered by MSAC in March 2019 proposed expanding MPN genetic testing by adding the *CALR* gene and the population of patients with PMF, the focused DCAR proposes an additional NGS panel option for consideration.

Description of Medical Condition
Myeloproliferative neoplasms are a group of phenotypically and genetically defined disorders in which bone marrow stem cells grow and reproduce abnormally. Philadelphia-negative MPNs include PV, ET, and PMF. The target population is people suspected to have one of the classical MPNs: polycythaemia vera (PV), essential thrombocythaemia (ET) and pre-fibrotic or overt primary myelofibrosis (PMF).

The focused DCAR stated that the *JAK2* V617F mutation is found in more than 50% of all three MPNs: 95% of patients with PV and approximately 60% of patients with ET or PMF. Except in rare circumstances, mutations in the three driver genes occur mutually exclusively. Detection of either a *CALR* or *MPL* variant provides support for a diagnosis in a further 30% of patients with ET or PMF, with the remaining classified as 'triple-negative'.

Detection of a pathogenic variant in other myeloid tumour suppressor genes may also establish clonality and support differentiation between a neoplastic and other causes of a cytosis, and thus is also a Major Diagnostic Criterion for PMF, and a Minor Diagnostic Criterion for ET in the absence of a driver mutation. Co-mutated genes occur in 80% of patients with PMF, and 53% of patients with ET and PV combined, and are considered predictors of adverse outcome in 56%, 15% and 15% of these MPNs, respectively. These variants contribute to the observed phenotype, to phenotypic shifts and to progression or transformation of the classical MPNs.

The focused DCAR stated that mutations in genes other than *JAK2*, *CALR*, or *MPL* are found in 81% of patients with PMF, 53% with PV, and 53% with ET[8,9]. The clinical utility of extending molecular testing to these other variants, particularly when *JAK2/CALR/MPL* testing is negative, or uninformative, is both diagnostic and prognostic. The diagnostic utility is to establish clonality in both ET and PMF, as recognised in the 2016 WHO Diagnostic Criteria, which include as a Major Criterion in pre-PMF or overt PMF, "Presence of *JAK2, CALR*, or *MPL* mutation or in the absence of these mutations, presence of another clonal marker (e.g. *ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, SF3B1*)…" and for ET as a Minor Criterion where there is no *JAK2/CALR/MPL* mutation, "Presence of a clonal marker or absence of evidence for reactive thrombocytosis."[10] This means these markers can support a

[7] Arber D, et al The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukaemia *Blood* (2016) 127 (20): 2391–2405.
[8] Tefferi A, Lasho TL, Guglielmelli P, et al. Targeted deep sequencing in polycythemia vera and essential thrombocythemia. Blood Adv. 2016;1(1):21-30.
[9] Tefferi A, Lasho TL, Finke CM, et al. Targeted deep sequencing in primary myelofibrosis. Blood Adv. 2016;1:105-111.
[10] Arber D, et al The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukaemia *Blood* (2016) 127 (20): 2391–2405.

diagnosis of ET and PMF, which are otherwise diagnoses of exclusion requiring extensive further investigations, and closer follow-up where residual uncertainty remains.

9. Comparator

The comparator used by the focused DCAR in financial modelling, was genetic testing with current MBS item 73325 (Table 8).

Table 8: Current descriptor for MBS item 73325

Category 6 - PATHOLOGY SERVICE	Group P7 - Genetics
Characterisation of mutations in: (a) the *JAK2* gene; or (b) the *MPL* gene; or (c) both genes; in the diagnostic work-up, by, or on behalf of, the specialist or consultant physician, of a patient with clinical and laboratory evidence of: a) polycythaemia vera; or b) essential thrombocythaemia; 1 or more tests	
Fee: $74.50 Benefit: 75% = $55.90 85% = $63.35	

Abbreviations: *JAK2*, Janus kinase 2; *MPL*, myeloproliferative leukaemia
Source: MBS Online, item descriptor for MBS item 73325 (accessed 21 Sep 2020)

The focused DCAR identified the comparators for this application to be the currently available testing versus the expanded testing, with demonstrated clinical utility, for the diagnosis and management of patients with suspected classical MPNs. Tests not currently funded are shown in bold font:

(a) For ET: *JAK2/MPL vs. JAK2* V617F/***CALR***/*MPL*/**other genes**
(b) For PMF: strictly, no genetic testing, (although *JAK2* V617F/*MPL* testing was probably accessed via ET/PV testing due to PMF being a diagnosis of exclusion of those conditions), therefore *JAK2/MPL vs.* ***JAK2/CALR/MPL*/other genes**
(c) For PV: current testing for *JAK2* mutations *vs. JAK2* mutations/**other genes**

10. Comparative safety

The focused DCAR stated that no assessment of the comparative safety of testing was deemed necessary due to the samples already being obtained for other diagnostic purposes.

