



Australian Government
Medical Services Advisory Committee

Public Summary Document

Application No. 1234 – An assessment of nucleic acid amplification testing for active mycobacterial infection

Applicant: Douglass Hanly Moir Pathology Pty Ltd

Date of MSAC consideration: MSAC 63rd Meeting, 1-2 April 2015

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, see at www.msac.gov.au

1. Purpose of application and links to other applications

Douglass Hanly Moir Pathology Pty Ltd submitted an application to the Department of Health requesting Medicare Benefits Schedule (MBS) listing of Nucleic Acid Amplification Testing (NAAT) to diagnose:

- (1) *Mycobacterium tuberculosis* (MTB) infections in persons with clinical signs and symptoms of tuberculosis (TB); or
- (2) Non-tuberculous mycobacteria (NTM) infections in patients suspected of having an NTM infection.

2. MSAC's advice to the Minister

After considering the available evidence presented in relation to safety, clinical effectiveness and cost-effectiveness of nucleic acid amplification testing (NAAT) to diagnose:

- *mycobacterium tuberculosis* (MTB) infections in persons with clinical signs and symptoms of tuberculosis (TB)
- non-tuberculosis mycobacteria (NTM) infections in patients suspected of having an NTM infection.

MSAC did not support a change in public funding of NAAT because of the uncertain incremental clinical benefit in a poorly defined patient population which made the cost-effectiveness indeterminable.

MSAC noted that there were certain Australian populations where there may be a more pressing need for rapid diagnosis and management of TB infections and proposed the applicant could consider investigating the clinical efficacy and cost effectiveness in these populations.

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

MSAC noted that clinical judgement was the determinant of treatment strategy for patients with signs and symptoms of TB in both the current and proposed treatment algorithm. This was the case, irrespective of whether suitable specimens for acid-fast bacilli (AFB) smear microscopy were available. Further to this, evidence suggests that clinicians would be reluctant to change patient management based on NAAT results.

MSAC considered the comparative safety of the NAAT test and noted that more patients will receive a false positive NAAT test compared to a false positive AFB test, indicating they could potentially have TB and will likely receive unnecessary anti-TB treatment with potential for an adverse reaction.

MSAC considered evidence of clinical efficacy of NAAT testing and noted that much of the evidence has been produced in high prevalence populations, so the applicability to a low prevalent Australian population may be limited. MSAC noted that there was consensus in the evidence that NAAT provided a comparably rapid diagnosis of TB (usually within 48 hours), particularly in patients who are AFB-smear negative. In terms of changes to patient management, studies that were conducted in low-incidence settings suggest clinicians would not change management based on NAAT results. For diagnosis of NTM in AFB-smear positive or negative patients, MSAC considered there was insufficient evidence to demonstrate the accuracy of NAAT in this patient population and was not convinced that there would be an impact on health outcomes using NAAT in addition to AFB microscopy testing. MSAC also noted advice from the National Tuberculosis Advisory Committee (NTAC) that MBS guidelines for NTM NAAT appear unnecessary.

MSAC noted that the use of NAAT in conjunction with AFB had a high false positive rate at 12% compared to 6% when using NAAT alone and 2% when using AFB alone. The committee noted issues estimating the false positive rate when the reference standard (culture and sensitivity test (C&S test)) is imperfect; a proportion of the false-positive patients may actually have TB. MSAC expressed concern about the clinical need for the proposed test, particularly in the general Australian population where the incidence of mycobacterial infection is low.

MSAC noted that there were certain Australian populations where there was a higher prevalence and there may be a more pressing need for rapid diagnosis and management of TB infections. In particular, Aboriginal and Torres Strait Islander people have rates that are 11 times higher than non-indigenous people. MSAC considered that the clinical need in this population as well as other specific populations such as remote communities and refugee centres will potentially be significant, and encouraged the applicant to investigate the clinical efficacy and cost effectiveness in these populations in a resubmission of their application. MSAC appreciated the importance of the public health issue that this test is attempting to address, but noted that the more pressing issue may be getting people, particularly in high risk communities, to access health care and not the test itself.

MSAC noted that of the five studies investigating the cost-effectiveness of NAAT in low prevalence populations, only three found the test to be cost-effective. The ICER for NAAT was \$90,728 per QALY, however this was sensitive to changes in TB prevalence and specificity of the test. MSAC considered population prevalence to be an important issue, and requested that the applicant reconsider the eligible population for this test. A more focused item descriptor that reserves NAAT testing for communities with a higher TB incidence may be more cost effective.

MSAC also noted that economic modelling based on disease transmission would provide more meaningful information as in the current model the cost of utility is only accruing to a second infection. More complex models would be able to assess utility in the prevention of two to three subsequent infections.

MSAC noted advice from NTAC that new assays are due to be available in the next two to five years which have technical efficiency similar to the C&S test, but with a short turnaround time.

4. Background

MSAC has not previously considered this application. However, MSAC considered a related application (1144 - Pathology testing for latent mycobacterial infection), in March 2012 and April 2013.

5. Prerequisites to implementation of any funding advice

The most widely used commercial NAAT for detection of MTB is endorsed by the World Health Organisation (WHO) and has been approved by the Therapeutic Goods Administration (TGA) for use on patient material, regardless of the AFB smear microscopy result. There are no commercially available kits for the detection of NTM approved by the TGA in Australia.

The Guidelines for Australian mycobacteriology laboratories (National Tuberculosis Advisory Committee 2006) state that ‘All NAAT methods must be properly validated before routine use’. Commercial tests that have been modified (e.g. for a novel use) and in-house methodologies must be validated according to the National Pathology Accreditation Advisory Council (NPAAC) guidelines for requirements for the development and use of in-house in-vitro diagnostic medical devices

6. Proposal for public funding

NAAT are part of the public health workup for the diagnosis and management of TB, in a person with clinical signs and symptoms of active TB infection or for the diagnosis and management of mycobacterial infection other than TB.

