Medical Services Advisory Committee

Public Summary Document

Application No. 1125 – Molecular testing for myeloproliferative disease

Sponsor: **Pathology Services Table Committee, Department of Health and Ageing**

Date of MSAC consideration: **47th MSAC meeting, 4 December 2009**

Part A – Polycythaemia vera, essential thrombocythaemia and primary myelofibrosis

1. Purpose of Application

An application from the Pathology Services Table Committee, Department of Health and Ageing was made to MSAC to conduct a systematic review of the literature and an economic evaluation of molecular testing in myeloproliferative disorders.

2. Background

Molecular testing for the diagnosis of polycythaemia vera (PV), essential thrombocythaemia (ET) and primary myelofibrosis (PMF) can establish the presence or absence of specific mutations known to occur in patients with these disorders. In particular, the exon 14 *JAK2* V617F mutation is known to occur in 85–95% of patients with PV and approximately 50% of patients with ET and PMF. Other clinically relevant mutations include various mutations in *JAK2* exon 12 found in about 7% of patients with PV and mutations in the thrombopoietin receptor (*MPL* W515L or MPL W515K) which are found in a small percentage of patients with ET and PMF.

Molecular testing alone does not provide a diagnosis for these disorders and may not change patient management. The molecular test would be performed where there was a reasonable suspicion based on blood film, splenomegaly, and venous thromboembolism (VTE) or abnormal bleeding. The results of such analysis need to be considered in addition to other clinical and laboratory information in order to provide or exclude a diagnosis of PV, ET or PMF.

For patients with suspected PV, molecular testing would occur in addition to the ascertainment of serum erythropoietin levels. For some patients in whom these results are equivocal, bone marrow biopsy may also be required. For patients suspected of ET, molecular testing will aid in deciding whether a patient also requires bone marrow biopsy. For patients suspected of PMF, molecular testing will be performed in addition to bone marrow biopsy.

MSAC discussed the issue of false positive and false negative test results with molecular testing. It was pointed out that molecular testing had a very low false positive rate for myeloproliferative disorders. Molecular testing is only useful for verifying, or ruling in, a disease such as PV; it is not used to rule out a myeloproliferative disorder. The molecular testing presented in the submission only considered mutations in JAK2 (exons 14 and exons 12) and mutations in the MPL gene. MSAC acknowledged there are other mutations that may be relevant to the development of bcr-abl negative myeloproliferative disease. For this reason a negative test for JAK2 or MPL could not be used to exclude myeloproliferative disease in a given individual.

MSAC also agreed that as molecular abnormalities are increasingly being defined for a wide variety of haematological conditions and malignant diseases, there was a need for a simpler generic approach to assessing new molecular tests as they emerge and to coordinate that activity with Pharmaceutical Benefits Advisory Committee decisions where approval of a drug is restricted to patients having a particular molecular abnormality, ie. the issues of hybrid or co-dependent technologies currently being developed by the ESC for MSAC's broader consideration.

3. Clinical Need

MSAC noted that myeloproliferative disorders are quite rare and that few data were available regarding the prevalence of PV in Australia, but that for the first time, a molecular or specific diagnosis will be available for certain groups of these patients. MSAC noted that the test may lessen the need for some patients to have bone marrow biopsy, potentially improving access especially to regional patients.

MSAC noted that the test should be restricted to specialist request to reduce the likelihood of inappropriate testing.

4. Comparator

MSAC noted that the comparator is present management without genetic testing, which may involve bone marrow examination and (for PV) red cell mass measurement which is not available in all centres.

MSAC agreed that the comparator was appropriate, noting that molecular testing for myeloproliferative disorders has been adopted by the World Health Organization (WHO) in its diagnostic criteria for these conditions.

5. Safety

MSAC agreed there were no particular safety issues with molecular testing as testing is on blood or marrow aspirate already collected, and compared with bone marrow biopsies it is likely to be safer.

6. Clinical effectiveness

The available evidence base for all indications was poor and there was no direct evidence identified of the relative effectiveness of molecular testing in the diagnosis of PV, ET or PMF. Therefore, a linked evidence approach, which considered the diagnostic accuracy, change in management and change in patient health outcomes associated with the use of molecular testing, was undertaken for all three indications.

The linked evidence approach was complicated with respect to diagnostic accuracy due to the imperfect nature of the reference standard.

MSAC noted the benefit to patients and practitioners of having certainty of diagnosis at a molecular level, which will improve disease classification and may direct future therapy development, and may avoid bone marrow biopsy in several of these patients. Therefore the new test is more effective and objective than the comparator.

The issue of sensitivity and specificity of molecular testing was discussed by MSAC. It was pointed out that the qualitative molecular test to sequence the JAK2 gene may not detect small numbers of abnormal cells in a peripheral blood sample, and may thus produce false negative results. The quantitative molecular testing described in the submission was designed to detect JAK2 V617F mutations. This assay is more expensive but is highly sensitive and specific. The use of only the quantitative assay will clearly not detect mutations in other sites in the JAK2 gene mutations or in other genes that may cause myeloproliferative disease.

MSAC noted that there was no evidence to support the use of molecular testing to monitor the progress of these diseases or their response to therapy.

7. Cost-effectiveness

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 was also not possible due to the lack of evidence of measurable health outcomes. MSAC considered whether the use of a narrow, highly sensitive test to identify JAK2 and thus possibly avoid a bone marrow biopsy was cost-effective.

