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Consultation Protocol
to guide the
assessment of
Nucleic Acid
Amplification Test for
Active Mycobacterial
Infection

January 2014

Table of Contents

MSAC and PASC 2

 Purpose of this document 2

Purpose of application 4

Background 4

 Current arrangements for public reimbursement 4

 Regulatory status 7

Intervention 8

 Description 8

 Delivery of the intervention 14

 Prerequisites 15

 Co-administered and associated interventions 16

Listing proposed and options for MSAC consideration 16

 Proposed MBS listing 16

 Clinical place for proposed intervention 17

Comparator 0

Clinical claim 2

Outcomes and health care resources affected by introduction of proposed intervention 3

 Clinical outcomes 3

 Health care resources 4

Proposed structure of economic evaluation (decision-analytic) 4

MSAC and PASC

The Medical Services Advisory Committee (MSAC) is an independent expert committee appointed by the Minister for Health and Ageing (the Minister) to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Minister on the evidence relating to the safety, effectiveness, and cost-effectiveness of new and existing medical technologies and procedures and under what circumstances public funding should be supported.

The Protocol Advisory Sub-Committee (PASC) is a standing sub-committee of MSAC. Its primary objective is the determination of protocols to guide clinical and economic assessments of medical interventions proposed for public funding.

Purpose of this document

This document is intended to provide a draft decision analytic protocol that will be used to guide the assessment of an intervention for a particular population of patients. The draft protocol will be finalised after inviting relevant stakeholders to provide input to the protocol. The final protocol will provide the basis for the assessment of the intervention.

The protocol guiding the assessment of the health intervention has been developed using the widely accepted "PICO" approach. The PICO approach involves a clear articulation of the following aspects of the question for public funding the assessment is intended to answer:

- P**atients – specification of the characteristics of the patients in whom the intervention is to be considered for use
- I**ntervention – specification of the proposed intervention and how it is delivered
- C**omparator – specification of the therapy most likely to be replaced by the proposed intervention
- O**utcomes – specification of the health outcomes and the healthcare resources likely to be affected by the introduction of the proposed intervention

Summary of matters for consultation by PASC

PASC requests consultation advice about the following matters in relation to nucleic acid amplification tests in patients with the active signs and symptoms of TB and in patients with a tissue biopsy with histopathology consistent with mycobacteria

- *There is a paucity of information about the types of mycobacterial infection responsible for pulmonary disease in Australia. Extrapolation from overseas populations will probably be required to estimate the proportion of patients in this clinical algorithm. Consultation is requested on the collection of data in Australia (or failing that overseas) on different types of non-TB mycobacterial infection, their prevalence, incidence and sequelae and pathology tests (other than NAAT) used for testing.*
- *The assessment should present any limitation in evaluating the evidence of the effectiveness of NAAT in detecting NTMB. These limitations are likely to be that there may be no reliable reference standard available for diagnosing NTMB and secondly, NAAT testing in NTMB usually relies on "in-house" assays with limited validation. It may therefore be difficult to interpret results. For example, where the NAAT is negative and an "in-house" assay has been used, the evidence may not be available to ascertain the ability of this assay to differentiate for different types of MB, as well, as the types of MB tested for by this "in-house" assay. In addition, where the NAAT is positive this result may not be sufficient to convince clinicians that this is the cause of symptoms (with the exception of MTB) because of the ubiquity of mycobacteria and its potential to contaminate a specimen. Expert advice is that currently, clinicians often require two positive cultures of MB before the result is considered to have clinical relevance. **Consultation is required on situations where MC&S is not able to be obtained whether a metric of additional benefit to clinicians in diagnosing the MB infections, if available, should be presented.***
- *Cost of hospitalisation for TB treatment and any isolation required (data will be required as an input to the model of the proportion of patients treated in the hospital, how long they are hospitalised for, and what clinical factors decide if a patient is no longer infectious if AFB smear cannot guide a clinician). Consultation is requested on these model parameters.*

Purpose of application

A proposal for an application requesting MBS listing of pathology testing for active mycobacterial infections was received from Douglass Hanly Moir Pathology Pty Ltd by the Department of Health and Ageing in 28 September 2009.

The application is for Nucleic Acid Amplification Tests (NAAT) for the 1) diagnosis and management of tuberculosis infection in a person with clinical signs and symptoms of TB; or 2) NAAT for the diagnosis and management of mycobacterial infection other than TB in tissue biopsy with consistent histopathology.

The Deakin Health Technology Assessment Group, under its contract with the Department of Health and Ageing, drafted this decision analytical protocol to guide the preparation of an assessment of the safety, effectiveness and cost-effectiveness of pathology testing for active TB infection and non-TB mycobacterial infection to inform MSAC's decision-making regarding public funding of the intervention.

Background

Current arrangements for public reimbursement

Treatment for tuberculosis is provided free of charge to patients in Australia. The test to confirm active mycobacterial infection is only covered if the patient is a public patient in a public hospital or if the test performed is covered by a Medicare item number. Standard microbial testing for tuberculosis in people with signs and symptoms of active disease in Australia comprises microscopy of a smear (for acid fast bacilli - AFB) and MC&S (Microscopy, Culture and Sensitivity) of suitable specimens.

Testing for Mycobacteria is currently listed on the MBS. Table 1 lists the tests that are currently available for the diagnosis of Tuberculosis and non-TB mycobacteria. Acid Fast Bacilli (AFB) smear and MC&S are two separate tests usually performed together on the same specimen. However, the results for these two tests are separated in time; AFB results are reported within 24-48 hours, but culture and sensitivity results are reported at 6-8 weeks.

Other tests available on the MBS are used to determine if a patient has been infected with the *Mycobacterium tuberculosis*, but not whether they have progressed to TB disease. The diagnosis of Latent TB infection (LTBI) is where a person is infected with *Mycobacterium tuberculosis* but does not have TB disease. These people are not infectious and cannot spread TB to others however they are at risk of developing active TB if their health circumstances change which is why knowledge of their status is desirable. A person with LTBI is able to be treated for latent TB if considered necessary by their clinician. In Australia, these tests are routinely used for screening people such as health care workers, recent immigrants from high incidence countries, a person who has had recent contact with someone with active TB and people who are immunosuppressed due either to disease or as a result of medical treatment. Testing for these populations was covered in a recent MSAC application 1144 and will not be considered further as part of this application. Tests for latent TB infection (LTBI) are not relevant to this application but are provided in Table 2 for information only.

Table 1: Current MBS item descriptor for diagnosing active mycobacterial infection.

Category 6 – Pathology Services
<p>69324</p> <p>Microscopy (with appropriate stains) and culture for mycobacteria - 1 specimen of sputum, urine, or other body fluid or 1 operative or biopsy specimen, including (if performed): (a) microscopy and culture of other bacterial pathogens isolated as a result of this procedure; or (b) pathogen identification and antibiotic susceptibility testing; including a service mentioned in item 69300</p> <p>Fee: \$43.00 Benefit: 75% = \$32.25 85% = \$36.55</p>
<p>69325</p> <p>A test described in item 69324 if rendered by a receiving APP* (Item is subject to rule 18)</p> <p>Fee: \$43.00 Benefit: 75% = \$32.25 85% = \$36.55</p>
<p>69327</p> <p>Microscopy (with appropriate stains) and culture for mycobacteria - 2 specimens of sputum, urine, or other body fluid or 2 operative or biopsy specimens, including (if performed): (a) microscopy and culture of other bacterial pathogens isolated as a result of this procedure; or (b) pathogen identification and antibiotic susceptibility testing; including a service mentioned in item 69300</p> <p>Fee: \$85.00 Benefit: 75% = \$63.75 85% = \$72.25</p>
<p>69328</p> <p>A test described in item 69327 if rendered by a receiving APP (Item is subject to rule 18)</p> <p>Fee: \$85.00 Benefit: 75% = \$63.75 85% = \$72.25</p>
<p>69330</p> <p>Microscopy (with appropriate stains) and culture for mycobacteria - 3 specimens of sputum, urine, or other body fluid or 3 operative or biopsy specimens, including (if performed): (a) microscopy and culture of other bacterial pathogens isolated as a result of this procedure; or (b) pathogen identification and antibiotic susceptibility testing; including a service mentioned in item 69300</p> <p>Fee: \$128.00 Benefit: 75% = \$96.00 85% = \$108.80</p>
<p>69331</p> <p>A test described in item 69330 if rendered by a receiving APP (Item is subject to rule 18)</p> <p>Fee: \$128.00 Benefit: 75% = \$96.00 85% = \$108.80</p>

*APP=approved pathology practitioner

Table 2: Current MBS item descriptors for detecting mycobacterium tuberculosis.