There are no adverse consequences anticipated from the use of any of the proposed tests. None of the proposed tests are considered experimental, however their use could potentially lead to a risk stratification that would direct treatment selection more appropriately, including the avoidance of harm from a treatment unlikely to offer a favourable benefit-risk ratio.

11. Comparative effectiveness

Regarding direct effectiveness, the focused DCAR stated that according to the supportive WHO classification in the case of the tests for MPNs, each test for the driver mutations has diagnostic, and/or prognostic utility. The WHO classification acknowledges the diagnostic and prognostic role of additional genes in ET and PMF but does not formally identify those genes. Since the classification was first released, many such genes have subsequently been

identified and formally incorporated into prognostic models and clinical practice and as such are proposed for MSAC's consideration for funding.

The WHO Guidelines, which were updated four years ago, only include genetic biomarkers into their classification when these biomarkers have been shown to have diagnostic, prognostic and/or predictive value. The genes nominated for inclusion (*JAK2*/*CALR* and *MPL* for PMF, and *CALR* for ET) have accepted diagnostic and prognostic clinical utility. The focused DCAR states that the clinical utility for each of the proposed tests is demonstrated by their inclusion in the relevant WHO Guidelines documents and prognostic models recommended by international guidelines.

Clinical claim

The clinical claim made by the focused DCAR is that each of the proposed tests offers superior effectiveness, with no direct impact on safety as any samples required will have already been taken for other purposes. However, the indirect effect of the testing of classifying risk status more precisely may prevent harm from both the avoidance of unnecessary therapy in some MPNs or early institution of potentially effective therapies.

12. Economic evaluation

The first DCAR stated that the cost consequences of availability of *CALR* testing are:

- Avoidance of over-investigation for other causes in those with a positive diagnosis through identification of *CALR* – 65 patients/year
- Potentially avoid or delay allogeneic stem cell transplant (ASCT) in those with *CALR* Type 1/like pathogenic variants – 46 patients/year. Proportion who would have proceeded otherwise to ASCT dependent on multiple patient factors.
- Immediate, independent classification as being at high risk through triple-negative status – 26 patients/year – proportion of these patients proceeding to ASCT dependent upon multiple patient factors.

The focused DCAR did not present economic analyses, but rather financial analyses as below.

13. Financial/budgetary impacts

Inputs to financial modelling

The focused DCAR assumed a diagnosis of a classical MPN is established from 40% of patients tested after review by a haematologist, and estimated proportions of patients with a *JAK2* V617F variant as below (Table 9).

Table 9 Estimated incidence of the condition and tests to be undertaken following initial JAK2 V617F testing

Condition (estimated incidence)	% *JAK2* V617F +	Diagnosed with *JAK2* V617F testing	Not yet diagnosed	Suspected as having the condition – needing further testing (assuming 40% diagnostic yield)
PV (520)	95%	500	20	50
ET (520)	60%	312	208	520
PMF (260)	60%	156	104	260
All MPNs	1300	968	332	830

Source: Focused DCAR, Table 11

Patients with PV also have a 3% frequency of *JAK2* exon 12 variants (focused DCAR, clinical utility section). Amongst patients with ET, 22% have *CALR* indels[11], 3-4% have *MPL* variants[12,13] and 15% are triple negative. Variants in other genes coexist with *JAK2/CALR/MPL* variants in up to 53% of patients with ET, and adverse variants in *SH2B3, EZH2, IDH1/IDH2, SRSF2*, or *SF3B1* in 15%[14]. Amongst patients with PMF, 25% have *CALR* indels and 5% have *MPL* variants[15], and 10% are triple negative. More than 80% have a 'high-risk mutation' in *ASXL1*[16,17], *SRSF2*[18], *EZH2, IDH1, IDH2, TP53* or *SH2B3* co-occurring with a driver mutation.