At a 100% sensitivity rate, there is potential for a cost saving of $1,073 per patient if the more expensive quantitative test is used and $1,216 per patient if the less expensive qualitative test is used. If 30% of tests are assumed to be qualitative and 70% quantitative, an estimated $1,115 cost saving per patient results. Even if the test used is only 50% sensitive, the economic model predicts there is still a cost saving per patient of around $400. Key drivers of the incremental cost comparison were the actual fee charged (the proposed MBS fee was used in the analysis), the reduction in the rates of bone marrow biopsy and abdominal ultrasound, and the sensitivity and specificity of the molecular test. It was pointed out that this test alone would not be likely to directly impact on the Medicare Safety Net.

It was agreed that the sensitivity and specificity of the test would influence to some extent whether molecular testing was cost effective, but that the exact specificity and sensitivity were unknown. Further it was noted that multiple molecular tests may be conducted as part of an analysis of a patient sample. Also the algorithm used by the molecular laboratory for testing samples from patients with myeloproliferative disease may vary between laboratories and also will evolve over time.

MSAC acknowledged that it was difficult to assign a value to diagnostic certainty, either for the patient or for the treating clinician. MSAC also agreed that the "base case" in the assessment report was likely to represent the "best case".

8. Financial/budgetary impacts

MSAC noted that insufficient evidence was available to establish the comparative safety and effectiveness of molecular testing in the diagnosis of PV, ET and PMF, and to support an economic evaluation. However, since cost savings may be realised as a result of the avoidance of bone marrow biopsy in patients suspected of PV and ET, an indicative economic evaluation was performed for the PV and ET scenarios. It was estimated that there could be savings of between $1.6 million and $1.8 million per year (1,500 potential patients) if there were a reduction in the number of bone marrow biopsies performed as a result of molecular testing being reimbursed.

MSAC agreed that cost savings for PV are primarily associated with the avoidance of bone marrow biopsy in patients investigated for suspected PV. The extent of savings will depend on both the diagnostic accuracy of molecular testing and serum erythropoietin determination, and the prevalence of disease in the population tested.

The cost of the molecular testing strategy for the investigation of ET would result in a financial burden of between $4,684,000 and $5,325,000 per year to the Australian healthcare system, which compares favourably with the cost of the comparator test strategy ($6,087,000). For those patients investigated in the private healthcare sector, molecular testing would result in a cost saving of between $195,000 and $337,000 per year relative to the comparator strategy. The States/Territories would also benefit from a cost saving of between $152,000 and $281,000 per year relative to the comparator, depending on the molecular methods used.

The savings described are expected to depend on the diagnostic accuracy of JAK2 analysis and the prevalence of the mutation within the population tested.

Savings are not expected to be realised as a result of avoiding bone marrow biopsy in patients with PMF. The financial impact to the Australian healthcare system overall of molecular testing in the investigation of PMF would be an additional cost of $16,000 and $41,000 per year. This includes an estimated cost to the Commonwealth of between $4,000 and $25,000 to investigate 140 patients with PMF in the private sector. The States/Territories are expected to incur a cost of between $3,000 and $8,000 per year for the 35 patients expected to be investigated for PMF in the public healthcare system.

In discussing possible costs to the States/Territories and the MBS for qualitative and quantitative molecular tests, MSAC also questioned the calculation of the MBS rebate in the economic model at 75% rather than 85% of the MBS fee, and also unit cost per test to the MBS for the qualitative item which was considerably lower than either 75% or 85% of the schedule fee.

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

MSAC agreed that in the appropriate clinical setting, positive molecular testing gave diagnostic certainty and reassurance for some patients with suspected myeloproliferative disease and may in some cases avoid a bone marrow biopsy.

MSAC voted to advise the Minister that:

- **Polycythaemia vera (PV) and essential thrombocythaemia (ET)**

  In patients with either suspected PV or ET, MSAC noted that a positive test for the *JAK2* mutation would generally obviate bone marrow biopsy, although the frequency of mutations is much higher in PV (85-90%) than in ET (50%). Economic modelling demonstrates some cost savings, primarily through a reduction in the rate of bone marrow biopsy.

- **Primary Myelofibrosis (PMF)**

  MSAC agreed that molecular testing is an adjunct to the diagnosis of PMF. It does not avoid the need for bone marrow biopsies, and thus would represent an additional cost.

10. MSAC's advice to the Minister

MSAC agreed that, for a proportion of patients with suspected PV or ET, but not PMF, molecular testing may remove the need for and cost of a bone marrow biopsy and may improve diagnostic certainty.

On this basis MSAC supported public funding of molecular testing for polycythaemia vera and essential thrombocythaemia. As the number and sequence of actual molecular tests may vary, the MBS item descriptor(s) for molecular testing of a patient for either of these two conditions should reflect the intention of confirming the clinical diagnosis with the most efficient use of suitable molecular tests, and that a positive molecular test should obviate the need for further testing for the clinical diagnosis once a definitive molecular diagnosis has been established.

MSAC did not support public funding of molecular testing for primary myelofibrosis.

11. Context for Decision

This advice was made under the MSAC Terms of Reference:

- Advise the Minister for Health and Ageing on the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported.
- Advise the Minister for Health and Ageing on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness.
- Advise the Minister for Health and Ageing on references related either to new and/or existing medical technologies and procedures.
- Undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC) and report its findings to the AHMAC.

12. Linkages to Other Documents

MSAC's processes are detailed on the MSAC Website at: www.msac.gov.au.

The MSAC Assessment Report is available at http://www.msac.gov.au/internet/msac/publishing.nsf/Content/MSACCompletedAssessments1120-1140