Title:	Molecular testing for myeloproliferative disease *Part A – Polycythaemia vera (PV), essential thrombocythaemia (ET) and primary myelofibrosis (PMF)* *Part B – Systemic mast cell disease (SMCD), hypereosinophilic syndrome (HES) and chronic eosinophilic leukaemia (CEL)*
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Part A - Polycythaemia vera (PV), essential thrombocythaemia (ET) and primary myelofibrosis (PMF)

Aim:

To assess the safety, effectiveness and cost-effectiveness of the addition of molecular testing for relevant mutations to the investigation of suspected PV, ET and PMF. Consequently the comparator for this assessment is the investigation of suspected PV, ET and PMF without molecular testing.

Results and Conclusions:

Safety:

There was a lack of data regarding the safety of molecular testing in the diagnosis of PV, ET and PMF. However, it can be readily argued that any adverse events associated with molecular testing would be as a result of sample collection. The risk of serious adverse events is expected to be low.

Furthermore, as molecular testing is expected to result in the avoidance of bone marrow (BM) biopsy in the majority of suspected PV cases, and in approximately 30% of patients with suspected ET, it is likely that the addition of molecular testing to the investigation would be safer than investigation without molecular testing.

It is not expected that patients suspected of PMF would avoid BM biopsy following molecular testing hence, its addition to the investigation of these patients, would be as safe as the comparator.

Effectiveness:

Direct evidence of a change in patient health outcomes following the addition of molecular testing to the investigation of suspected PV, ET and PMF was unavailable. Hence, a linked evidence approach was used to identify evidence of diagnostic accuracy, change in management and treatment effectiveness.

Evaluation of diagnostic accuracy was complicated by the imperfect nature of the reference standard which is unlikely to be as accurate as the investigation with molecular testing. Evidence, although limited, was available to indicate that molecular testing would change some diagnoses determined on the basis of testing with the reference standard. Furthermore, evidence also indicated that treatment was likely to change as a result of more accurate diagnosis following the use of molecular testing.

In patients investigated for suspected ET or PMF, no comparative data of diagnostic accuracy was available. However, it would be reasonable to expect that a change in management would occur as a result of more accurate diagnosis using molecular methods. As disease-relevant

mutations are only present in 50% of patients who have ET and PMF, the overall benefit of molecular testing in the investigation of these diseases remains uncertain.

Cost Effectiveness:

Although there was insufficient evidence to support an economic evaluation, there are possible cost savings to be realised due to the avoidance of BM biopsy in patients suspected of PV and ET. Hence, an indicative economic evaluation was performed for these scenarios to determine the diagnostic accuracy that would be required of an investigation with molecular testing in order to realise such cost savings. In addition, the cost implications to the Australian healthcare system were estimated for all indications.

Polycythaemia vera

For an estimated 1,500 investigations per year, cost savings for the Australian health system overall are expected to range from $1,610,000 to $1,823,000.

These cost savings are primarily associated with the avoidance of BM biopsy in patients investigated for suspected PV. Although the extent of savings is dependent on the diagnostic accuracy of molecular testing, serum erythropoietin determination and the prevalence of disease in the population tested, it is likely that cost savings between $445 and $1,175 per patient would still be realised even if the sensitivity and specificity of molecular testing was no better than 50%.

Essential thrombocythaemia

It is expected that 4,500 patients would be investigated per year as a result of suspected ET. The cost of the molecular testing strategy for the investigation of ET would result in an annual cost saving to the Australian healthcare system in the range of $762,000 - $1,403,000. These savings are likely to depend on the diagnostic accuracy of *JAK2* analysis as well as the prevalence of the mutation within the population tested. The base case analysis of the impact of the diagnostic accuracy of molecular testing and the prevalence of the mutation indicates that cost savings are likely to be realised when the sensitivity and specificity of molecular testing is greater than 60%. If the population tested were expanded to reflect a more clinically relevant scenario, the sensitivity and specificity required to be a cost-saving testing strategy would need to increase to at least 80–85%.

Primary myelofibrosis

The addition of molecular testing to the investigation of suspected PMF is not expected to enable the avoidance of bone marrow biopsy. Hence, savings are not expected to be realised in this group of patients.

The financial impact of molecular testing to the Australian healthcare system overall would be an additional cost of $16,000 – $41,000 per year for the estimated 175 investigations per year.

Part B – Systemic mast cell disease (SMCD), hypereosinophilic syndrome (HES) and chronic eosinophilic leukaemia (CEL).