The focused DCAR noted that the incidence of MPNs varies widely amongst the various European registries[19], without a clear reason. Estimated incidences of 2 (PV), 2 (ET), and 1 (PMF) cases per 100,000 population per year were used in subsequent modelling.

The focused DCAR noted the steadily increasing trend in utilisation of MPN testing, and predicted utilisation based on utilisation data for existing MBS item 73325. The 17,386 services requested under this item number in 2019-20 was multiplied by the 93% of patients where a single service provision was billed in 2017-18, to arrive at the estimated 16,170 (rounded) tests per annum.

The focused DCAR noted that if an NGS-based approach is used to assess the *CALR* gene – noted to be accepted as one of the best methodologies for the assessment of *CALR* in the literature and in the response from the RCPA - then it would be more cost-effective to proceed directly to Option 2, because the proposed cost of an individual *CALR* test followed by *MPL* testing and any separate *JAK2* Exon 12 testing would exceed the charge for the NGS myeloproliferative multigene panel. A sequential approach loses the efficiencies offered by panel testing.

Summary of financial analysis

The focused DCAR summary of the financial evaluation is shown in Table 10.

[11] Tefferi, A and Pardanani Myeloproliferative neoplasms A contemporary review *JAMA Oncol.* 2015;1(1):97–105. doi:10.1001/jamaoncol.2015.89

[12] Rumi E, Pietra D, Ferretti V, et al. JAK2 or CALR mutation status defines subtypes of essential thrombocythemia with substantially different clinical course and outcomes. *Blood*. 2014;123(10):1544-1551.

[13] Pardanani, A et al. MPL515 mutations in myeloproliferative and other myeloid disorders: a study of 1182 patients. Blood. 2006 108, 3472–3476.

[14] Tefferi A, Lasho TL, Guglielmelli P, et al. Targeted deep sequencing in polycythemia vera and essential thrombocythemia. Blood Adv. 2016;1(1):21-30.

[15] Tefferi A Primary myelofibrosis: 2019 update on diagnosis, risk-stratification and management Am J Hematology 2018 93(12): 1551-60

[16] Tefferi A et al Driver mutations and prognosis in primary myelofibrosis: Mayo-Careggi MPN Alliance study of 1095 patients. Am J Hematology 2018 93(3) 438-55.

[17] Vannucchi A et al Mutations and prognosis in primary myelofibrosis *Leukemia*. 2013;27(9):1861-1869. doi:10.1038/leu.2013.119

[18] Tefferi A et al Driver mutations and prognosis in primary myelofibrosis: Mayo-Careggi MPN Alliance study of 1095 patients. Am J Hematology 2018 93(3) 438-55.

[19] Moulard O et al Epidemiology of myelofibrosis, essential thrombocythemia, and polycythemia vera in the European Union Eur J Haematology 2014 92(4): 289-97

Table 10: Summary of financial evaluation of options 1A, 1B, and 2

Options	Total impact on MBS per annum	Incremental impact on MBS per annum
Current usage per Item 73325 at 85% rebate $63.35 (17386 tests in 2019/20)	$1,101,403	-
OPTION 1A: *(3 item numbers)* *Step 1 JAK2* V617F test, then *Step 2* Sequential, reflex *CALR/MPL* (non-NGS) for ET/PMF, plus *JAK2* Exon 12 for PV	$1,358,130	+$256,727
OPTION 1B: *(3 item numbers)* *Step 1 JAK2* V617F test, then *Step 2* Simultaneous *CALR/MPL* (non-NGS) for ET/PMF, plus *JAK2* Exon 12 for PV	$1,373,430	+$272,027
OPTION 2: *(3 item numbers)* *Step 1 JAK2* V617F test, then *Step 2* NGS MPN gene panel for ET/PV and NGS Myeloid gene panel for PMF	$1,618,400	+$516,997

Source: Focused DCAR, Table in Executive summary.

The focused DCAR estimated the cost of initial *JAK2* V617F triage testing (utilised in options 1A, 1B, and 2) as per proposed revised item 73325 to be $1,237,005 per annum. For comparison, the focused DCAR also estimated the cost of upfront testing using a 7-9 gene NGS panel (including *JAK2* V617F and exon 12, *CALR* and *MPL*), as proposed by the applicant, for all patients with suspected MPN at $4,054,628 per annum.