Treatment for TB is provided free of charge to public patients in Australia. The test to confirm active mycobacterial infection is covered by the state and territory health systems if the patient is a public patient in a public hospital or by the MBS if the test is being performed for a private patient and is listed on the MBS. The tests currently listed on the MBS are AFB microscopy and culture of suitable specimens. NAAT is not currently listed on the MBS.

Mycobacterium tuberculosis (MTB) infections

TB usually attacks the lungs but can also affect other parts of the body. Common symptoms include a chronic cough (sometimes accompanied by haemoptysis), fever and night sweats, loss of weight and feeling generally tired and unwell. TB is transmitted mainly by inhalation of infectious droplets produced by persons with pulmonary or laryngeal TB during coughing, laughing, shouting, singing or sneezing. Rarely, invasion of MTB may occur through mucous membranes or damaged skin. Extra-pulmonary TB, other than laryngeal, is generally not communicable, although can be associated with pulmonary TB.

Most infections in humans result in an asymptomatic, latent infection. In the immunocompetent host, subsequent progression to active TB occurs in only 5–10 per cent of those infected. This progression can occur from weeks to decades later although half will occur within two years from initial infection. Infection with the MTB complex (responsible for most cases) without disease can persist for a lifetime. Active disease if left untreated kills more than 50% of those infected.

Non-tuberculous mycobacteria (NTM) infections

NTM are environmental mycobacteria, and do not include the MTB pathogens or *M. leprae* that causes Hansen's disease or leprosy (Runyon 1959). Disease caused by NTM is not notifiable in Australia; hence, there is little information on the incidence or prevalence of NTM disease.

NTM organisms originate from environmental sources such as food, other animals, soil or water. Pulmonary NTM infections are the most common and are usually caused by the MAC group. *M. kansasii*, *M. xenopi* and *M. malmoense* are the next most common causes. Skin and soft-tissue NTM infections, often originating from a cut or graze, manifest clinically as rashes, ulcers, nodules, granulomas, cellulitis or abscesses. NTM skeletal infections of bones, joints and tendons primarily occur following accidental trauma, surgery, puncture wounds or injections. These infections can be localised or multifocal, and can progress to septic arthritis, osteomyelitis and even bacteraemia.

An MBS item descriptor was not proposed in the PASC-ratified protocol. Suggested MBS item descriptors, as recommended by the Pathology Services Advisory Committee (PSAC) are provided in Table 1.

Table 1 Suggested MBS item descriptors

Category 6 – PATHOLOGY SERVICES	
MBS item number	Nucleic acid amplification test for the detection of <i>Mycobacterium tuberculosis</i> complex in patients with signs and symptoms consistent with active tuberculosis.
Fee: To be advised	
MBS item number	Nucleic acid amplification test for the detection of non-tuberculous mycobacteria species in patients with a compatible clinical disease.
Fee: To be advised	

7. Summary of Public Consultation Feedback/Consumer Issues

No specific Consumer impact statement was provided in the assessment.

8. Proposed intervention's place in clinical management

Mycobacterium tuberculosis (MTB) infections

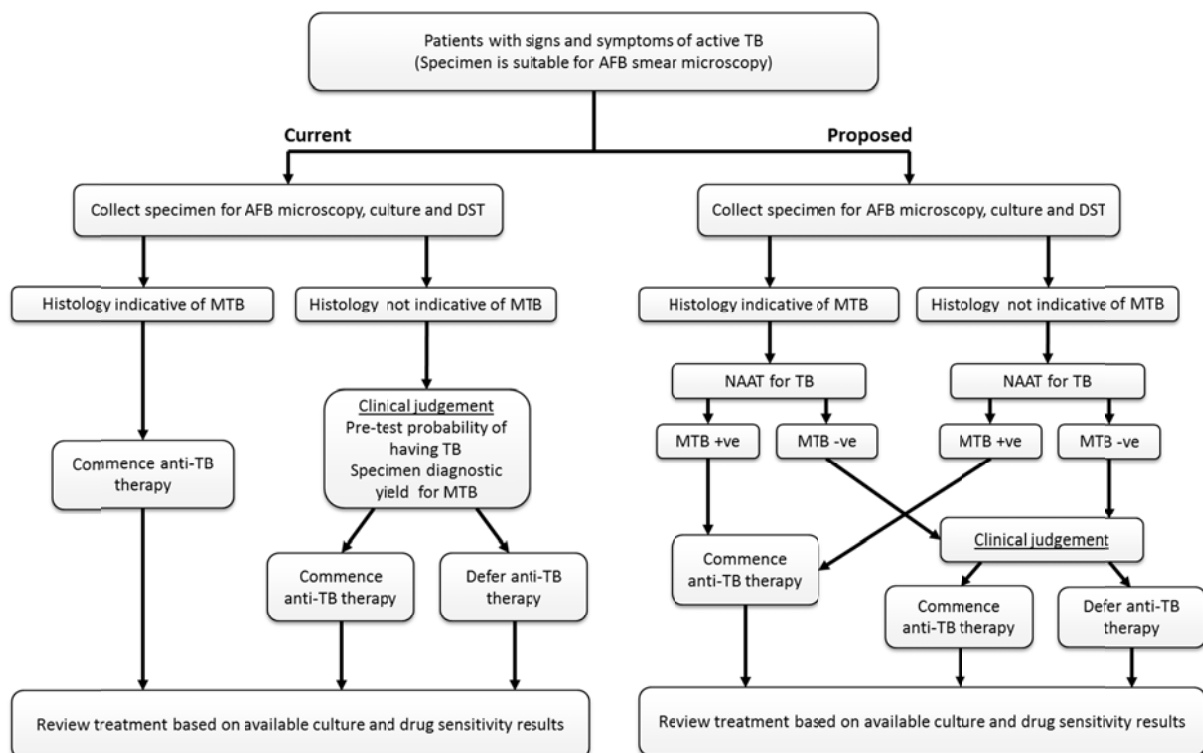
The use of NAAT in the diagnosis and management of active TB infection is proposed to be an additional diagnostic tool and not a substitute for any of the current tests. NAAT is intended for use with specimens from untreated patients (< 3 days of anti-TB drug treatment) for whom there is clinical suspicion of TB. As the number of bacilli reduces rapidly within days to 2 weeks after commencing appropriate TB treatment (providing the MTB is not drug resistant), MTB cannot be reliably detected in treated patients.