Category 6 – Pathology Services	
73811	Mantoux test
Fee: \$11.20 Benefit: 75% = \$8.40 85% = \$9.55	
69471	Test of cell-mediated immunity in blood for the detection of latent tuberculosis in an immunosuppressed or immunocompromised patient - 1 test
Fee: \$34.90 Benefit: 75% = \$26.20 85% = \$29.70	

Table 3: Utilisation data for MBS items—July 2012 to June 2013

MBS items	State								Total
	NSW	VIC	QLD	SA	WA	TAS	ACT	NT	
	Services								
69324	10117	6563	5396	1842	1387	462	415	486	26668
69325	716	208	811	31	1346	16	5	13	3146
69327	1414	837	931	348	236	25	45	64	3900
69328	7	24	134	0	265	0	0	0	430
69330	2249	1928	1831	418	359	92	68	94	7039
69331	4	29	45	0	202	0	0	0	280
Total	14507	9589	9148	2639	3795	595	533	657	41463

Table 3 shows that the six items listed for microscopy and culture for mycobacteria (69324, 69325, 69327, 69328, 69330, 69331) total 41,463 services. It is not possible to separate these items into investigations for mycobacterium tuberculosis (MTB) or non-tuberculous mycobacteria (NTMB). Items 69330 & 69331 are more likely to refer to MTB as it is reimbursement for 3 specimens of sputum, urine or other body fluid which is the recommendation for increasing the likelihood of detecting MTB. The combined number of services covered by the two items, 69330 and 69331, equals 7,319, this is likely to represent a minimum of the number of services that would be utilised by NAAT testing for MTB.

The control of TB in Australia is achieved through strong State and Territory based TB programs, with a close working relationship between public health, laboratory, and clinical services, with strategic advice provided by the National Tuberculosis Advisory Committee (NTAC). The NTAC provides expert strategic advice to the Communicable Diseases Network Australia (CDNA), a sub-committee of the Australian Health Protection Principal Committee (AHPPC)¹.

The Commonwealth, together with NTAC, monitors the incidence of TB on a national basis using agreed enhanced data provided by State and Territory health authorities and laboratories, in conjunction with the National Notifiable Diseases Surveillance System (NNDSS).

The key elements of TB surveillance include:

- maintenance of the NNDSS and enhanced data systems; and
- reporting to the World Health Organisation (WHO).

The governments of Australia need to maintain national TB surveillance in order to inform TB policy. This requires close working relationships with the States and Territories and national bodies, including NTAC, the Department of Immigration and Citizenship, and the Public Health Laboratory Network (PHLN).

Routine mycobacterium culture is performed by most large pathology laboratories. Positive isolates are referred to State TB reference laboratories for identification and antibiotic susceptibility testing. The five State Mycobacterium Reference Laboratories (MRLs) undertake the following functions:

- provision of basic TB diagnostic services in cooperation with other public and private laboratories;
- provision of specialised TB diagnostic services, such as mycobacterial identification, drug susceptibility testing, and rapid molecular detection of drug resistance;
- provision of molecular epidemiological typing by a nationally-approved method;
- provision of specialised diagnostic services for the investigation of clinically-significant non-tuberculous mycobacteria (NTM) infections;
- delivery of national quality assurance programs; and
- training of clinical, public health and laboratory personnel to maintain expertise in mycobacterial diagnostics in both the public and private sectors¹.

State public health bodies would absorb the majority of the costs associated with the treatment of TB as patient are most likely to be treated in tertiary public teaching hospital with infectious disease specialists. This is aside from the costs associated with surveillance and screening of populations at risk of active TB and LTBI.

Regulatory status

The nucleic acid amplification test for the detection of mycobacteria may be an in-house assay or a commercial kit. There is only one NAAT registered on the TGA the Xpert[®] MTB/RIF Assay for use with the Cepheid GeneXpert system. This is a semi-quantitative, nested real-time PCR (polymerase chain reaction) in-vitro diagnostic test for the detection of:

- Mycobacterium tuberculosis complex DNA in sputum samples or concentrated sediments prepared from induced or expectorated sputa that are either acid-fast bacilli (AFB) smear positive or negative
- Rifampicin-resistance associated mutations of the rpoB gene in samples from patients at risk for rifampicin resistance

The Xpert[®] MTB/RIF Assay is intended for use with specimens from untreated patients for whom there is clinical suspicion of tuberculosis.

The US Food and Drug Administration (FDA) currently lists eight commercially available nucleic acid based tests for mycobacterium tuberculosis on their site². Four of the tests are produced by Gen-Probe Inc, with one each from Syngene Inc, Roche Molecular System Inc, Becton, Dickinson & Co and Cepheid.

NAAT tests appear to have been first approved by the FDA in 1995. The Amplified Mycobacterium tuberculosis Direct Test (MTD, Gen-Probe, San Diego, California) was approved by the FDA in 1995 for use with AFB-smear-positive respiratory specimens, and in a supplement application, an enhanced MTD test was approved in 1999 for use with AFB smear-negative respiratory specimens from patients suspected to have TB. Additionally, Amplicor Mycobacterium tuberculosis Test (Amplicor, Roche Diagnostics, Basel, Switzerland) was approved by FDA in 1996 for use with AFB smear-positive respiratory specimens from patients suspected of TB³.

There are no commercially available nucleic acid based kits for diagnosing non-TB mycobacteria registered with the TGA. The US FDA has nine commercially available kits listed, of these three kits are specific for the detection of *Mycobacterium avium*, one kit each for *Mycobacterium kansasii*, *Mycobacterium gordonae*, *Mycobacterium intracellulare* and 3 kits for rapid diagnosis system for mycobacteria⁴.

Intervention

Description

NAAT tests provide a qualitative result—yes or no to the presence of the mycobacteria strain being tested for.

There is no description of the commercially available tests or in-house assays used for detection of Mycobacteria provided with the application.

The following is a description of the commercially available NAAT test for *MTB*, listed on the ARTG. Xpert® MTB/RIF Assay is an automated *in vitro* diagnostic test for the qualitative detection of *Mycobacterium tuberculosis* (MTB)-complex DNA and the genetic mutations associated with rifampicin (rif) resistance in raw sputum samples or concentrated sputum sediments from patients for whom there is clinical suspicion of TB and who have received no antituberculosis therapy, or less than 3 days of therapy. The primers in this test amplify a portion of the *rpoB* gene containing the 8q1 base pair core region. The probes are designed to differentiate between the conserved wild-type sequence and mutations in the core region that are associated with rif resistance. The assay is performed on Cepheid GeneXpert® Instrument Systems⁴.

The Xpert MTB/Rif Assay simultaneously detects MTB-complex and the genetic mutations associated with rifampicin resistance by amplifying a MTB-complex specific sequence of the *rpoB* gene.

For the purposes of estimating usage, it is likely that a NAAT test would only be required to be performed once per patient. It is recommended that a follow-up test not be performed within a minimum re-test period if a patient has been treated for TB.

The National Pathology Accreditation Advisory Council has published standards and guidelines for laboratories performing NAAT³. The NPAAC document addresses specimen collection, transportation, reagent preparation, nucleic acid extraction, amplification, product detection, data recording, reporting, sample storage and quality assurance. Laboratories performing NAAT for TB diagnosis must

comply with these NPAAC recommendations. Some of the standards and guidelines of particular relevance to TB NAAT are highlighted below.

1. Samples that have been used for other tests prior to NAAT are at increased risk of cross-contamination. Wherever possible, NAAT should be performed on dedicated samples or on aliquots taken before other tests are performed.
2. The efficiency and quality of DNA extraction impacts greatly on the final test result. The extraction methods performed on various specimen types must be documented in the laboratory manuals and validated.
3. All NAAT methods must be properly validated before routine use. When a commercial test is used according to the manufacturer's instructions, no re-validation is required. Modified commercial tests and 'in house' methodologies must be validated as outlined in the NPAAC publication Requirements for the validation of in-house in vitro diagnostic devices (IVDs).
4. NAATs are capable of detecting very small quantities of nucleic acid and are therefore liable to false-positive results due to contamination events. Staff competence, laboratory design and routine use of controls limit and detect these contamination events. Three physically-separated areas are required in a NAAT laboratory for: DNA extraction, reagent preparation, and amplification/product detection. The movement of specimens and equipment shall be unidirectional from pre- to post-amplification areas. At least one negative control and a weak positive control must be subject to the whole test process including DNA extraction.

External quality assurance programs in the USA have demonstrated that laboratories performing NAAT for detecting TB but not conforming to these basic requirements have higher rates of false-positive reactions despite using FDA-approved commercial assays.

PASC agreed that the submission should provide evidence, in patients with the signs and symptoms of active TB, of the analytical and clinical sensitivity and specificity of both commercially available and in-house NAAT assays. In addition a comparative analysis between in-house assays and commercial kits, in the diagnosis of TB in patients with the signs and symptoms of active TB, if evidence is available should be presented.

PASC agreed that evidence should be presented for NAAT testing in patients with the signs and symptoms of active TB, for both assays that include or exclude antibiotic mutation testing.

PASC agreed that the submission should provide evidence of the analytical and clinical sensitivity and specificity of both commercially available and in-house NAAT testing of tissue biopsy with histopathology consistent with mycobacteria.

Tuberculosis

Tuberculosis remains a major global health problem, in 2012, an estimated 8.6 million people developed TB and 1.3 million died from the disease including 320,000 deaths among HIV-positive people⁵.

Tuberculosis is a notifiable disease in Australia and the focus of public health guidelines for monitoring, tracing and treating the disease. Much of the following has been sourced from the Communicable Disease Network Australia guidelines on tuberculosis⁶.

Tuberculosis usually attacks the lungs but can also affect other parts of the body. TB is transmitted mainly by inhalation of infectious droplets produced by persons with pulmonary or laryngeal tuberculosis during coughing, laughing, shouting, singing or sneezing. Rarely, invasion of *M. tuberculosis* may occur through mucous membranes or damaged skin. Extra-pulmonary tuberculosis, other than laryngeal, is generally not communicable, although can be associated with pulmonary tuberculosis.