In the pre-ESC response, the applicant expressed concern regarding the focused DCAR's financial analysis of these two initial triage options, and reiterated their support for upfront testing with a *JAK2/CALR/MPL* NGS panel. The applicant stated that if there are currently 1,300 MPN diagnoses per year (equating to a diagnostic yield of 8% of 16,170), then *JAK2* V617F testing of 16,170 patients is expected to identify 968 (60% of 1,300) *JAK2* V617F positive patients, leaving 15,202 negative tests for review by a specialist or consultant physician. Costings for subsequent testing options assume that only 830 of these 15,202 patients (5%) will require any further genetic testing. This number is constituted by the estimated 40% of *JAK2* V617F negative MPN patients (of 1,300 diagnoses per year = 332) and includes an assumed diagnostic yield of 40% (332/0.4 = 830) upon specialist review. These assumptions require careful review considering the 8% diagnostic yield across all tests currently. If original tests are appropriately requested, then it would be reasonable to assume that all 15,202 negative tests will require further testing to rule out a suspected MPN diagnosis, which will substantially increase the costings of all the proposed options. Alternatively, if the diagnostic yield of these tests truly increases to 40% when requested by a specialist or consultant physician, then restricting the ordering of these tests to this group would vastly decrease the test numbers per year (1,300/0.4 = 3,250) and therefore the total cost of all options, making upfront *JAK2/CALR/MPL* testing of a smaller cohort a more cost-effective option than the alternative proposed options.

In the rejoinder, the HTA group responded to the above analyses stating that the downward adjustment of the number of tests being ordered from 16,170 to 3,250 tests per annum seems unlikely and a very high risk assumption. Promoting broad upfront testing earlier in the clinical assessment is likely to result in a significant proportion of patients being tested who would not have been otherwise.

Sequential, reflex testing (option 1A) is estimated to additionally cost $3,825 for *JAK2* exon 12 testing, $66,300 for *CALR* testing, and $51,000 for *MPL* testing (focused DCAR, Table

12). Simultaneous testing (option 1B) was estimated to additionally cost $3,825 for *JAK2* exon 12 testing, $66,300 for *CALR* testing, and $66,300 for *MPL* testing (Table 10).

The MBS saving of using the reflex testing strategy is therefore estimated by the focused DCAR to be $15,300 per annum. This is based on not testing 180 *CALR*+ patients for *MPL* from the pool of ET and PMF patients suspected of having the condition. The focused DCAR notes that if the tests are performed sequentially, then a definitive result of double-negative status or MPL+ would take up to 4 weeks. Whether this saving is sufficient to compensate the additional work and delay in results is referred for MSAC's consideration.

Using NGS panels after the *JAK2* V617F screen (option 2) was estimated to additionally cost $203,490 for myeloproliferative panel tests (Table 6), and $177,905 for myeloid panel testing (Table 7; comprised of $154,700, plus $23,205 to test 25% of patients with *JAK2* V617+ PMF for other prognostic genes to inform decision-making – in particular, transplant eligibility).

Forward estimates

The focused DCAR provided forward estimates of costs to the MBS for two financial years (Table 11). The focused DCAR noted that the costs of the subsequent panel testing have not been increased beyond the 1-2% anticipated population growth (set at 1.5% in the table below), and *JAK2* V617F testing rates have been modelled as increasing by 5% per annum in line with the current testing rate expansion of Item 73325 (with the use as a single test assumed to be 93% of the rate of expansion of the current usage of Item 73325).