In clinical practice, diagnosis of TB and the selection of an appropriate treatment regimen would be determined by the clinician after taking into account the patient's history and clinical symptoms along with the results of AFB microscopy, NAAT and culture plus drug susceptibility testing (DST). The AFB microscopy and NAAT results would both be available within a day or two, and the interpretation of the AFB and NAAT results would be inter-related. For example, a positive AFB could be the result of an NTM infection rather than MTB, and this would be resolved by the NAAT result.

The clinical management algorithms for patients with the signs and symptoms of active TB are shown in Figure 1 and Figure 2.

Figure 1 presents the current and proposed clinical management algorithms for patients with the clinical signs and symptoms of active TB and for whom AFB microscopy can be done; that is, the patient can provide a sample for testing.

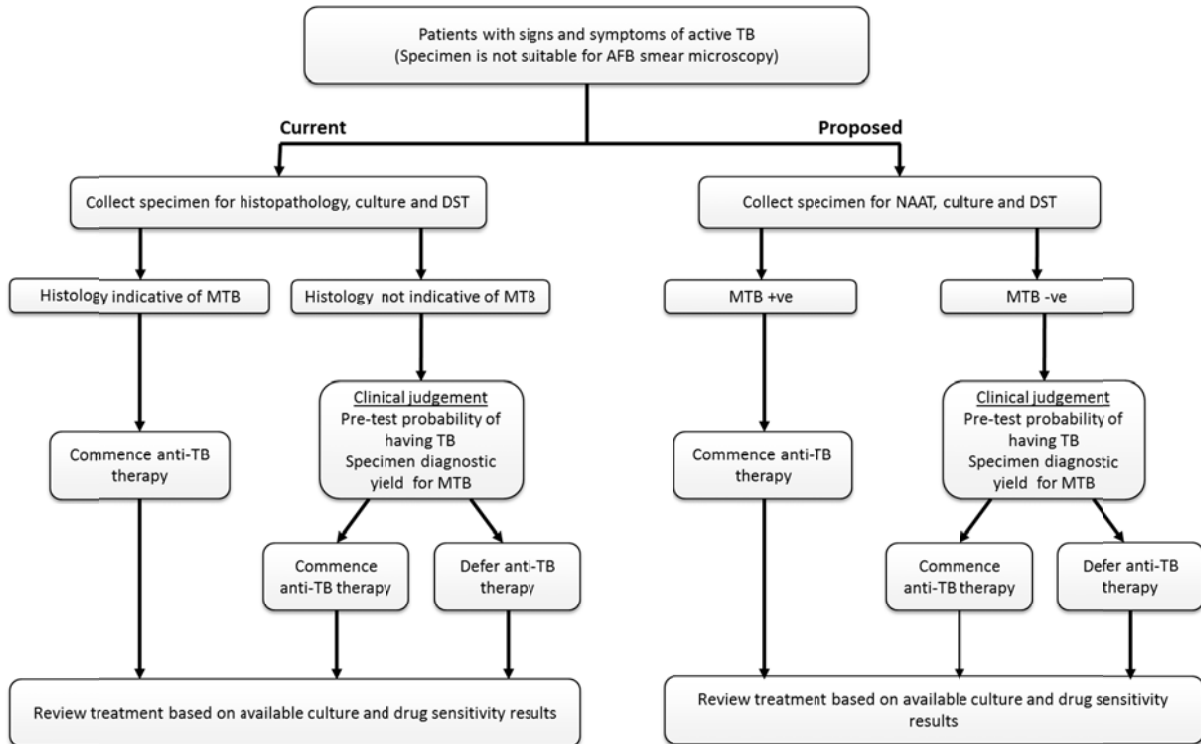
Figure 1 Current clinical management of TB and proposed use of NAAT for active TB where AFB is obtained



AFB = acid-fast bacilli; DST = drug susceptibility testing; MTB = *Mycobacterium tuberculosis*; NAAT = nucleic acid amplification testing; TB = tuberculosis

Figure 2 presents the current and proposed clinical management algorithms for patients who present with the clinical signs and symptoms of active TB and from whom it is not possible to obtain a specimen suitable for AFB microscopy.

Figure 2 Current clinical management and proposed algorithm with use of NAAT for active TB where AFB microscopy is not able to be obtained