Aim:

To assess the safety, effectiveness and cost-effectiveness of the addition of molecular testing for relevant gene rearrangements to the investigation of suspected SMCD, HES or CEL. The comparator for this assessment is the investigation of suspected SMCD, HES or CEL without molecular testing.

Results and Conclusions:

Safety:

There was a lack of data regarding the safety of molecular testing in the investigation of SMCD, HES and CEL. Again, it is reasonable to expect that any adverse events would be as a result of sample collection, and those that did occur are unlikely to be of a serious nature.

Effectiveness:

SMCD

Weak direct evidence was available from one study to suggest that health outcomes improved for a very small subset of patients with SMCD associated with eosinophilia, after the addition of molecular testing to the diagnostic strategy.

As direct evidence was limited, a linked approach was undertaken to identify evidence of diagnostic accuracy, change in management and treatment effectiveness. Studies of diagnostic accuracy only evaluated the analysis of *KIT* mutations in patients with and without SMCD. In this scenario, molecular testing is unlikely to report any false positives (specificity = 100%) however, it is unable to rule out the presence of SMCD (sensitivity = 88–99%) as the mutation is not present in 100% of people with the disease.

No evidence was available which identified a change in management subsequent to the inclusion of molecular testing in the investigation of these diseases. However, the direct evidence implies that patients with the *FIP1L1-PDGFRA* rearrangement would receive imatinib mesylate therapy. Additionally, studies in other populations with primary eosinophilia have identified this rearrangement as a target for imatinib mesylate therapy. This provides further argument that the addition of molecular analysis to the testing strategy is likely to result in a change of management.

Because of this likely change in management, treatment effectiveness was assessed only in patients with SMCD with associated eosinophilia. Low level evidence showed there was considerable benefit from imatinib therapy in patients with a *CHIC2* deletion compared to patients with the *KIT* mutation.

Overall, the available evidence indicates that the investigation of patients with SMCD with the addition of molecular analysis is likely to be at least as effective as the comparator test strategy in providing improved patient outcomes. In patients with suspected SMCD associated with a persistent eosinophilia, the addition of molecular analysis is likely to be more effective than the comparator with the caveat that molecular analysis in patients with suspected SMCD should consist of both *KIT* and *FIP1L1-PDGFRA* analysis.

HES and CEL

Direct evidence of the effectiveness of molecular testing was available only from a small case series that provided weak evidence of a benefit in health outcomes to patients diagnosed with CEL with the addition of molecular analysis to the testing strategy.

Given that the effectiveness of imatinib therapy has already been established in this population, linked evidence required evidence of improved diagnostic accuracy to establish that patient outcomes are likely to improve as a consequence of molecular testing.

Only low-level evidence was available which assessed test accuracy and the results were inconsistent. In the absence of comparative data, it is not possible to establish the accuracy of diagnosis with molecular analysis; however, as it would be used in addition to the

comparator, it is likely that it would be at least as accurate as diagnosis without molecular analysis.

Economic considerations:

SMCD

In the absence of adequate data and some uncertainty regarding the extent of any net benefit of using molecular analysis in the diagnosis of SMCD, only the financial implications have been considered.

With an expected 134 investigations required per year, it is estimated that 80% of investigations would be eligible for Medicare reimbursement. Consequently, the cost implications of the addition of molecular analysis of both *KIT* and *FIP1L1-PDGFRA* to the diagnostic strategy would result in a cost of $22,000 per year.

The cost to the Australian healthcare system overall, including the cost of treatment with imatinib mesylate in patients with SMCD associated with eosinophilia and the *FIP1L1-PDGFRA* rearrangement, would result in an additional cost of $234,000 per year. The majority of this can be attributed to the cost of imatinib mesylate therapy.

HES and CEL

Again, the absence of comparative evidence for the effectiveness of molecular analysis in the diagnosis of HES and CEL prevented formal economic evaluation of this testing strategy. Consequently, the direct costs have been considered with respect to the Australian healthcare system overall and to the Commonwealth.

The expert opinion of the Advisory Panel estimated that up to 50 investigations of suspected HES or CEL would be required per year, of which 80% would be eligible for Medicare reimbursement. Overall, the addition of molecular analysis would result in an additional burden of $11,800 to the Australian healthcare system per year.

Methods:

Medline, Embase, The Cochrane Library, and several other biomedical databases, HTA and other internet sites were searched (2005 - February 2009). Specific journals were handsearched and reference lists pearled. Studies were included in the review using pre-determined PICO selection criteria and reasons for exclusion were documented. Study quality was appraised, data extracted in a standardised manner, and findings synthesised qualitatively.

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