Table 11 Total costs to MBS of expansion of Item 73325 and creation of additional Item numbers to characterise genetic variants in the diagnostic work-up and management of patients with suspected classical MPNs

	Current year (2019-20)	Year 1 (2020-21)	Year 2 (2021-22)
Current MBS listing			
Services MBS (73325)	17,386	18,255	19,168
Subtotal cost (85%, $63.35 per test – see Table 8)	**$1,101,403**	***$1,156,454***	***$1,214,293***
Proposed MBS listing – Step 1 modified Item 73325 quantitative *JAK2* V617F			
Services: amended Item 73325	16,170	16,977	17,826
Subtotal cost (85%; $76.50 per test – see Table 2)	$1,237,005	$1,298,741	$1,363,689
Proposed MBS listing – Step 2 Option 1A *JAK2* Exon 12 for PV plus non-NGS testing methods with reflex *CALR/MPL* testing for ET and PV			
Services: new Item number non-NGS *JAK2* exon 12	50	51	52
Subtotal cost (85%; $76.50 per test – see Table 3)	$3,825	$3,902	$3,978
Services new Item number non-NGS *CALR/MPL*	1,380	*1401*	*1422*
Subtotal cost (85%; $85 per test – see Table 4)	$117,300	*$119,085*	*$120,870*
Total proposed Step 1 plus Step 2 Option 1A	$1,358,130	*$1,421,727*	*$1,488,537*
Incremental impact to MBS using Option 1A	**$256,727**	***$265,273***	***$274,244***
Proposed MBS listing – Step 2 Option 1B *JAK2* Exon 12 for PV plus non-NGS testing methods with simultaneous *CALR/MPL* testing for ET and PV			
Services: new Item number non-NGS *JAK2* exon 12	50	51	52
Subtotal cost (85%; $76.50 per test – see Table 3)	$3,825	$3,902	$3,978
Services new Item number non-NGS *CALR/MPL*	*780*	*792*	*804*

	Current year (2019-20)	Year 1 (2020-21)	Year 2 (2021-22)
Subtotal cost (85%; $170 per test – see Table 5)	$132,600	*$134,640*	*$136,680*
Total proposed Step 1 plus Step 2 Option 1B	$1,373,430	*$1,437,282*	*$1,504,347*
Incremental impact to MBS using Option 1B	**$272,027**	***$280,828***	***$290,054***
Proposed MBS listing – Step 2 Option 2 NGS Myeloproliferative gene panel for ET and PV and NGS Myeloid gene panel for PMF			
Services: new Item number NGS myeloproliferative panel	570	579	*588*
Subtotal cost (85%; $357 per test – see Table 6)	$203,490	$206,703	*$209,916*
Services new Item number NGS myeloid gene panel	*299*	*303*	*308*
Subtotal cost (85%; $595 per test – see Table 7)	*$177,905*	*$180,285*	*$183,260*
Total proposed Step 1 plus Step 2 Option 2	$1,618,400	*$1,685,729*	*$1,756,865*
Incremental impact on MBS using Option 2	**$516,997**	***$529,274***	***$542,572***

Source: based on focused DCAR Table 22, with the addition of figures for the current year, and option 1A (source: focused DCAR Tables 10, 12, 16 and 18). Italics indicate figures added (option 1A forward estimates, calculated using 1.5% growth rate as described) or corrected (comparator forward estimates cost corrected from $63.10 to $63.35 per test; option 1B service numbers corrected to number of simultaneous services; option 2 current and forward estimates corrected to include additional myeloid panel tests; option 2 myeloproliferative panel number of services corrected to also use the described 1.5% growth rate in year 2; all options forward estimates incremental impact on MBS corrected to use recalculated comparator cost) by the Department.

14. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
MSAC March 2019 considerations: 1. clinical algorithm, nature and order of testing; and the consequential proposed item descriptor 2. any pathologist-determinable reflex test or further testing by clinician 3. cost of testing (fee justification) 4. simplified linked prognostic variation analysis and utility of this testing for subsequent clinical management decisions (clinical effectiveness) 5. further analysis of current utilisation estimates and budget implications.	ESC consideration of addressment of MSAC's March 2019 requests: 1. The proposed stepwise testing clinical algorithm was supported by ESC. The initial *JAK2* V617F triage test reflects clinical practice, and having this as a separate MBS item supports monitoring use. 2. Restricting requestors to specialists and consultants may support appropriate usage, but could differentially limit access to testing for rural and remote patients. 3. If recommended for reimbursement, the proposed fee for a next-generation sequencing (NGS) panel of genes with established clinical utility will be dependent on the size of the panel. The total financial impact of adding an NGS panel after initial *JAK2* V617F testing is compared against single-gene testing. 4. Clinical effectiveness: the proposed testing including *CALR*, or a panel of tests, would improve confidence in ascertaining a diagnosis, and additionally provide information to patients on prognosis. NGS panel testing in patients with PMF who are transplant eligible would align with the WHO recommendations. 5. Although this was addressed as best as possible by an epidemiological approach, given the data limitations due to the rarity of myeloproliferative neoplasms, uncertainty remains.
Clinical management algorithm	Consider including broader next-generation sequencing (NGS) panel testing for genes with established clinical utility, instead of solely testing for *CALR*/*MPL* after a negative *JAK2* V617F test.
Item descriptors	Once per lifetime limit for testing is appropriate if intended for diagnosis. If no limit is set, consider early auditing of use. Consider exemplar gene panel as minimum for testing. Consider NGS panel testing at least for primary myelofibrosis.
NPAAC concerns	Consider whether a quality framework is required for any NGS testing.