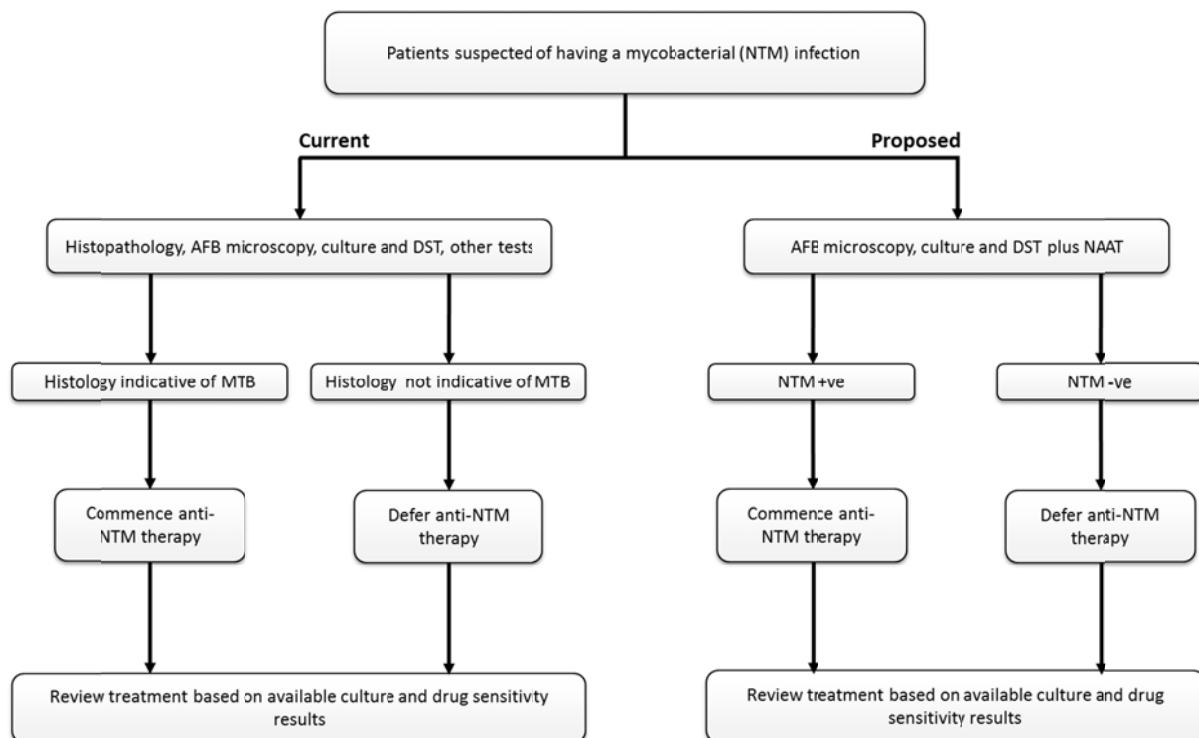
AFB = acid-fast bacilli; DST = drug susceptibility testing; MTB = *Mycobacterium tuberculosis*; NAAT = nucleic acid amplification testing; TB = tuberculosis

Non-tuberculous mycobacteria (NTM) infections

In patients suspected of having NTM infections, the applicant proposed that NAAT is expected to provide additional diagnostic information to the tests currently performed to diagnose NTM. The use of NAAT in this population is, therefore, proposed to be superior to the situation where NAAT is not available.

Error! Reference source not found.3 presents the current and proposed clinical management algorithms for patients who are suspected of having an NTM infection.

Figure 3 Current clinical management algorithm and proposed algorithm with use of NAAT for patients who are suspected of having an NTM infection



AFB = acid-fast bacilli; DST = drug susceptibility testing; MTB = *Mycobacterium tuberculosis*; NAAT = nucleic acid amplification testing

9. Comparator

Patients with the clinical signs and symptoms of active TB will receive NAAT in addition to AFB microscopy. Standard microbial testing in Australia for TB, in people with signs and symptoms of active disease, involves AFB microscopy and culture of suitable specimens. As both the intervention and comparator groups receive AFB testing, the main comparator for NAAT is culture alone.

The patient population suspected of having an NTM infection receive NAAT in addition to culture, and this may replace further testing such as additional biopsies. Therefore, the appropriate comparator in the identified population is current testing without NAAT.

Key differences in the delivery of the proposed medical service and the main comparator

Currently, most testing for MTB occurs using the AFB smear microscopy and culture tests. Although they are two separate tests, they are usually performed at the same time using the same specimen. The results for the two tests are delivered at different times; AFB microscopy results are reported within 24-48 hours whereas culture results are reported at 6–8 weeks. NAAT would be performed at the same time as AFB microscopy and culture, with results available in the same timeframe as the AFB results.

10. Comparative safety

For TB infections, studies that investigated the use of NAAT (with or without AFB microscopy) compared with ‘no NAAT’ (AFB microscopy and culture for diagnostic accuracy studies) in patients suspected of having TB and who have had < 3 days of anti-TB treatment and reported appropriate outcomes, were included for further review.

For NTM infections, studies that investigated the use of NAAT (with or without AFB microscopy) compared with ‘no NAAT’ (AFB microscopy and culture or clinical diagnosis) in patients suspected of having an NTM infection were also included.

Two studies assessed the direct health impact of NAAT compared with no NAAT on patients suspected of having TB. Seventeen studies reported on the impact of NAAT on the clinical management of patients and nine studies provided data on the impact of these changes in management on the health outcomes of patients.

Due to the large volume of evidence available on the accuracy of NAAT relative to culture, only studies published after 2005, with 2x2 data suitable for meta-analysis, were included in the final analysis. Studies on the only commercial NAAT product (Xpert) available in Australia were published in 2006 onwards. In-house NAAT, on the other hand, was available before 2005. However, as there have been significant changes in laboratory practice over the past 10 years (Boyle & Pai 2012; Moore, Guzman & Mikhail 2005; Nybo 2012; Public Health and Ambulatory Care 2012), it seemed reasonable to limit study eligibility to publications in the previous decade. A total of 79 studies provided extractable data and were included.

Twelve studies were identified that reported on the diagnostic accuracy of NAAT for the detection of NTM infections and were included in the review. Literature searches spanned the period 1990–2014.

No studies were identified that reported on the safety of NAAT compared with current testing. As NAAT is usually conducted on the same samples used for other testing, and there is no need for resampling, no adverse events (AEs) are expected from the testing procedure. However, more patients will receive a false-positive NAAT than a false-positive AFB result. Therefore, more patients will receive treatment for a disease they do not have and will possibly have an adverse reaction to the anti-TB drugs until clinical unresponsiveness is noted or culture results become available.

11. Comparative effectiveness

Effectiveness of NAAT in the diagnosis of MTB

Direct evidence: does NAAT improve health outcomes?