TB is caused by the *M. tuberculosis* complex. *M. tuberculosis* is responsible for most cases. *Mycobacterium bovis* (*M. bovis*)*, *M. africanum*, *M. canettii* and *M. caprae* also cause a small number of TB cases in Australia. Humans are the primary reservoir for *M. tuberculosis* complex, although it is also found in other animals, predominantly primates⁷. *M. bovis* particularly is found in cattle and other mammals.

M. bovis tuberculosis results mainly from ingestion of unpasteurised milk and dairy products. However, aerosol transmission of *M. bovis* has been reported among abattoir and dairy workers and other workers butchering or cutting infected animals (e.g. cattlemen, veterinarians).

Most infections in humans result in an asymptomatic, latent infection. The time from infection to the primary lesion or measurable significant immunological reaction e.g. response to tuberculin Purified Protein Derivative (PPD), can vary from 2-10 weeks⁷. 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 2 years from initial infection. Infection with the *M. tuberculosis* complex without disease can persist for a lifetime. Active disease if left untreated kills more than 50% of those infected.

A person is infectious as long as viable bacilli are being discharged from the sputum. In practice, the greatest risk of transmitting infection is in the period prior to diagnosis and effective treatment of a pulmonary TB case. The risk of transmitting infection is reduced within days to two weeks after commencing appropriate TB treatment providing there is no drug resistant TB. A sputum smear positive case is more infectious than a case that is only culture positive.

The degree of communicability depends on:

- intimacy and duration of exposure
- number of bacilli discharged, infectivity of bacilli
- adequacy of ventilation and exposure of bacilli to sun or UV light
- opportunities for aerosolisation⁷⁷.

Over half of all cases in Australia present with pulmonary TB (disease involving the lungs) and can have the following common symptoms:

- A chronic cough, sometimes accompanied by haemoptysis
- Fever and night sweats
- Loss of weight
- Feeling generally tired and unwell.

Clinical suspicion of TB should be high in any person with exposure to risk factors and a respiratory infection unresponsive to standard treatments or an unexplained non-respiratory illness. This particularly includes:

- new arrivals and recently returned travellers from high incidence countries
- contacts of an active case within the past 5 years
- those with a history of previous TB treatment
- Indigenous Australians in localised areas (e.g. Northern Territory, Queensland)
- HIV positive patients.

Non-pulmonary TB (disease involving organs other than lungs) can present with a wide range of symptoms dependant on the site of disease and is often accompanied by intermittent fever or weight loss.

The use of standardised TB treatment for an appropriate period of time will result in cure rates over 98 per cent in drug sensitive disease⁸. Deaths from TB in the Australian setting are a rare occurrence and usually reflect co-morbidities and delayed or missed diagnosis and treatment. The success of treatment relies heavily on health care provider compliance, ensuring the right treatment is prescribed i.e. the right dose, drug combination and duration with the capacity to deliver the drugs without supply interruption, and patient adherence. Health care provider compliance and patient adherence are important to prevent the development of drug resistance and relapse. The disease does not always confer protective immunity as reinfection can occur.

People at increased risk of infection due to risk of exposure include:

- those in close contact with a case of TB (including household members)
- overseas-born health care workers (HCW) and HCW returning from working in high incidence countries
- new arrivals from countries (e.g. South Africa, Philippines, Vietnam, India, South Korea, Malaysia and China) or areas (e.g. in Africa or Pacific Islands) with a high incidence of TB
- people living in overcrowded conditions (e.g. some Indigenous Australians communities) or in institutions.

Almost everyone is susceptible to infection, however some groups are more susceptible to infection and progression to active TB than others. Those at increased risk of infection due to clinical vulnerability include those with HIV infection and other forms of immuno-suppression.

The risk of developing the disease once infected is high in the following groups of people⁹:

- children under 5 years of age, adolescents and the elderly
- those who are malnourished
- those immuno-compromised by disease, such as people living with HIV, diabetes and renal failure
- those on immuno-modulating therapies such as corticosteroids, anti-TNF inhibitors and anti-cancer treatments.

People with features consistent with inactive TB on CXR (e.g. fibrotic areas, apical scarring or blunted costo-phrenic angles) are at increased risk of progression to disease.

Aboriginal people and Torres Strait Islanders in some parts of Australia are at increased risk of TB due to adverse social and health factors. These include overcrowding and high rates of chronic diseases that increase the risk of reactivation of TB and some that can confound the diagnosis of TB such as the presence of chronic lung disease¹⁰.

PASC agreed that due to the different sensitivity and specificity of clinical testing in patients with HIV compared to patients without HIV, a separate analysis in these two populations should be presented.

Australia has one of the lowest rates of TB in the world, 4.7 cases per 100,000 population in 2010¹¹. Nevertheless, TB continues to pose ongoing challenges, reflecting the ongoing global problem. These challenges include an increasing incidence of multi-drug-resistant TB (MDR-TB), the development of extensively drug-resistant TB (XDR-TB), the human immunodeficiency virus (HIV) pandemic, and immigration to Australia, particularly from countries with high rates of TB. Australia faces a particular threat through the porous nature of our borders between the Torres Strait and Papua New Guinea (PNG).

In Australia 2 to 3% of cases are resistant to at least isoniazid and rifampicin (defined as MDR-TB)¹¹. Extensively drug-resistant TB (XDR-TB) refers to MDR-TB with resistance also to any fluoroquinolone and any of the second-line anti-TB injectable drugs, amikacin, kanamycin or capreomycin. Although XDR-TB is uncommon in Australia, approximately 25,000 XDR-TB cases are estimated to emerge globally every year and are associated with high mortality¹². Compared to the treatment of drug-sensitive disease, the treatment of MDR-TB and XDR-TB takes considerably longer (up to 2 years or more to complete), requires multiple drugs that are less potent and more toxic, and outcomes are poorer.

Two sets of data on TB are collected in Australia, the Australian Mycobacterium Reference Laboratory (AMRLN) Network compile data on cases of bacteriologically-confirmed tuberculosis whereas the National Notifiable Diseases Surveillance system (NNDSS) also includes cases that have been identified on the basis of clinical and epidemiological information, or on non-bacteriological laboratory investigations. In 2010, the AMRLN reports 1051 bacteriologically confirmed cases (4.7 cases per 100,000) versus the 1,327 (5.9 rate per 100,000) notified communicable disease as reported by the NNDSS¹³.

The World Health Organisation (WHO), 2013 report on tuberculosis, reports Australian TB data in much greater detail, Table 4.

Table 4: Case notifications, incidence, and case detection rates all forms, 1990-2012 Australia

Year		1990	1995	2000	2005	2010	2011	2012
New cases	New and relapse	1016	1073	1043	1046	1257	1239	1305
	Smear +ve			251	241	274	301	290
	Smear – ve/unknown			362	339	410	436	408
	Extra-pulmonary			369	450	457	463	498
	Other					5	2	63
	relapse			17	16	41	20	26
	Re-treat				27	24	29	20
	Excl relapse			17	43	65	49	46
	Total retreat					70	17	20
	History Unknown							
% Smear POS among New PULM			41	42	40	41	42	
	Population (Millions)	17	18	19	21	22	23	23
Incidence (including HIV)	Number (thousands)	1.2 (1.0-1.3)	1.2 (1.1-1.4)	1.2 (1.1-1.4)	1.2 (1.1-1.4)	1.4 (1.3-1.6)	1.2 (1.2-1.6)	1.5 (1.3-1.7)
	Rate ^a	6.8 (6.0-7.7)	6.8 (6.0-7.7)	6.2 (5.5-7.0)	5.9 (5.1-6.6)	6.5 (5.7-7.3)	6.3 (5.5-7.1)	6.5 (5.7-7.4)
Incidence HIV-positive	Number (thousands)	0.028 (0.024-0.031)	0.047 (0.041-0.053)	0.029 (0.026-0.033)	0.028 (0.025-0.032)	0.036 (0.031-0.041)	0.036 (0.031-0.040)	0.038 (0.033-0.043)
	Rate ^a	0.2 (0.14-0.18)	0.3 (0.23-0.29)	0.2 (0.13-0.17)	0.1 (0.12-0.16)	0.2 (0.14-0.18)	0.2 (0.14-0.18)	0.2 (0.14-0.19)
NOTIFIED NEW AND RELAPSE ^B	Number	1016	1073	1043	1046	1257	1239	1305
	Rate ^a	5.9	5.9	5.4	5.1	5.6	5.4	5.7
Case detection	Percent	87 (77-99)	87 (77-99)	87 (77-99)	87 (77-99)	87 (77-99)	87 (77-99)	87 (77-99)
Mortality (excluding HIV)	Number (thousands)	0.061	0.027	0.036	0.041	0.051	0.04	0.045
	Rate ^a	0.36	0.15	0.19	0.2	0.23	0.18	0.19
Prevalence (including HIV)	Number (thousands)	1.7 (0.750-2.9)	1.7 (0.740-3.0)	1.7 (0.740-3.0)	1.6 (0.650-3.0)	2.0 (0.830-3.6)	1.9 (0.740-3.0)	2.0 (0.860-3.7)
	Rate ^a	9.7 (4.4-17)	9.4 (4.1-17)	8.7 (3.9-16)	7.8 (3.2-14)	8.8 (3.7-16)	8.2 (3.3-15)	8.8 (3.7-16)

a rates are per 100 000 population

b NOTIFIED NEW AND RELAPSE includes cases for which the treatment history is unknown

Source⁵: Tables A4.1, A4.2, A4.3, A4.4, A4.5, A4.7

Absolute numbers of TB notifications in Australia are increasing with most new cases occurring in arrivals from countries with high rates of TB. In the Australian-born population the rate of TB is very low. The aim of Government policy is to prioritise higher-risk groups, Aboriginal and Torres Strait Islander Peoples and overseas-born persons (includes immigrants, students, health care workers), engagement in regional TB control programs and ensuring that there is a high standard of diagnosis and treatment¹⁴.