ESC discussion

ESC noted that this application was for expanding MBS item 73325 (genetic variant testing for *JAK2* and *MPL* in MPNs) to include calreticulin (*CALR*) gene testing and patients with primary myelofibrosis (PMF), as advised by the Genetics Working Group. The MPNs represented by these three genes are polycythaemia vera (PV), essential thrombocytosis (ET) and PMF.

MSAC deferred its advice at its March 2019 meeting and requested the following:

- consultation with haematologists and pathology laboratories to determine the clinical algorithm, nature and order of testing if a simultaneous panel test or next-generation sequencing (NGS) is not considered optimal; and the consequential proposed item descriptor
- whether triage testing should include any pathologist-determinable reflex test or be separated into steps requiring further testing by clinician
- cost of testing (fee justification)

- simplified linked analysis summarising prognostic variation discerned by testing three genes across three subtypes of MPN and utility of this testing for subsequent clinical management decisions (clinical effectiveness)
- further analysis of current utilisation estimates and budget implications, as MSAC was concerned that the data indicated that increases in testing are more than the estimated number of patients needing an MPN diagnosis.

ESC noted that the Haematology Society of Australia & New Zealand (HSANZ) was targeted for clinical advice, and that there was a lack of consumer feedback for this application.

ESC noted that *CALR* testing can define the diagnosis in 20–30% of patients with ET who would otherwise rely on bone marrow morphology and exclusion of reactive causes; thus, a benefit of *CALR* testing is a reduction in other non-genetic testing methodologies. In addition, *CALR* testing also has prognostic value for patients with ET. ESC noted that other genes are involved and their variants are associated with poorer outcomes (increase in myelofibrosis, leukemia and death) and can support diagnosis of ET.

ESC also noted that *CALR* testing can help to improve confidence in diagnosis in 25–30% patients with PMF, and also has prognostic value in this condition. ESC noted that variants in other genes are also prognostic, and the number of pathogenic variants correlates with increasing leukemia risk and poorer overall survival. The genetic profile influences the timing of stem cell transplant in patients with PMF.

ESC noted that HSANZ recommends at least NGS panel testing in patients with PMF who are transplant-eligible, which is consistent with the 2016 World Health Organization diagnostic criteria.

ESC noted the complex clinical diagnostic algorithm, which was confirmed by a haematologist specialising in the diagnosis and treatment of MPNs. In the first instance, all patients would be recommended for *JAK2* V617F testing, which reflects current clinical practice, as *JAK2* V617F is, on average, present in more than 50% of MPNs; among patients with PV over 95% of patients have a *JAK2* mutation.

Patients with a negative *JAK2* V617F test would then progress to additional testing, either by:

- Options 1A or 1B, to test *JAK2* exon 12 and *MPL*/*CALR* either sequentially or simultaneously, respectively
- Option 2 is for an NGS myeloproliferative (MP) panel and the myeloid gene panel, which includes *JAK2* exon 12 and *MPL*/*CALR* testing.

ESC noted MSAC's March 2019 request that a triage approach be explored from a costing perspective (i.e. option 1A). However, the Department and the assessment group presented two other options (1B and 2) for consideration, which are clinically relevant.

ESC noted the applicant's preference in the pre-ESC response for all testing to be done through a single NGS panel instead of the stepwise progression. ESC agreed with the HTA group rejoinder that this approach does not support clinical decision-making after the initial *JAK2* V617F test result, to determine whether further genetic tests are required. ESC considered that the upfront panel approach would result in much more NGS testing than necessary, and it also does not reflect current clinical practice. ESC also noted that *JAK2* V617F testing may be used for monitoring, and thus including this test on a panel or alongside other genes may not be appropriate.