Both studies assessing the direct health impact of NAAT were conducted in a setting with a high TB prevalence; therefore, the applicability to the Australian healthcare system is questionable. A high-quality randomised controlled trial (RCT) reported no difference in morbidity outcomes at 2 and 6 months follow-up when NAAT and AFB microscopy were compared. However, a strong trend indicating fewer deaths in the NAAT group compared with the AFB microscopy group was observed at 2 months, but this trend was no longer apparent at 6 months. A historical control study of medium quality found no difference in the mortality rate at 2 months follow-up when comparing NAAT with no NAAT. However, both

studies were confounded by high levels of treatment initiation based on clinical evidence in the comparator groups.

The difference in treatment initiation between groups in the study by Theron et al. (2014) is unlikely to be reflected in treatment initiation rates in Australia because NAAT is suggested to be used as an adjunct to AFB testing. The incremental impact of NAAT over current testing practice in Australia, and the impact on patient morbidity and mortality, cannot be estimated from this study.

Linked evidence of effectiveness of NAAT in the diagnosis of MTB

Meta-analysis of studies investigating the diagnostic accuracy of NAAT compared with culture showed that both in-house NAATs and the commercial Xpert NAAT have diagnostic value for confirming or excluding culture-positive disease. Overall, patients with a positive NAAT result are likely to have culture-positive TB, whereas patients with a negative NAAT result are unlikely to be falsely negative.

In the context of interpreting NAAT results in conjunction with AFB findings, when specimens are AFB smear-positive a negative NAAT result can confidently exclude the likelihood of an MTB infection (as determined by culture), but a positive NAAT result does not eliminate the possibility of being culture-negative. The explanation for this is that culture is an imperfect reference standard. Culture in AFB smear-positive specimens likely resulted in misclassification of many of the 22% false-positive results recorded for NAAT.

In AFB smear-negative specimens a positive NAAT result is likely to correctly confirm the presence of MTB. However, interpretation of a negative NAAT result is dependent on the type of specimen tested. In patients with AFB smear-negative sputum, a negative NAAT result indicates that the patient may not be culture-positive but it cannot be ruled out. In patients with AFB smear-negative non-sputum specimens, a negative NAAT result provides no additional useful information. This is likely due to the low numbers of bacilli present in AFB smear-negative specimens. It should be noted that if few bacilli are present in the specimen, the possibility of a false-negative result would increase for all three tests.

When the results of the included studies were meta-analysed (k=11), NAAT was found to be both highly sensitive (93%, 95%CI 85, 97) and highly specific (98%, 95%CI 96, 99), compared with culture-based DST, in identifying rifampicin-resistant MTB.

Further analyses indicated that there was no difference in the diagnostic accuracy of AFB microscopy or NAAT, compared with culture, in HIV-positive and HIV-negative patients (k=7 and k=6 studies, respectively). As HIV-positive patients commonly produce AFB smear-negative sputum samples, the difficulty associated with diagnosis of TB in HIV-positive patients is related to the reduced sensitivity of NAAT in this specimen type when compared with AFB smear-positive specimens.

Does it change patient management?

All studies were in agreement that the use of NAAT resulted in a quicker diagnosis of patients with TB, especially in those who were AFB smear-negative (k=14). Predictably, this also resulted in earlier treatment in NAAT-positive patients. A historical control study of poor quality and a retrospective cohort study of medium quality reported that the median duration of unnecessary and/or over-treatment of TB was shorter in patients when NAAT was used to guide treatment decisions compared with when NAAT was not available.

There were conflicting data on the likely impact of NAAT in the clinical setting. A retrospective cohort study of poor quality and a high risk of bias, conducted in the UK (medium TB incidence), concluded that clinician decision-making would be affected by NAAT results and that there would be significant clinical benefits from the use of NAAT in low-prevalence settings. Two cohort studies of medium quality, one retrospective and conducted in Saudi Arabia (medium TB incidence) and the other conducted in Canada (low TB incidence), suggest that clinicians would be reluctant to change patient management based on the NAAT result.

Does change in management improve patient outcomes?

Two prospective cohort studies of poor quality, conducted in countries with a low incidence of TB, reported that a delay in time to diagnosis was significantly associated with an increased risk of transmission of TB among contacts. A retrospective cohort study of poor quality, conducted in New Zealand, indicated that, for the individual patient, the time between development of symptoms and diagnosis was not significantly associated with achieving a favourable treatment outcome (i.e. cure or treatment completed). Three cohort studies (two retrospective) of medium quality provided some evidence that patients with rifampicin-resistant TB who received a rifampicin-containing Category II treatment, before receiving the results of DST had slightly poorer health outcomes than those who did not.

All TB patients are at risk of adverse health events (e.g. hepatitis) associated with first-line treatment. Two SRs, one of medium quality and one of poor quality, found that some, but not all, AEs as a consequence of patients with active TB receiving inappropriate antibiotic treatment (due to MTB resistance) may be avoided with appropriate treatment, to which the MTB strain is sensitive. One SR of good quality found that patients have a higher risk of developing multidrug-resistant TB (MDR-TB) if they receive inappropriate drug treatment.

Overall conclusion with respect to comparative effectiveness

Comparison of AFB, NAAT, and AFB plus NAAT, using culture as the reference standard, showed that AFB plus NAAT (the testing strategy proposed in the application) had the highest false-positive rate of 12%, with NAAT alone at 6% and AFB alone at 2%. A false-positive result means that a patient will receive treatment for a short time (until clinical unresponsiveness is noted or culture results are available) for a disease they do not have. However, as culture is an imperfect reference standard, a large proportion of these false-positive patients may actually have clinical disease. AFB microscopy alone had the highest false-negative rate at 38%, whereas NAAT alone or AFB plus NAAT were much lower at 11% and 6%, respectively. The consequences of a false-negative result are much more severe, as the patient may remain untreated for a longer time period and could potentially spread the disease to more individuals in the community.

