Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1144 – Pathology tests for latent mycobacterial infection

Applicant: Dr Miriam Paul.

Date of MSAC consideration: 29 March 2012.

1. Purpose of application

In October 2009, the Department of Health and Ageing received an application from Dr Miriam Paul, requesting MBS listing of interferon gamma release assays (IGRAs) for diagnosis of latent tuberculosis infection (LTBI).

IGRAs are whole-blood *in vitro* tests used to diagnose latent infection with *Mycobacterium tuberculosis* (*M. tuberculosis*) by measuring immunological response to *M. tuberculosis*-specific antigens. When whole blood taken from an individual infected with *M. tuberculosis* is mixed with *M. tuberculosis*-specific antigens, effector T-cells that recognise the antigens are stimulated and release interferon-gamma (IFN-γ). The production and subsequent measurement of IFN-γ forms the basis of IGRAs. The use of IGRA tests for the LTBI is a relatively new approach.

Tuberculosis (TB) is an infectious bacterial disease caused by pathogens from the *M. tuberculosis* complex (MTBC). It is transmitted primarily by airborne droplet nuclei from individuals with pulmonary or laryngeal TB. The primary manifestation in infected individuals who develop the disease is pulmonary TB, but it can occur in any organ of the body. Symptoms include persistent cough, chest pain, blood-stained sputum, weakness or fatigue, weight loss, loss of appetite, chills, fever, and sweating at night.

Latent tuberculosis infections are considered a serious international public health issue because of the risk of progression to active disease. Patient groups with an increased risk of LTBI are immunosuppressed and immunocompromised patients, immigrants from high incidence countries, healthcare workers, and recent contacts of patients with active tuberculosis.

2. Background

IGRA testing for LTBI is listed on the MBS, item 69471. The descriptor is "Test for cell mediated immunity in blood for the detection of active tuberculosis or atypical mycobacterial infection in an immunosuppressed or immunocompromised patient".

3.   Prerequisites to implementation of any funding advice

QuantiFERON®-TB Gold ELISA (single device) was listed on the TGA in May 2004 while QuantiFERON®-TB Gold (QTF-G) and QuantiFERON®-TB Gold In-Tube (QTF-GIT) (device kits) were listed in April 2007. T.SPOT®-TB is not TGA approved. Given the need to include data across the range of IGRAs, the decision was made to include T.SPOT®-TB, which is not TGA-approved but used worldwide.

4.   Proposal for public funding

The applicant did not provide a proposed item descriptor. The assessment report used an estimate of $55.10 for an IGRA test. Pathologists conduct IGRA blood testing.

5.   Consumer Impact Statement

There is a concern that MBS listing of IGRAs may affect the availability of tuberculin skin test (TST), particularly in remote areas. The potential effect on consumers in remote areas was sought. Respondents from the Northern Territory acknowledged the potential benefit of IGRAs, but they also noted numerous logistical issues, particularly for communities that are located considerable distances from pathology laboratories.

MSAC noted these concerns, but also noted that some IGRA testing is already being conducted in patients in remote areas.

6.   Proposed intervention's place in clinical management

It was decided to consider the scenario in which IGRA testing would replace the tuberculin skin test (TST), or Mantoux test, for the detection of LTBI in high-risk patients.

7.   Other options for MSAC consideration

Nil.

8.   Comparator to the proposed intervention

The appropriate comparator for the assessment of IGRAs for the diagnosis of LTBI in the target populations is the TST.   TST is listed on the MBS, having item number 73811 and an item descriptor of "Mantoux test". TST was listed on the MBS in February 1992.

9.   Comparative safety

Studies that specifically investigated the safety of IGRAs as a test, including use for the diagnosis of LTBI were not identified. IGRAs require patients to undergo venipuncture for collection of blood. It is anticipated that the only safety concerns likely to be associated with this intervention are those associated with venipuncture.

Clinical management of LTBI, including IGRAs is considered to be as safe as current clinical management without the use of IGRAs.

10.   Comparative effectiveness

Assessment of comparative effectiveness focussed on whether IGRAs, compared with TST, more accurately predict if patients with LTBI will or will not develop active TB disease.