One of the big concerns of Australian Government TB policy is the emergence of the MDR-TB and XDR-TB and entry of these cases into Australia through the porous borders between Australia and Papua New Guinea via the Torres Strait. During 2012 the Queensland government shut down health clinics on Boigu and Saibai islands and returned 92 PNG nationals from Cairns to Daru Island for completion of their tuberculosis treatment. Amid concern that these patients were unlikely to receive

adequate treatment support, the Federal Government committed \$8.5 million via AusAid to improve services at the regional hospital on Daru Island and to support tuberculosis services throughout the Western Province (including the South Fly district) between 2011 and 2015¹⁵. A recent Press release from the Queensland Chief Health Officer reaffirmed that re-opening of the Saibai and Boigu island tuberculosis clinics for Papua New Guinea nationals was likely to increase the risk of cross-border infection for the Torres Strait and would likely also increase the risk of drug-resistant TB entering Queensland and so a decision was made to keep these clinics closed. Locally-controlled programs, as endorsed by the World Health Organization, have been significantly strengthened as the most effective method of combating TB in PNG¹⁶.

Non-tuberculosis mycobacteria

Non-tuberculous mycobacteria (NTMBs) are everywhere in nature, such as in water, food, soil, plants, animals and other sites. Many NTMB species have clinical significance, and the rapid and reliable identification of Mycobacterium tuberculosis complex (MTBC) and NTMB species is important. It is reported that NTMB disease has accelerated rapidly since the first reports of NTMB in AIDS patients in 1982 in the United States. Queensland has reported increasing incidence of pulmonary disease due to environmental NTMB. Clinically significant cases represent approximately one-third of all NTMB patient-isolates processed by laboratories in the state. Postulated reasons for this increase include increased awareness of mycobacteria as pulmonary pathogens, improvements in methods of detection and culture and an ageing population (as this is often a disease of the elderly)¹⁷. Another reason for this increase is the introduction of new technologies in laboratories that allow better recovery and more accurate identification of new species of NTMB¹⁸. NTMB is not a notifiable disease in Australia and there is a dearth of prevalence or incidence data identified.

Delivery of the intervention

For the diagnosis of a patient with active TB, the NAAT is only able to be performed in patients who are untreated, that is patients who have less than 7 days of treatment.

In this population the NAA test should only be performed in institutions proficient in the culture and identification of *MTB*. Transport and storage is important for this test and it should be stored at 2-8°, and samples preferably should not be stored but read within 24-48 hours (prolonged storage > 4 days has been reported to impact on results). Results can be provided to clinicians within 24-48 hours.

The Xpert® MTB/RIF Assay includes single-use disposable cartridges and sample reagent for sample preparation. The Xpert® MTB/RIF cartridges contain reagents for the detection of MTB-complex DNA and Rif resistance associated mutations. A Sample Processing Control (SPC) and a Probe Check Control (PCC) are also included in the cartridge. The SPC is present to control for adequate processing of the target microorganism and to monitor the presence of inhibitors in the PCR reaction. The Probe Check Control (PCC) verifies reagent rehydration, PCR tube filling in the cartridge, probe integrity and dye stability⁴.

Specimens for testing are of particular concern with TB testing, due to the diseases highly infectious nature and the need to obtain sufficient sample for microbiologist testing and culture. The following is the recommendations for obtaining specimens¹⁹.

Pulmonary TB:

- Sputum should be collected as early-morning samples on 3 separate days for highest sensitivity.
- The “spot-morning-spot” protocol of a spot sputum collected when seen, then the next morning and again when seen the next day is efficient, almost as sensitive as 3 separate day collections and more convenient for out-patients.
- Sputum induction (using nebulised hypertonic saline) or gastric lavage may be attempted in appropriate patients unable to expectorate.

Extra-pulmonary TB:

- The investigation of extra-pulmonary TB is often problematic and requires the collection of samples from normally-sterile sites (e.g. CSF, bone, lymph node, and peritoneum) by radiological guidance or at operation.
- Surgeons and operating room staff must be specifically directed to place specimens in saline and NOT formalin so that culture and drug susceptibility testing are possible.

Inhibitors may be present in the PCR reaction but it is expected that laboratories will only report NAAT results once they have tested for inhibitors. It is estimated that in patients with the signs and symptoms of active TB, only one NAAT per patient per year will be required. Repeat testing may be required, in patients who have tested negative and are not treated or in later years in the event that a patient relapses or is reinfected.

In patients who have tissue biopsy with histopathology consistent with mycobacteria, no limitation on the number of tests is proposed. Separate NAAT tests are available for testing for different mycobacteria and a sample may require multiple NAAT tests.

Prerequisites

It is not anticipated that the ordering of the NAAT test will be limited to a specific type of referrer.

It is anticipated that the test will only be able to be undertaken by laboratories that are already equipped to test for *MTB*. There are recognised guidelines²⁰ for Australian Mycobacteriology Laboratories specifying biosafety safety procedures, infrastructure, equipment and work practices required by the laboratory. Laboratories performing TB cultures must participate in a recognised QAP program.

The guidelines recommend that all mycobacteriology investigations be undertaken in PC2 facilities with additional processes and precautions in place. Laboratories undertaking more than 5,000 cultures per year, performing drug sensitivity testing (DSTs), or knowingly handling MDRTB strains should have PC3 facilities.

Approximately 80 laboratories in Australia perform smear microscopy then forward the specimen to another laboratory for mycobacterial culture. The microscopy-only laboratories almost universally perform direct Ziehl-Neelsen (ZN) smears.

Laboratories should perform drug sensitivity tests (DSTs) or refer isolates to reference laboratories for DSTs in the following circumstances:

- all initial isolates of *M. tuberculosis*;
- isolates from patients who remain culture-positive after 3 months of treatment;
- isolates from patients who are clinically failing treatment; or
- an initial isolate from a patient relapsing after previously successful TB treatment.

The minimum DSTs that should be performed are for isoniazid (high- and low-level concentrations as appropriate), rifampicin, ethambutol, +/- streptomycin.

Referral of non-tuberculous mycobacteria cultures

With the low incidence of TB in Australia, the culture, identification and susceptibility testing of non-tuberculous mycobacteria represents an increasing proportion of the workload for the MRL network. It is recommended that investigations should not be performed on every NTMB isolate (as many represent colonisation or contamination) but only when clinically relevant. Diagnostic criteria have been described for determining the significance of a pulmonary NTMB isolate, particularly *M. avium* complex (MAC) and *M. abscessus*.

Co-administered and associated interventions

NAAT for diagnosis of TB infection in a person with clinical signs and symptoms of active TB does not require any co-administered and associated interventions. NAAT for mycobacterial infection other than tuberculosis in tissue biopsy with consistent histopathology does not require any co-administered and associated intervention.

Listing proposed and options for MSAC consideration

Proposed MBS listing

The application did not provide a proposed MBS item descriptor.

Patients with the signs and symptoms of active TB, and patients with tissue biopsy with histopathology consistent with non-TB mycobacteria are two different populations and require different NAAT tests.

The proposed target populations for the NAAT test are:

Patients with the signs and symptoms of active tuberculosis

It is proposed that nucleic acid amplification (NAAT) for the diagnosis and management of TB will be assessed for use in the following two populations:

1. Patients with the clinical signs and symptoms of active TB from whom a specimen is obtained that is able to have an acid fast bacilli smear (AFB) test and culture and susceptibility performed. Included within this population are two sub-groups:

a. patients with the signs and symptoms of active TB whose background epidemiology gives rise to a high pre-test probability they will have active TB (e.g. they come from a country with high rates of endemic TB). This sub-group is further subdivided into:

i. patients whose specimen has a high diagnostic yield for AFB test (likely high bacterial load e.g. sputum)

ii. patients whose specimen has a low diagnostic yield for AFB test (likely low bacterial load, e.g. tissue, lymph node, CSF)

b. patients with the signs and symptoms of active TB whose background epidemiology gives rise to a low pre-test probability that they will have active TB, but for which a diagnosis of TB must be excluded. This sub-group is further subdivided into:

i. patients whose specimen has a high diagnostic yield for AFB test

ii. patients whose specimen has a low diagnostic yield for AFB test

2. Patients with the clinical signs and symptoms of active TB from whom it is not possible to obtain a specimen that is able to have an AFB smear test performed but the specimen is able to have a culture and susceptibility. Included in this population are two types of patients, those:

a. with the signs and symptoms of active TB whose background epidemiology gives rise to a high pre-test probability that they will have active TB.

b. with the signs and symptoms of active TB whose background epidemiology gives rise to a low pre-test probability that they will have active TB but for which a diagnosis of TB must be excluded.