The results of the meta-analyses presented in this report suggest that NAAT would be a useful addition to AFB microscopy and culture in the diagnosis of both pulmonary and extrapulmonary TB. Patients with a positive AFB test or NAAT result are likely to have culture-positive TB, and it becomes almost certain if both tests are positive. No useful information can be obtained directly from a negative AFB result, as these patients may or may not have TB. A negative NAAT result should be interpreted with reference to the AFB result—in a patient who was AFB smear-positive it almost completely eliminates the likelihood of being MTB culture-positive; conversely, in a patient who was AFB smear-negative it does not eliminate the possibility of culture-positive disease.

The use of NAAT enables quicker diagnosis and treatment of patients with TB, especially in those who are NAAT-positive and AFB smear-negative. It also reduces the duration of

unnecessary and/or over-treatment for TB, particularly in those patients who are NAAT-negative and AFB-positive.

The accuracy of NAAT compared with culture-based DST indicates that NAAT can accurately identify patients with rifampicin-resistant MTB. Thus, NAAT could be used to inform the type of antibacterial treatment offered to TB patients. This would help avoid side effects such as hepatitis from inappropriate use of rifampicin, and earlier appropriate treatment for rifampicin resistance would also reduce the risk of developing MDR-TB.

Linked evidence of diagnostic effectiveness of NAAT in the diagnosis of NTM

NAAT to detect NTM could be separated into three distinct categories: detecting NTMs in general (NTM-NAAT), specifically detecting *M. avian* complex (MAC) strains (MAC-NAAT), and detecting *M. ulcerans* in patients suspected of having Buruli ulcer. The pooled accuracy of MAC-NAAT compared with culture showed that patients with a positive MAC-NAAT result were most likely to be infected with *M. avian*, but it is equivocal whether patients with a negative result have a culture-positive MAC infection (k=5 studies). Patients with a positive NTM-NAAT were more likely to have an infection than not, and patients with a negative result were more likely to be uninfected with NTM than to be infected (k=5 studies). The area under the summary receiver–operator characteristic (SROC) curve indicated that both NTM- and MAC-NAAT performed well in predicting culture positivity. There was insufficient evidence of the accuracy of NAAT in the diagnosis of NTM in AFB smear-positive or -negative specimens, so no conclusions could be reached about the value of NAAT in conjunction with AFB microscopy in the detection of NTM infections.

It should be noted that culture is an imperfect reference standard. When compared with a clinical reference standard, the median sensitivity for NTM-NAAT (k=2) was higher than for culture or AFB microscopy. NAAT appears to be able to identify a larger proportion of patients with an NTM infection than either AFB microscopy or culture. The results of these meta-analyses should be viewed with caution due to the small number of studies included and the wide 95% confidence intervals (CIs) for many of the analyses.

12. Economic evaluation

A cost–utility analysis is presented to assess the cost-effectiveness of adding NAAT to AFB smear microscopy, and culture and sensitivity (C&S), testing in a population with clinical signs and symptoms of active TB.

As clinical management in Australia differs depending on the clinical suspicion (pre-test probability) of TB, the model is separated into patients with:

- a high clinical suspicion of TB, where treatment is initiated based on clinical suspicion, and the benefit of NAAT is to identify resistance mutations and initiate appropriate earlier treatment for MDR; and
- a low clinical suspicion of TB, where treatment decisions are initiated or delayed based on AFB ± NAAT results. In addition to earlier MDR treatment initiation, additional benefits of NAAT include the ability to differentiate between patients with MTB and NTM infections (who would have previously been treated on the basis of the AFB results alone), and to reduce the delay in treatment in those with true TB who returned a negative AFB result (who would not have been treated without the availability of NAAT).

Additional scenarios are presented to examine the extent to which treatment initiation decisions based on clinical suspicion affect the cost-effectiveness of NAAT.

Key model assumptions

- When AFB smear and NAAT are discordant, the treatment decision is based on NAAT (i.e. consistent with PASC protocol).
- C&S testing (the reference standard) is assumed to be 100% sensitive and specific, as all patients have C&S testing and at the end of 2 months all will have a correct diagnosis (i.e. MDR-TB, TB or no TB).
- Once the decision to initiate or delay treatment has been made, the model assumes that there will be no change in treatment until the results of C&S are available. This assumption may favour NAAT, as the earlier initiation of resistant drugs in the comparator arm would reduce the benefit of introducing NAAT.
- Cost and utility penalties associated with the secondary transmission of TB are applied for each index case in the model, but the consequences (i.e. cost or health outcome) of further ongoing transmissions (e.g. tertiary transmissions and beyond) are not included in the base-case.

The incremental cost-effectiveness of NAAT is presented, incorporating costs in a stepped manner. The base-case incremental cost-effectiveness ratio (ICER) for NAAT is \$90,728/QALY. The addition of NAAT leads to more patients initially receiving the correct treatment, due to improved sensitivity in conjunction with AFB and the ability of NAAT to identify MDR-TB. The incremental cost of NAAT is driven predominantly by the cost of testing, offset by reduced TB transmissions and hospitalisation costs. The incremental QALY gain is driven by the shift in patients from being initially untreated TB (or standard treatment in the case of MDR-TB) to receiving correct treatment.