A review of the literature identified a total of 18 studies with follow-up evidence indicating whether patients progressed to active TB in the longer term. All were non-randomised, prospective studies assessing the diagnostic accuracy of IGRAs. Of the 18 studies, six compared QTF-GIT and TST, four compared QTF-G and TST, three compared T.SPOT®.TB and TST, three compared ELISPOT and TST, and two compared QTF-GIT, T.SPOT®.TB and TST.

Meta analyses were conducted to compare the proportions of patients testing positive or negative to either IGRA or TST who then developed active TB within the study periods. Three overall comparisons across the two tests were made:

      i.   an assessment of false-negatives, that is, the proportion of patients who had a negative test result but who developed active TB.

      ii.   an assessment of true-positives, that is, the proportion of patients who had a positive test result and who developed active TB.;

      iii.   an assessment of overall test positives, that is, the proportion of patients who had a positive test result.

Table 1 provides a summary of results comparing IGRAs and TST. While there are no statistically significant differences in the occurrence of false-negatives or true-positives between IGRAs and TST, the analysis of overall positives demonstrates that significantly fewer patients test positive to IGRA than to TST (OR [odds ratio] = 0.42; 95% CI: 0.31, 0.57).

Table 1:   Results of meta-analyses comparing IGRAs and TSTs for the development of TB

	QTF-GIT vs. TST OR (95% CI)	QTF-G vs. TST OR (95% CI)	T.SPOT®-TB vs. TST OR (95% CI)	ELISPOT vs. TST OR (95% CI)	Overall OR (95% CI)
False-negatives	0.87 (0.43, 1.77)	0.07 (0.00, 1.26)	0.43 (0.11, 1.73)	0.99 (0.50, 1.96)	0.80 (0.51, 1.27)
True-positives	1.80 (0.89, 3.67)	2.08 (0.38, 11.48)	1.17 (0.60, 2.29)	1.49 (0.54, 4.11)	1.42 (1.02, 1.99)
Overall positives	0.31 (0.18, 0.54)	0.21 (0.04, 1.07)	0.95 (0.25, 0.81)	0.45 (0.25, 0.81)	0.42 (0.31, 0.57)

TST = tuberculin skin test; QTF-G = QuantiFERON®-TB Gold; QTF-GIT = QuantiFERON®-TB Gold In-Tube; ELISPOT = enzyme-linked immunosorbent assay; TB = tuberculosis; OR = odds ratio; NR = not reported.

Given that the smaller proportion of patients testing positive with IGRA occurs with no increase in risk of false-negatives, this suggests that IGRA may be a more efficient test for LTBI than TST. The main advantages of IGRA vs. TST would be to reduce the number of patients under surveillance and the proportion of these who might undergo treatment. The assessment report captured these reductions mainly in terms of cost savings rather than as changes in health outcomes for patients.

11.   Economic evaluation

The applicant did not provide a proposed fee for IGRAs. Advice provided by the Victorian Infectious Disease Reference Laboratory (VIDRL) indicated that the cost of QTF-GIT is approximately $48.00. In addition, IGRAs also require payment of a pathology patient episode initiation fee.

Given the lack of available information regarding cost for IGRAs and longer-term outcomes, a simplified cost comparison has been conducted. It is not possible to accurately estimate costs to the MBS or Government.

Using an estimated cost of $55.10 for an IGRA test, a cost comparison analysis was conducted. This analysis indicated that testing for LTBI using IGRAs appears to be cost-saving compared to using TST, with an estimated saving of $35.52 per patient.

This may be a conservative estimate because the cost of adverse drug reactions in patients unnecessarily treated with prophylaxis (due to false-positive results) are not included. Sensitivity analyses indicate that the analysis is most sensitive to the extent of difference in proportion of patients testing positive to IGRA compared with proportion testing positive to TST.

As there is a lack of information available regarding the use of IGRAs, in particular, there is uncertainty concerning potential shift from the public to the private sector and a lack of information regarding the cost of IGRAs; therefore, an estimate of expected uptake and cost to the MBS has not been provided.