Patients with histopathology consistent with Non-Tuberculous Mycobacteria

On the basis of clinical need, NAAT for the diagnosis of infection due to non-tuberculous mycobacteria will be assessed for use in the following population:

1. Patients with tissue biopsy with histopathology consistent with non-TB mycobacteria.

Clinical place for proposed intervention

In proposing the use of NAAT in diagnosis and managing active TB infection, the application has referred to the CDC guidelines which propose that NAAT be an addition to the clinical algorithm for the diagnosis of TB and not a substitute for any current test.

The CDC recommendations for NAAT testing (January 2009)²¹ is that:

“NAAT testing should be performed on at least one respiratory specimen from each patient with signs and symptoms of pulmonary TB for whom a diagnosis of TB is being considered but has not yet been established, and for whom the test result would alter case management or TB control activities.”

These guidelines were developed prior to the availability of NAAT tests also able to detect antibiotic resistance, in particular rifampicin.

Expert opinion is that a major factor in the clinical management of a patient with the signs and symptoms of active TB is the patient's pre-test probability of having TB. That is a patient is from one of the recognised high risk groups. The following clinical management algorithms have been developed incorporating expert opinion and CDC guidelines.

Figure 1 presents current and proposed clinical management algorithms for patients with the clinical signs and symptoms of active TB and for whom an AFB microbiology test can be done on multiple specimens e.g. sputum or on a single specimen e.g. CSF or urine. Currently, clinicians will rely on the results of the AFB as well as patient's background epidemiology of high or low pre-test probability that they will have active TB as the basis to initiate or defer antibiotic treatment. Treatment decisions will also be influenced by the type of specimen that is obtained from the patient. This is because a specimen for an AFB test can have a high diagnostic yield (likely high bacterial load), or a specimen for an AFB has a low diagnostic yield (e.g. ascitic fluid, urine). The proposed introduction of the NAAT will be used as an adjunct test to AFB, either after or alongside. Treatment decisions will continue to be influenced by a patient's pre-test probability of active TB.

Figure 2 presents 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 for AFB smear testing. These are patients who present with, for example, a lymph node from which a biopsy can be obtained, but smear examination is not possible (but MC&S is possible). Histology is not able to differentiate between TB and NTMB or in many instances, from pathology other than mycobacterial disease. It is anticipated that this will be a very small population. Treatment decisions are influenced by patient's pre-test probability of active TB and specimen diagnostic yield for MTB. In this population it is anticipated that NAAT testing will substitute for the current testing.

For the target population in Figure 1, those patients with the clinical signs and symptoms of active TB, for which a specimen for AFB smear can be obtained, it is assumed that MC&S will also be performed on the same specimens.

For target population in Figure 2, those patients with the clinical signs and symptoms of active TB, for which a specimen for AFB smear is unable to be obtained, it is assumed that a specimen will be obtained for which MC&S can be performed.

PASC agreed that an assessment of the utility of NAAT in patients for whom a clinical diagnosis of active TB is made, but in whom it is not possible to obtain a sample for culture and susceptibility, will lie outside the scope of this application.

The application has not indicated where NAAT for non-tuberculosis mycobacterium (NTMB) infection will sit within the clinical algorithm.

Figure 3 presents current and proposed clinical management algorithms, for patients, on the basis of clinical need. NAAT for the diagnosis of infection due to non-tuberculosis mycobacteria will be assessed in patients with tissue biopsy where histopathology is consistent with non-TB mycobacteria. It is assumed that a culture for diagnosis and susceptibility will also be performed. For this population it is assumed that the proposed NAAT will substitute for current testing.

CONSULTATION

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

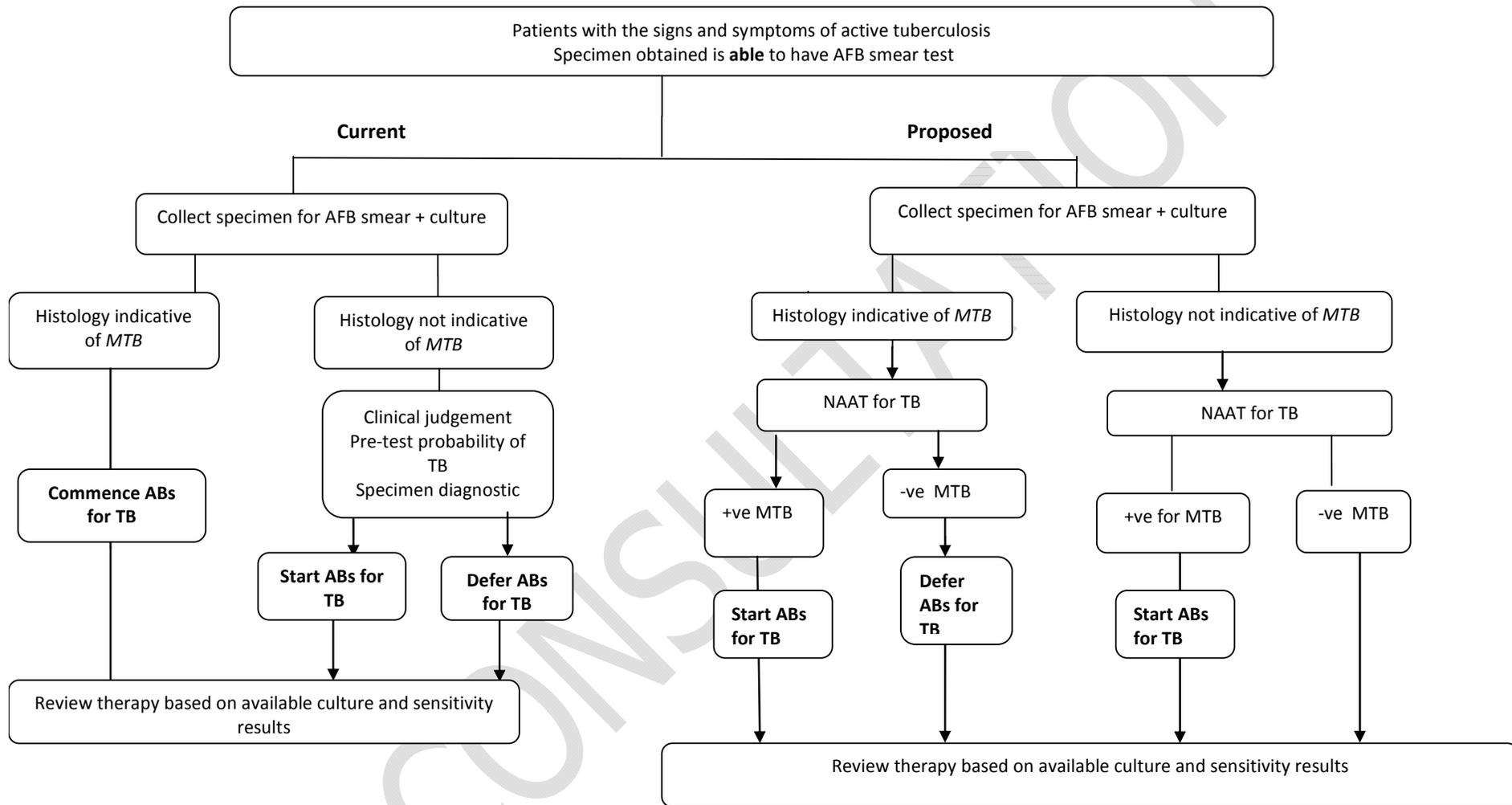


Figure 2: Current clinical management of TB and proposed algorithm with use of NAAT for active TB where AFB is not able to be obtained