ESC noted the data provided on current pathology gene testing fees:

- $85 or $90 for *CALR* testing, stated by private pathology service websites in Australia, although this may be subject to change without notice and the methodology is not specified, or
- $250 for a single gene *CALR* test using NGS testing methodology from a public hospital laboratory, or
- from $250 (MP gene panel) to $600 (myeloid gene panel) for comprehensive testing including *JAK2* exons 12 and 14, *CALR* and *MPL* plus other prognostic genes
- no satisfactory fee structure could be identified for the option of an individual item for *CALR* gene testing for suspected ET/PMF due to the methodological differences between non-NGS and NGS gene testing and associated costs.

ESC noted that step one of the testing for *JAK2* V617F already costs the MBS $1.1 million each year through claiming MBS item 73325. Using a fee of $90 for *JAK2* exon 12 testing, plus a fee of $100 for each of *CALR* and *MPL* testing, and assuming the frequencies of each pathogenic variant in the clinical utility section of the focused DCAR, ESC noted that options 1A or 1B would add an additional $256,727 or $272,027 to the MBS each year, respectively. Option 2 would add an additional $516,997 to the MBS each year based on a fee of $90 for *JAK2* exon 12 testing, $420 for the MP panel and $700 for the myeloid panel.

Although more costly, ESC noted that including an NGS panel after the initial *JAK2* V617F test would help to "future proof" the MBS listing by allowing the NGS panels to be expanded in response to future clinical evidence. Furthermore, an NGS panel could include genes for the four other MPNs that are not currently encompassed by MBS-funded testing. ESC considered that this would likely not result in leakage because these other MPNs are rare. ESC noted that, if NGS panel testing is recommended, a decision will likely need to be made regarding handling the expansion of knowledge for these MPNs.

ESC noted that recommending any option (1A, or 1B, or 2) would require three different MBS items, including an amendment to the descriptor for MBS item 73325.

ESC noted that the key factor in the analysis driving the population deemed eligible is the utilisation of the existing item 73325. However, ESC noted that the current volume of testing does not reflect the expected incidence of PV, ET and PMF. ESC noted that one possible explanation is that general practitioners (GPs) receive laboratory reports for patients with high platelet or high haemoglobin results, and the reports recommend that the clinician consider *JAK2* V617F testing. This could lead to GPs ordering *JAK2* V617F testing prior to referral to a haematologist. However, ESC noted that from the information currently available it cannot be determined who is ordering the tests and therefore whether the current increase in the rate of testing will continue when the only service provided is *JAK2* V617F testing. ESC considered that a review may be required to monitor the appropriateness of test utilisation if MSAC recommends funding.

ESC noted that restricting requestors to specialists and consultants may be appropriate to encourage more appropriate use of the test, but this restriction will potentially impact rural and remote patients disproportionately due to their relative lack of access to specialist haematologists.

ESC noted that, as the assessment report only provided a costing study of testing, there is no information on the cost implications on other contingent health care resources.

ESC noted that, for an NGS panel, the National Pathology Accreditation Advisory Council (NPAAC) recommended that MSAC consider setting a minimum list of genes. ESC also queried whether a quality framework for testing multiple genes with NGS is necessary, to help establish an exchange program among laboratories.

Consumer issues noted by ESC included accessibility to testing for remote and rural patients, and ensuring NGS panels are appropriate for people under-represented in genomic databases. A more detailed cost breakdown was requested. In general, as the costs of genomics technologies decrease, fees for panel tests should be regularly reviewed to ensure they continue to reflect contemporary costs.

15. Other significant factors

Nil.

16. Applicant comments on MSAC's Public Summary Document

The Royal College of Pathologists of Australasia (the College) and Fellows would all like to express their delight in MSAC approving the revision to MBS item number 73325, which will result in better outcomes for Australian patients. The College thanks the Department for its assistance throughout MBS review and application process.

The item descriptors do not appear to fulfil their stated brief, which may be an error of omission. The working party have discussed this at length, and are of the opinion that feedback on this issue may be more meaningful once the draft descriptors have been made available.

17. Further information on MSAC

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