Table 2 The incremental cost-effectiveness of NAAT

Utilities considered	Costs included (NAAT cost applied in AFB + NAAT arm)	ICER
Index patient utility	Treatment only	\$188,307
	Treatment and AEs	\$188,238
	Treatment, AEs and management	\$185,882
	Treatment, AEs, management and hospitalisation	\$145,956
	Treatment, AEs, management, hospitalisation and transmission	\$103,978
Index and secondary case utility	Treatment, AEs, management, hospitalisation and transmission	\$90,728

AEs = adverse events; ICER = incremental cost-effectiveness ratio

Sensitivity analyses for the base-case (TB mixed) scenario were conducted around a number of parameters included in the economic modelling (using 95%CI or plausible upper and lower limits). The ICER is most sensitive to changes in the prevalence of TB in the tested population (decreasing the prevalence from 22% to 10% in the tested population increases the ICER to \$967,000) and the specificity of NAAT (ICERs exceeding \$200,000 when the lower limit of NAAT specificity estimates are used).

13. Financial/budgetary impacts

A market-based approach is taken, using MBS data to estimate the number of patients who utilised at least one item of mycobacterial AFB microscopy, culture and sensitivity (MC&S) testing in 2009–13, and to project the expected number of patients who would be eligible for NAAT for TB and NTM (as requested) in 2015–19. One NAAT is assumed per eligible patient. However, as this assumption may underestimate the number of tests when multiple mycobacteria are suspected (i.e. TB may be initially suspected with a pulmonary infection, but if negative then NAAT may be used to test for *M. kansasii* and/or MAC). It is unclear how often this situation would occur—the applicant has estimated this in approximately 30% of patients initially suspected of TB.

As NAAT is not intended to replace current testing, the estimated net financial implication to the MBS is equal to the cost of the requested NAAT listings multiplied by the expected number of services. The financial implications to the MBS resulting from the proposed listings of NAAT are summarised in Table 3.

Table 3 Financial implications of proposed NAAT listings

	2015	2016	2017	2018	2019
Projected number of patients eligible for NAAT	37,575	39,299	41,022	42,745	44,468
<i>Population suspected of TB</i>					
Proportion of patients suspected of TB	50%	50%	50%	50%	50%
Number of patients suspected of TB	18,788	19,650	20,511	21,373	22,234
Proposed NAAT fee	\$130.00	\$130.00	\$130.00	\$130.00	\$130.00
Proportion of patients bulk-billed	61%	61%	61%	61%	61%
MBS fees associated with TB listing	\$2,442,440	\$2,554,500	\$2,666,430	\$2,778,490	\$2,890,420
MBS benefits payable (85%)	\$2,076,074	\$2,171,325	\$2,266,466	\$2,361,717	\$2,456,857
Patient co-payments ^a	\$144,715	\$151,354	\$157,986	\$164,626	\$171,257
<i>Population suspected of NTM</i>					
Proportion of patients suspected of NTM	50%	50%	50%	50%	50%
Number of patients suspected of NTM	18,788	19,650	20,511	21,373	22,234
Proportion of initial TB suspects tested	30%	30%	30%	30%	30%
Number of initial TB suspects tested	5,636	5,895	6,153	6,412	6,670
Total number of patients tested for NTM	24,424	25,545	26,664	27,785	28,904
Proposed NAAT fee	\$50.00	\$50.00	\$50.00	\$50.00	\$50.00
Proportion of patients bulk-billed	61%	61%	61%	61%	61%
MBS fees associated with NTM listing	\$1,221,220	\$1,277,250	\$1,333,215	\$1,389,245	\$1,445,210
MBS benefits payable (85%)	\$1,038,037	\$1,085,663	\$1,133,233	\$1,180,858	\$1,228,429
Patient co-payments ^a	\$72,357	\$75,677	\$78,993	\$82,313	\$85,629
MBS fees associated with NAAT listings	\$3,663,660	\$3,831,750	\$3,999,645	\$4,167,735	\$4,335,630
MBS benefits payable (85%)	\$3,114,111	\$3,256,988	\$3,399,698	\$3,542,575	\$3,685,286
Patient co-payments ^a	\$217,072	\$227,031	\$236,979	\$246,938	\$256,886

^a Only payable by patients who are not bulk-billed

NAAT = nucleic acid amplification test; NTM = non-tuberculous mycobacteria; TB = tuberculosis

The approach used may overestimate the population eligible for NAAT, as testing of patients suspected of *M. leprae* may be included (but would not be eligible for NAAT) and, as these tests are used to monitor treatment effectiveness, patients may receive testing across multiple years for the same infection. Furthermore, the current MBS items are not restricted to patients with clinical signs and symptoms of a mycobacterial infection; as testing may be ordered as part of the initial work-up of a chronic obstructive pulmonary disease or some renal diseases, this approach may further overestimate the eligible population.

Given the uncertainties in estimating the eligible population, the financial implications of introducing NAAT are uncertain. However, as NAAT is proposed to be used as an add-on test, net costs to the MBS are implied. Estimates presented in the assessment (\$3.7 – \$4.3 million over the 5-year period) are likely to represent the upper limits of proposed use, as all assumptions regarding the eligible population are likely to be overestimated. The financial implications are most sensitive to changes in the cost per test. While benefits associated with reduced transmissions may be expected, these have not been quantified. As NAAT is currently being used (the extent of which is uncertain), some shifting of costs from the states to the federal health budget is anticipated, and so the net societal cost of NAAT may be lower than the net costs to the MBS.

14. Key issues from ESC for MSAC

ESC noted that the proposed NTM population eligible for NAAT had been expanded from the population specified in the Protocol to include all patients suspected of having NTM infection. ESC considered that although there was an insufficient evidence-base for NTM infections as a whole there was value in including patients with other specimen types such as HIV-positive with *M. avium* complex (MAC) disease or patients with disseminated bacteraemia.

NAAT testing identifies a complex of mycobacteria however, there are different NAAT tests for different types of mycobacteria. ESC considered that under certain circumstances for one patient for the same episode multiple NAAT tests may be required.

ESC agreed that the proposed comparators were appropriate. However, ESC noted that culture is an imperfect reference standard and therefore a large proportion of false-positive patients (NAAT positive & culture negative) could have clinical disease.