12.   Financial/budgetary impacts

An estimate of the number of IGRAs likely to be conducted has not been calculated because of the lack of information available. To derive the number of tests likely to be used, there would have to be an estimate of the proportion of tests that may shift from the public to the private system, as well as an estimate of the number of TSTs conducted. In addition, the applicant did not provide a proposed fee for IGRAs, and consequently an assessment of the financial implications of the listing of the test cannot be conducted.

13.   Key Issues for MSAC

With respect to the evidence and conclusions for the safety of IGRAs and given the nature of the tests, it is not anticipated that there will be any additional safety issues beyond those associated with collection of blood by venipuncture.

While there is considerable evidence available assessing the concordance of IGRAs and TST, the available evidence addressing comparative predictive accuracy for progressing to active TB is based on relatively short-term studies. Although there is a statistically significant advantage for IGRAs compared to TST in overall positive test results, this advantage does not occur across all of the outcomes.

The comparison of IGRAs and TST indicates no statistically significant difference between the two tests regarding the occurrence of false-negative or true-positive results. The comparison of overall positive test results indicates that IGRAs may be a more efficient test for LTBI than TST. Significantly fewer patients tested positive to IGRA than to TST, with no increase in risk of false-negatives. However, the comparison of overall positive results had high heterogeneity ($I^2 = 95\%$) so the results should be interpreted with caution.

14.   Other significant factors

The National Tuberculosis Advisory Committee (NTAC) has recently released a draft position statement, pending approval by the Communicable Diseases Network Australia (CDNA) on IGRAs for use in the detection of LTBI. NTAC has stated that a review of recent literature on IGRAs indicates that the evidence has not clearly demonstrated that IGRAs are superior to TST. NTAC also noted a continuing absence of cost-effectiveness studies of IGRAs under Australian TB program conditions, and that the long history of use of TST and longitudinal data provides important predictive information that is not yet available with IGRAs. On this basis, NTAC has concluded that TST remains the preferred test for LTBI in most patient groups. NTAC has recommended that IGRA may be used as supplemental tests to improve specificity in screening immunocompetent subjects and also be used in addition to TST in immunocompromised patients at high risk of LTBI.

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

MSAC formed the view that, although it is not a notifiable condition, latent tuberculosis infection (LTBI) is an important public health issue. The tuberculin skin test (TST), or Mantoux test, is a well-established test in this context, with a long history of use and well-supported by longitudinal data, and retains an important place on the MBS. However, there are some subgroups of patients with an increased risk of LTBI where TST is known to be sub-optimal, and some subgroups where the interferon gamma release assay (IGRA) may be preferred or added.

MSAC noted that IGRA involves venipuncture, which is acceptable level of safety typical of other blood-based tests. TST is known to occasionally elicit strong reactions in some patients which can be associated with significant patient morbidity over several weeks. The assessment of comparative analytical performance across TST and IGRA is hindered by the absence of a clear reference standard. Reliance on the subsequent development of active tuberculosis as a reference standard is further limited by the duration of follow-up in the included studies being about two years on average.

A total of eighteen studies and 15,698 test results contributed to the assessment of comparative analytical validity. This focussed on three test performance measures, with meta-analyses showing statistically significantly increased odds of true positives (odds ratio = OR 1.42; 95% confidence interval = CI: 1.02, 1.99), statistically significantly decreased odds of overall test positives (OR 0.42; 95% CI: 0.31, 0.57) and non-significant difference in odds of false negatives (OR 0.80; 95% CI: 0.51, 1.27). These data were interpreted as suggesting that IGRA may be a more efficient test for LTBI than TST.

MSAC noted these analyses did not compare false positive rates (which would be the measure of interest to compare specificity), did not distinguish between patients who had been BCG-vaccinated or not, excluded instances of test failures or indeterminate results with IGRA (which would require a repeat IGRA test to resolve). MSAC considered that there is less overall experience with IGRA than with TST.

MSAC noted that the economic evaluation presented relied on the conclusion of greater efficiency of IGRA over TST, which resulted in claims of cost offsets to the MBS and patients (due to a decreased need to follow patients with test positive results) and cost offsets to the PBS and patients (due to a consequential decreased need for isoniazid therapy). The cost analysis was limited to comparing single use of TST or IGRA as alternatives with an

equal 10% rate of repeat testing with either TST or IGRA. Options involving sequential testing (TST followed by IGRA or IGRA followed by TST) was not considered.