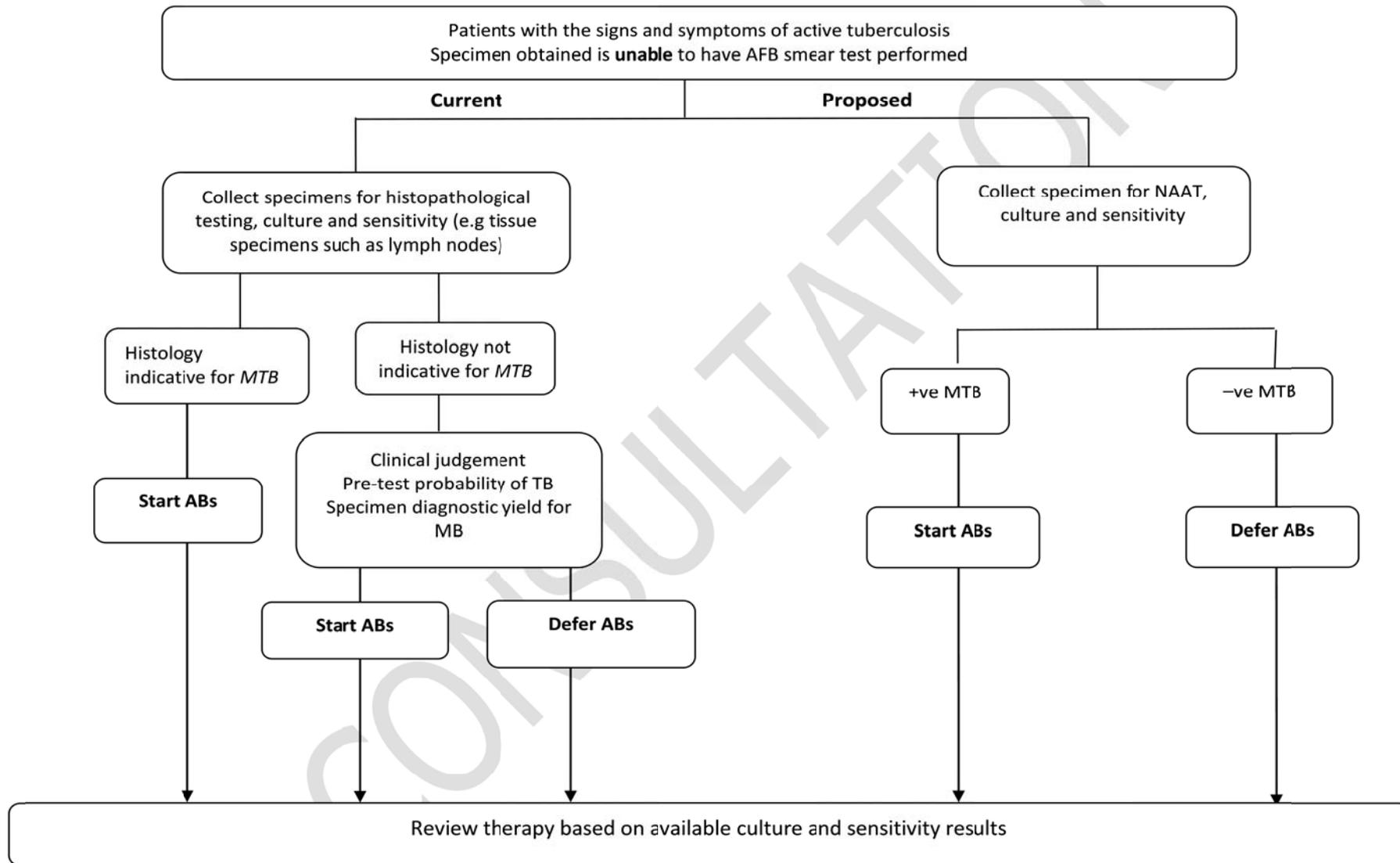
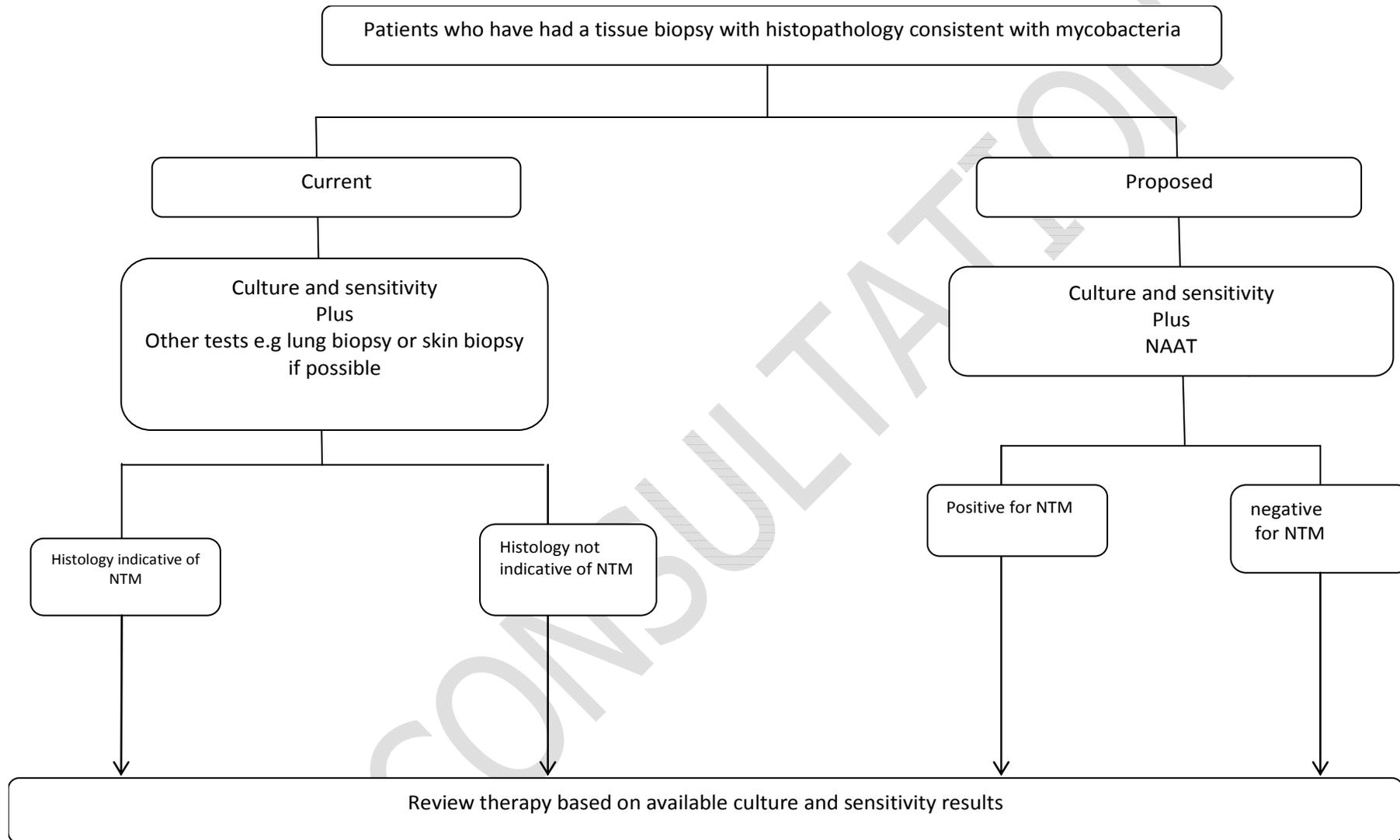


Figure 3: Current clinical management algorithm and proposed algorithm with use of NAAT for patients who have tissue biopsy consistent with mycobacteria



Although, currently multiple specimens can have an AFB test (e.g. 3 consecutive sputa) (and culture and susceptibility), it is not recommended that NAAT be performed on every suspected TB specimen²² Evidence will only be included if the diagnostic accuracy of the tests are determined by reference to MC&S. Where NAAT is performed on a specimen (in addition to MC&S) where an AFB smear cannot be done, it is anticipated that only one test per patient will be required. If the patient has a negative NAAT result, it is assumed repeat testing for inhibitors is not required and that laboratories will only report NAAT results after they have tested for inhibitors. Currently, AFB testing is also done to monitor a patient's response to therapy, i.e. the time it takes patients to convert to AFB smear negative. It is not anticipated that NAAT will be used by clinicians for this role.

Information collected for the National Surveillance Disease Database²³ which includes data such as a person's country of birth, extrapulmonary site, whether new or relapsed case, risk factors, age, and indigenous status should enable risk status of patients to be ascertained. It is anticipated that information about the likelihood that specimens have 'low' or 'high' diagnostic yield for AFB should be available from the literature. Similarly information about the likely tests undertaken when an AFB is unable to be obtained should also be available from the literature.

For patients where the tissue sample has histopathology consistent with mycobacterial infection, then the proposed intervention will consist of an NAAT to diagnose the infection (Figure 3)

- 1) Where the NAAT is positive this may not be sufficient to convince clinicians that this is the cause of symptoms (with the exception of MTB) because of the ubiquity of mycobacteria and its potential to contaminate a specimen. It is not anticipated that further testing will be required
- 2) Where the NAAT is negative it may be difficult to interpret because it is likely an in-house assay that has been used, and the ability of this assay to differentiate for different types of MB as well as the scope of the assay for testing for different types of MB may not be known.

In this group of patients, who have had a positive NAAT, separate NAAT testing for different strains of mycobacteria may need to be performed.

There is a paucity of information about the types of mycobacterial infection responsible for pulmonary disease in Australia. Extrapolation from overseas populations will probably be required to estimate the proportion of patients in this clinical algorithm. Consultation is requested on the collection of data in Australia (or failing that overseas) on different types of non-TB mycobacterial infection, their *prevalence, incidence and sequelae and pathology tests (other than NAAT) used for testing.*

Comparator

Mycobacterium Tuberculosis

1. It is proposed that the most appropriate comparator for NAAT testing for the population with the clinical signs and symptoms of active TB for whom a specimen is **able** to have an AFB test performed, then the comparison will be NAAT plus AFB compared to AFB alone.

2. It is proposed that the most appropriate comparator for NAAT testing for the population with the clinical signs and symptoms of active TB from whom a specimen that is able to have an AFB test is **not able** to be obtained the comparison will be NAAT alone compared to current standard testing, e.g. histology .

In relation to the assessment of the diagnostic accuracy of the technology in determining the presence of *MTB* in a specimen, culture and susceptibility will be used as the reference standard to determine the sensitivity and specificity of the test.

Non Tuberculous Mycobacteria

The application claims that the use of NAAT in patients with tissue samples with histopathology consistent with mycobacterial infection will not replace the use of any of the tests currently undertaken to diagnose NTMB infections. Therefore, the appropriate comparator in the identified population is “no use of NAAT”.