ESC noted that more patients were likely to receive a false-positive NAAT result than a false-positive AFB result indicating they could potentially have TB. Therefore, it was likely that these patients would receive treatment that was unnecessary and there was potential for adverse reactions to anti-TB treatment.

ESC considered that the two studies which provided direct evidence were not likely to be applicable to the Australian setting as they were conducted in a population with a high TB prevalence. The results were likely confounded by the high treatment initiation in the comparator arm.

ESC considered that NAAT was likely to be more effective at confirming the presence of an MTB infection than was indicated by the meta-analysis presented which used culture as a reference standard.

ESC noted that NAAT could potentially make the time to diagnosis shorter and allow earlier treatment, especially in patients who are AFB smear negative. However, ESC considered that a delay in time to diagnosis would not have a major impact overall except potentially on the risk of transmission; and that management of these patients is highly dependent on the clinical setting and their pre-test probability.

ESC considered there was insufficient evidence presented to demonstrate the accuracy of NAAT in diagnosis of NTM in AFB smear positive or negative patients. ESC was not convinced there would be value using NAAT in addition to AFB microscopy testing to impact health outcomes in this patient population.

ESC considered that the three key translation issues were:

- the poor to moderate quality of the studies;
- whether culture was an appropriate reference standard; and
- applicability of the studies conducted in countries with a high TB and/or high HIV population.

ESC noted that a cost-utility analysis was provided for the patient population with signs and symptoms of active TB with an AFB specimen. However, no economic evaluation was conducted in the patient populations with signs and symptoms of active TB but no AFB

specimen and suspected of NTM infection who have C&S testing, as there was no evidence of effectiveness.

ESC was concerned that the model assumed 100% sensitivity and specificity for culture and sensitivity testing when it is clearly an imperfect reference standard.

Cost and utility penalties associated with the secondary transmission of TB were appropriately applied for each index case, but ESC noted that the consequences (i.e. cost or health outcome) of further ongoing transmissions (e.g. tertiary transmissions and beyond) were not included in base-case.

ESC noted that the cost of NAAT is the main driver of the incremental costs in the economic modelling. The applicant did not propose a fee. The fees used in the model were based on a Victorian laboratory, \$130 for the NAAT TB test and \$50 for the NAAT NTM test although, there are large variations in test cost observed across Australian pathology providers.

Sensitivity analyses showed that the cost-effectiveness of NAAT is highly sensitive to reductions in the prevalence of TB in the tested population, ESC noted that decreasing the prevalence from 22% to 10% in the tested population increases the ICER to \$967,000. Sensitivity analyses also showed the ICER was sensitive to reductions in the specificity parameters of NAAT, ESC noted that the ICERs exceed \$200,000 when the lower limit of NAAT specificity estimates were used.

ESC considered that the estimated population was likely to be an overestimate, as it may have included patients who were ineligible for NAAT, such as those suspected of *Mycobacterium leprae*, patients receiving testing across multiple years for the same infection, or patients who did not have clinical signs and symptoms of a mycobacterial infection. ESC also noted that no data were provided to support the applicant's estimation that 50% of patients currently tested for mycobacterial infections are suspected of TB and 50% are suspected of NTM.

ESC noted that one NAAT is assumed per eligible patient and considered that this may underestimated the number of tests when multiple mycobacteria are suspected. ESC also noted that no data were provided to support the applicant's estimation that 30% of patients initially suspected of TB would undertake NAAT for NTM. ESC considered that the financial implications for listing NAAT on the MBS were unclear given the uncertainties with the estimated eligible population particularly as NAAT was an add-on test.

As NAAT is already well established within existing public health protocols for active TB (given it is a nationally notifiable disease) and NAAT testing more generally is believed to be widely disseminated across public health laboratory settings for use both in this and other clinical indications (the extent of which was not entirely clear in the documentation provided), some shifting of costs from the states to the federal health budget would be likely if a MBS item were granted but had not been costed in the financial analyses.

To further inform MSAC regarding these uncertainties, ESC requested that the department seek advice from the National Tuberculosis Advisory Committee (NTAC) and the Public Health Laboratory Network (PHLN), regarding current usage of NAAT testing in the management of active TB; including a better understanding of the relationship between private sector laboratories and public reference laboratories in both the coordination and confirmation of test results; as well as better understanding on the patient population

estimates. This information will better inform MSAC as to the potential consequences of changing current public funding arrangements for NAAT testing for the clinical indications under consideration in this application.

15. Other significant factors

TB in the Indigenous population

The incidence of TB in the Australian Indigenous population was 11 times higher than in the Australian non-Indigenous population in 2010¹. Higher rates of hospitalisation and mortality from TB also occur in the Indigenous population. The rapid diagnosis and treatment of TB is essential in remote communities in order to quickly contain the spread of infection. This is particularly important for children and infants, given the challenges in accessing adequate health care in these communities. Point-of-care testing with same-day results would likely offer easier access to diagnosis and more rapid treatment initiation in small regional hospitals and clinics in rural areas of Australia, if suitable training of personnel was available.

The first fully automated NAAT developed for the point-of-care diagnosis of MTB and rifampicin-resistant MTB, was endorsed by WHO in December 2010 (WHO 2014). Three studies that met the inclusion criteria looked at the use of this NAAT in a point-of-care setting. One study reported that nurse-administered results had substantial agreement with those done by a laboratory technician on paired sputum specimens ($\kappa=0.69$, 95%CI 0.64, 0.74), and a similar sensitivity and proportion of unusable results. Two studies reported that most patients who were NAAT-positive were started on anti-TB treatment on the same day as specimen collection, compared with a median delay of 13–14 days for NAAT-negative patients.

In addition, the early knowledge of rifampicin resistance may influence treatment decisions, ensuring that appropriate anti-TB drugs are given immediately, thus reducing the likelihood of developing MDR-TB.

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

The applicant had no comments.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website at: www.msac.gov.au.