An increased fee ($55.10 compared with the current $35.15) was proposed based on advice on the cost of one test option from one laboratory in Victoria. This basis was considered weak given that the relevant bulk billing rate across Australia is currently 86%. When associated GP costs are included, the overall costs of performing each test and interpreting its results was estimated to cost $99 for IGRA and $62.20 for TST, an increase of $30.58.

Based on an estimate test positive rate of 51% for TST and 34% for IGRA (a difference of 17%), cost off-sets of $33.40 for MBS items and $12.71 for PBS items were estimated, resulting in a claim of net saving both for the MBS items and also for the MBS and PBS items overall. These estimates included both the government and patient perspective. The current rate of test positive results for TST is unknown, so the applicability of these results and cost analysis to the MBS was unclear.

Sensitivity analyses showed that these estimates of net saving in the base case were most sensitive to extent of difference in the proportion of test positive results and net savings were no longer present for differences below 8% (i.e. when the difference was halved).

MSAC noted that the likelihood and extent of any savings would be increased if the current MBS fee were used rather than the proposed fee; the costs of managing isoniazid side effects were added; and the probability of dual testing of TST were increased. The likelihood and extent of any savings would be decreased if the probability of dual testing of IGRA were increased due to a greater rate of indeterminate results.

16. MSAC's advice to the Minister

MSAC advised the Minister that it supports the extension of the current item descriptor for the interferon gamma release assay (IGRA) to include additional subgroups of patients. The final item descriptor should be finalised by the Department in consultation with relevant groups such as the National Tuberculosis Advisory Committee (NTAC) and then with the MSAC Executive.

MSAC advised the Minister that the options to extend the item descriptor including the following subgroups of patients in descending order of the strength of evidence to support the advice from MSAC for that subgroup:

1. patients about to commence long-term immunosuppressive therapy (e.g. tumour necrosis factor [TNF] inhibitors), because it is clinically sensible to perform this assessment before starting long-term treatment with such therapies, rather than waiting until the patient becomes immunosuppressed
2. patients previously vaccinated with the Bacille Calmette Guérin (BCG) vaccine, because this is known to increase the likelihood of a false positive test result with the tuberculin skin test (TST), or Mantoux test, and so the higher specificity of IGRA in BCG-vaccinated patients especially is important
3. patients considered at low risk of latent tuberculosis bacillus infection (LTBI) with a positive TST result, because the evidence of comparative analytical validity between the two test options indicated a significantly lower test positive rate for IGRA without

a significantly increased rate of false negatives, leading to a reduction in unnecessary follow-up and unnecessary treatment

4. patients considered at high risk of LTBI with a negative TST result, because the evidence available was not analysed in terms of test negative rates and rates of false positives.

MSAC also advised the Minister that there was an insufficient basis to support any increase in the MBS fee associated with IGRA testing, noting the high proportion of bulk billing for current IGRA testing.

17.   Context for decision

This advice was made in accordance with MSAC Terms of Reference.

MSAC is to:

Advise the Minister for Health and Ageing on medical services that involve new or emerging technologies and procedures and, where relevant, amendment to existing MBS items, in relation to:

- the strength of evidence in relation to the comparative safety, effectiveness, cost-effectiveness and total cost of the medical service;
- whether public funding should be supported for the medical service and, if so, the circumstances under which public funding should be supported;
- the proposed Medicare Benefits Schedule (MBS) item descriptor and fee for the service where funding through the MBS is supported;
- the circumstances, where there is uncertainty in relation to the clinical or cost-effectiveness of a service, under which interim public funding of a service should be supported for a specified period, during which defined data collections under agreed clinical protocols would be collected to inform a re-assessment of the service by MSAC at the conclusion of that period;
- other matters related to the public funding of health services referred by the Minister.

Advise the Australian Health Ministers' Advisory Council (AHMAC) on health technology assessments referred under AHMAC arrangements.

MSAC may also establish sub-committees to assist MSAC to effectively undertake its role. MSAC may delegate some of its functions to its Executive sub-committee.

18.   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/app1144-1.