In relation to the assessment of the diagnostic accuracy of NAAT in determining the presence of NTBM, culture will be used as the reference standard. It will however, be important to acknowledge that there may be no reliable reference standard for the diagnosis of non- tuberculous mycobacteria. In addition, for a significant proportion of this population, tissue sample may be the only specimen available for testing

Table 5: Proposed MBS item descriptor for [item]

Category 6 – Pathology Services
MBS [item number] Nucleic acid amplification test for detection of mycobacteria - Fee: \${fee} [Relevant explanatory notes]

PASC advice is that no limit on the number of tests per year per patient be included in the MBS item descriptor.

The relevant explanatory notes included with this MBS item descriptor will include the information that any laboratory using an in-house assay to test for mycobacteria is also covered by the new TGA regulatory framework introduced in July 2010 under which in vitro diagnostics are included as a subset of medical devices.

The application reports that in Australia tuberculosis treatment is provided free of charge, however the diagnostic test is only eligible for a Medicare rebate if the test is covered by a Medicare item number i.e. AFB microscopy and culture only.

There are a number of nucleic acid amplification tests currently listed on the MBS. These range from detection of microbial nucleic acid (item 69494), with a Medicare fee of \$28.85; through to the

amplification and determination of Hepatitis C virus genotype, item 69491, with a Medicare fee of \$206.20. The application reports that the NSW state reference laboratory (ICPMR) charges \$200 for TB PCR which is billed to the patient. The Victorian state reference laboratory (VIDRL) charges \$88 for TB PCR which is also billed to the patient.

The item descriptor may need to be limited by the evidence available about NAAT testing according to particular specimens. For example, if the literature reports diagnostic accuracy of NAAT testing only in respiratory specimens, then the item descriptor may need to limit the test only to these specimens.

Clinical claim

Tuberculosis

It is proposed that patient outcomes will differ according to the pre-test probability of a patient having tuberculosis. For some patients who have clinical symptoms of active TB and a high pre-test probability of the disease, given the public health implications, antibiotic treatment is commenced based on clinical symptoms and pre-test probability. Therefore the potential of NAAT to significantly alter the case management or TB control activities is limited. In this population it is proposed that the use of NAAT is non-inferior to current practice.

The exemption may be where the NAAT also detects the rifampicin resistance associated mutation; this can provide clinicians with information on whether the patient's TB is resistant to the antibiotics being used. In this situation the use of NAAT may be superior because it provides clinicians with additional information that can lead to a change in case management, and provide public health benefits in reducing the infectiousness of the patient earlier. Currently a change in the antibiotic regime would be due to ongoing AFB tests (where they can be collected) indicating that a patient is not responding to treatment, or waiting for the result of the culture and susceptibility in 6-8 weeks.

For patients for whom an AFB test is able to be obtained and whose pre-test probability of TB is low then the clinical claim is that NAAT testing is superior to the current standard testing because a positive NAAT test would result in immediate treatment that would not have been indicated based on the low pre-test probability of TB.

For patients for whom an AFB test is not able to be obtained and whose pre-test probability of TB is low then the clinical claim is that NAAT testing is superior to the current standard testing e.g. histology.

Non-Tuberculous Mycobacteria

In patients with tissue culture with histopathology consistent with mycobacteria, NAAT is expected to be an additional test to the tests currently performed to diagnose NTMB, so the claim is that the use of NAAT in this population will be superior compared to no NAAT test.

Outcomes and health care resources affected by introduction of proposed intervention

Clinical outcomes

Active TB

- Diagnostic sensitivity and specificity of NAAT in conjunction with AFB compared to AFB alone. This information should be presented separately for AFB positive and AFB negative patients.
- If possible the assessment will present the diagnostic sensitivity and specificity of NAAT test alone compared to AFB test alone, especially in specimens from patients that are likely to have a low bacterial load
- Diagnostic sensitivity and specificity of NAAT compared to no NAAT (in the population who are unable to have an AFB smear).
- Change in patient management (this incorporates factors other than just a change in antibiotic treatment, for example, the need for isolation)
 - Appropriate antibiotic treatment

For patients with a low pre-test probability of disease, the addition of a NAAT test to an AFB test may result in different patient outcomes. For example, for patients whose AFB test is negative, but the NAAT is positive, NAAT has the potential to diagnose TB early with significant public health implications. In patients for whom clinical symptoms of active TB, and a high pre-test probability of disease, given the public health implications, antibiotic treatment is commenced on clinical symptoms and pre-test probability. In these patients the potential of NAAT to significantly alter the number of patients who will be treated or not treated is limited. For patients with a high pre-test probability of disease, the addition of a NAAT test that also tests for drug sensitivity to an AFB may change case management as discussed above. The other population is people for whom the addition of a NAAT test to standard testing, with a low pre-test probability of TB, may result in an increase in the number of patients diagnosed with TB or clinicians may be able to defer antibiotic treatment. For these populations the outcomes that should be reported is a change in clinical management (initiating or deferring antibiotic treatment) as a result of a discordant result between AFB and NAAT or the change in clinical management resulting from additional information provided to clinicians from the NAAT test.

Outcomes are to be reported up until the time that available MC&S results are available, 6-8 weeks. Outcomes are to be reported separately for patients who are HIV positive and patients who are HIV negative.

Non Tuberculous Mycobacteria

In assessing the evidence of the effectiveness of the NAAT in detecting NTMB, in tissue culture with consistent histopathology, the assessment should present the:

- Analytic sensitivity and specificity of NAAT

- The diagnostic sensitivity and specificity of NAAT compared to the reference standard of culture

*The assessment should present any limitation in evaluating the evidence of the effectiveness of NAAT in detecting NTMB. In addition, where the NAAT is positive this result may not be sufficient to convince clinicians that this is the cause of symptoms (with the exception of MTB) because of the ubiquity of mycobacteria and its potential to contaminate a specimen. Expert advice is that currently clinicians often require two positive cultures of MB before the result is considered to have clinical relevance. **Consultation is required on situations where culture is not able to be obtained whether a metric of additional benefit to clinicians in diagnosing the MB infections, if available, should be presented.***

There are unlikely to be any adverse events associated with the use of NAAT, aside from the harms associated with false positives and false negative results. The consequences of a false negative may have important implications for infection control. The consequences of a false positive result may be the inappropriate treatment of patients with isoniazid, an antimicrobial that is associated with known safety concerns.

Health care resources

The health care costs that will be used to deliver this intervention are:

- Cost of the testing kit (where commercially available kits are used).
- If the test is performed as an in-house assay then the costs used by the laboratory to determine the cost
 - Labour costs,
 - System used
 - overhead costs
- Cost of antibiotic regime for TB treatment
- Cost of treatment for non-TB mycobacteria
- Cost of hospitalisation for TB treatment and any isolation required (*data will be required as an input to the model of the proportion of patients treated in the hospital, how long they are hospitalised for, and what clinical factors decide if a patient is no longer infectious if AFB smear cannot guide a clinician*). Consultation is requested on these model parameters.
- Cost of contact tracing for TB
- Cost of changing TB drug regime

Proposed structure of economic evaluation (decision-analytic)

Table 6 sets out a summary of the extended PICO for the comparison of NAAT plus AFB compared to AFB only, or NAAT alone compared to AFB alone, or NAAT compared to standard tests (no NAAT) for diagnosing tuberculosis. Table 5 sets out a summary of the extended PICO for the comparison of NAAT compared to standard tests (no NAAT) for diagnosing non-tuberculous mycobacteria.

Table 6: Summary of extended PICO to define the question for public funding that assessment will investigate

Patients	Intervention	Comparator	Outcomes to be assessed	Healthcare resources to be considered
Patients with clinical signs and symptoms of active TB whose specimen is able to have an AFB smear and MC&S	NAAT (+AFB smear)	AFB smear	-Diagnostic accuracy of NAAT with AFB vs AFB (ref standard MC&S) -change in clinical management -appropriate antibiotic regimen earlier	-Testing kit - Laboratory costs - Hospitalisation - Contact tracing - Antibiotic regime
Patients with the signs and symptoms of active TB whose specimen is unable to have an AFB smear test but specimen able to have MC&S	NAAT	Current testing (e.g. tissue biopsy)	Diagnostic accuracy of NAAT vs no NAAT (ref standard MC&S) -change in clinical management	Testing kit -Laboratory costs - hospitalisation - contact tracing -antibiotic regime
Patients with tissue biopsy with histopathology consistent with non-TB mycobacteria and able to have MC&S	NAAT	No NAAT	-Diagnostic sensitivity and specificity of NAAT compared to the reference standard of MC&S	-Testing kit -Laboratory costs
<p><u>Active TB</u> What is the effectiveness, safety and cost effectiveness of NAAT versus NAAT plus AFB smear in diagnosing tuberculosis in patients who have the clinical signs and symptoms of tuberculosis? What is the effectiveness, safety and cost effectiveness of NAAT versus current testing r in diagnosing tuberculosis in patients who have the clinical signs and symptoms of tuberculosis for which a AFB smear (pulmonary specimen) is not obtainable?</p> <p><u>NTMB</u> What is the effectiveness, safety and cost effectiveness of NAAT in diagnosing NTMB in patients with tissue histopathology consistent with NTMB compared to no NAAT ?</p>				

The decision analytic that is proposed, Figure 4, will follow a cohort of patients who present with the signs and symptoms of active TB. Currently patients with a high probability of TB are treated as if they have TB irrespective of the results of their AFB test. If an AFB test is able to be obtained and is positive, then it can be used monitor the success of drug therapy and to determine infectiousness. Culture results should also provide information on drug sensitivity and the drug regimen may be adjusted accordingly. However, for these patients even a negative culture, on top of a negative AFB, may not result in treatment being ceased. Other factors, including tests such as X-ray, as well as the public health implications of TB play a part in determining clinical management aside from diagnostic tests. The introduction of a NAAT is unlikely to have much of an impact on this population because as already noted if the patient has risk factors associated with TB and presents with the signs and symptoms of active TB they will be treated accordingly. The exception is that, if the NAAT test proposed is able to test for rifampicin mutations, then for those patients whose TB shows resistance to rifampicin, their drug regimen can be adjusted, without needing to wait for culture results, resulting in the appropriate pharmacotherapy and reducing the length of their drug regimen. There is a low incidence of drug resistant TB in Australia, so these results are unlikely to be a major driver in the model, but these results will be explored in the model. Similarly to the current situation it is unlikely that a negative culture result will result in a cessation of drug therapy.

People with a 'low' probability of TB, i.e. they have none of the risk factors associated with TB infection, will receive the same tests as a 'high' risk person but test results are more likely to drive treatment decisions. Antibiotics for TB are more likely to be initiated based on test results; a positive AFB will initiate antibiotics for TB, which will continue until the results of the MC&S are received. A person whose AFB is negative for *MTB* is unlikely to receive antibiotic treatment for TB, clinicians will await MC&S results. The sensitivity and specificity of AFB for *MTB* will inform this part of the model as it has the potential to affect a clinician's case management. In the comparator arm of the model, this population will also receive a NAAT test which allows for the differentiation of *MTB* from NTMB. Clinicians will be faced with two test results to guide their decision making. Where an AFB and NAAT test are both positive or negative for a patient, case management is unlikely to change. However, for patients with a negative AFB but positive NAAT test, case management is likely to change, antibiotics will be commenced and contact tracing commence. The sensitivity and specificity of a NAAT to detect *MTB* in smear-negative patients will inform this part of the model. A person in the model who has a 'low' probability of TB, and whose AFB is positive, but the NAAT is negative for *MTB*, clinicians will likely defer antibiotics (the positive AFB may be attributable to mycobacterial contamination) and delay contact tracing and await MC&S results. The sensitivity and specificity of a NAAT to detect *MTB* in smear-positive patients will inform this part of the model. A proportion of this group who previously were treated with ABs on the basis of a positive AFB will not receive treatment and wait for culture results. Although, people with a 'low' probability of TB, are as a group those least likely to require testing for TB, they will be the most likely driver of results in this model, as it is this population where use of the NAAT is most likely to drive a change in case management.

In the current scenario people in the model, with the signs and symptoms of active TB, for whom a specimen for AFB test is unable to be obtained, and who have a 'low' probability of TB, will have antibiotic treatment commence if they have histology indicative of *MTB*. In the model, NAAT will be used in addition to this test and a positive NAAT will result in antibiotic treatment and contact tracing. A negative NAAT will result in deferring of antibiotic treatment until culture results are available. The sensitivity and specificity of NAAT to detect *MTB* in this type of specimen (e.g. lung tissue) will inform this part of the model.

The model will be used to investigate any consequences from deferring antibiotic treatment until culture results are available in 6-8 weeks. These consequences might include any effects to the patient from delayed treatment and the probability that other people might become infected as a result of this person remaining infectious in the community. In addition, the model will investigate any consequences to the patient from receiving unnecessary antibiotic treatment for TB, as these drugs can have significant side effects.

Figure 4: Decision analytic of changes to current treatment from the proposed intervention

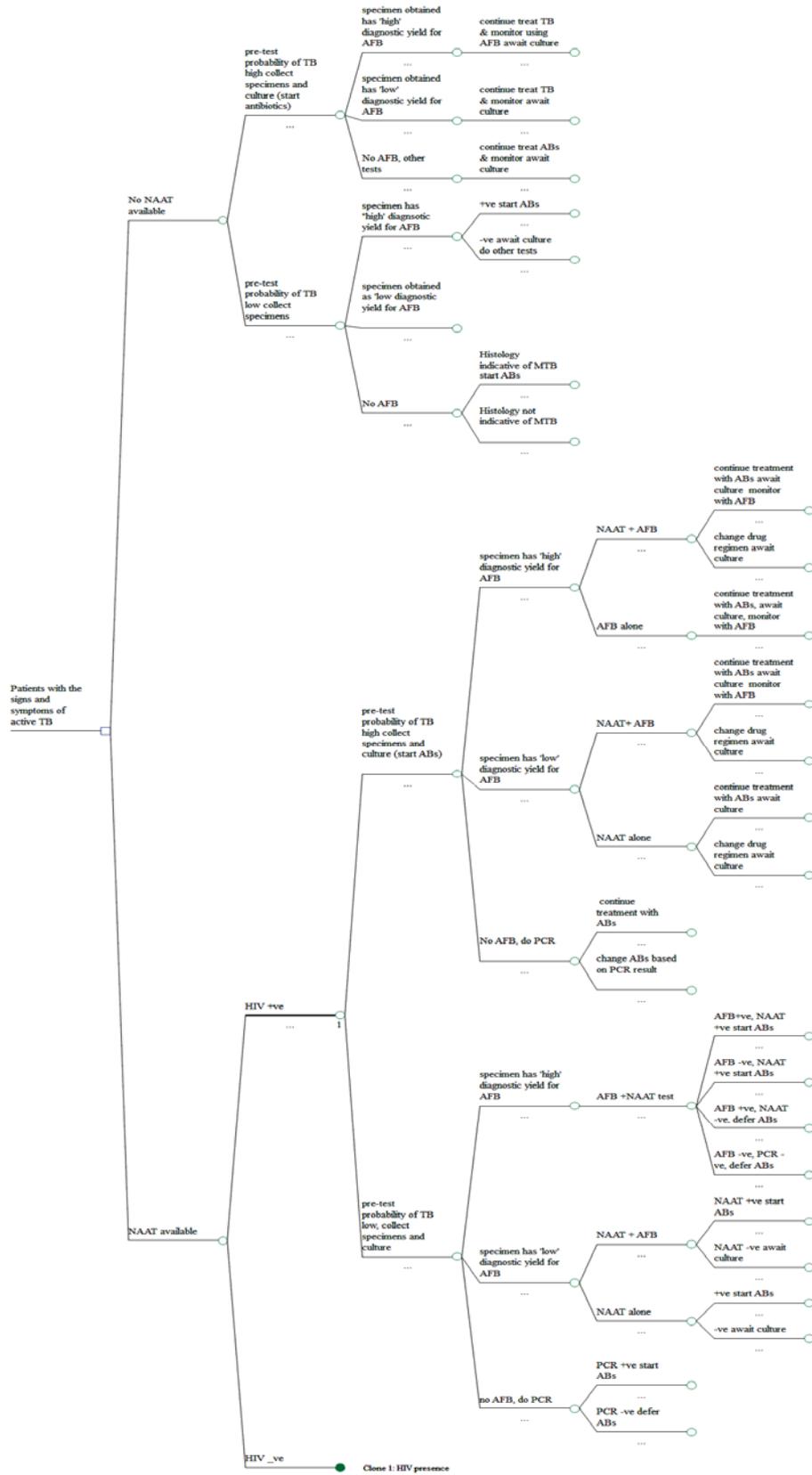


Table 7: List of resources to be considered in the economic analysis

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS	Safety nets*	Other govt budget	Private health insurer	Patient	Total cost
Resources provided to identify eligible population										
- Resource 1										
- Resource 2, etc										
Resources provided to deliver proposed intervention										
- Testing kit	company	lab								?
- Lab costs (labour, overheads)	lab	lab								?
Resources provided in association with proposed intervention										
- Contact tracing										
- Cost of ABs										
- Cost of hospitalisation incl isolation										
- Microscopy for AFB & culture					69330				\$19.20	\$128.00
Resources provided to deliver comparator 1										
- Microscopy for AFB & culture									\$19.20	\$128.00
-										
Resources provided in association with comparator 1 (e.g. pre-treatments, co-administered interventions, resources used to monitor or in follow-up, resources used in management of adverse events, resources used for treatment of down-stream conditions)										
- Contact tracing										
- Cost of antibiotics										
- Cost of hospitalisation incl isolation										
- Microscopy for AFB & culture										

* Include costs relating to both the standard and extended safety net.

¹ The strategic plan for control of tuberculosis in Australia: 2011-2015. *Communicable Diseases Intelligence Volume 36 No 3 - September 2012*

²

<http://www.fda.gov/medicaldevices/productsandmedicalprocedures/invitrodiagnostics/ucm330711.htm>

³ Update guidelines for the use of Nucleic Acid Amplification Tests in the Diagnosis of Tuberculosis

⁴ US Food and Drug Administration, 510(k) Decision Summary (K131706) Xpert[®] MTB/RIF Assay <http://www.fda.gov/medicaldevices/productsandmedicalprocedures/invitrodiagnostics/ucm330711.htm> (accessed 4/11/2013)

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