



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1646 – Whole genome sequencing of antimicrobial-resistant pathogens

Applicant: Royal College of Pathologists of Australasia

Date of MSAC consideration: 31 March – 1 April 2022

1. Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of pathogen whole genome sequencing (WGS) for five indications for antimicrobial drug susceptibility testing (DST) was received from the Royal College of Pathologists of Australasia by the Department of Health. PASC advised that the mycobacterial indication should be assessed first. The exemplar for this indication is patients diagnosed with tuberculosis with confirmed *Mycobacterium tuberculosis*. DST allows patients to be treated with antibiotics the organism is likely to respond to, improving the health of the affected individual, and decreasing the likelihood of further resistance developing.

The comparative clinical claim made by the applicants is that use of WGS is non-inferior to phenotypic drug susceptibility testing (pDST) alone. However, the evidence supported a claim of superior effectiveness and superior safety compared to pDST alone.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC supported whole genome sequencing of *Mycobacterium tuberculosis* complex (MTBC) to speciate the organism and characterise its resistome, at initial diagnosis and at recurrence, on the basis that the proposed testing is safe and more effective than current phenotypic based drug susceptibility testing, is probably cost-effective, and would have a modest financial impact.

Consumer summary

MSAC noted that this is an application from the Royal College of Pathologists of Australasia requesting Medicare Benefits Schedule (MBS) listing of pathogen whole genome sequencing for antimicrobial drug susceptibility testing (DST) in patients who have an infection caused by a pathogen in the *Mycobacterium tuberculosis* complex.

Pathogens are organisms, such as bacteria and viruses, that cause disease in other organisms. Some bacteria develop resistance to common medications. This means that the medication can no longer kill the pathogen, so they are more easily able to spread disease, leading to increased disability and death.

Consumer summary

Tuberculosis is a disease that is caused by infection with bacteria from a group called the *Mycobacterium tuberculosis* complex. In Australia, people who get tuberculosis are more likely to have been born overseas, and to be living in remote and regional areas. Tuberculosis most commonly affects a person's lungs, but can also affect other parts of the body and can cause serious illness. Tuberculosis is usually treated with antibiotics, but when an antibiotic is given to people whose infection is resistant to that drug, then there will be delays in their recovery, or it may not work at all. If a patient receives an inappropriate medication, it also makes it more likely that new drug resistant strains of tuberculosis will evolve. At the moment, after an initial test shows that a patient has tuberculosis, laboratories work out which drugs a patient's pathogen is resistant to by seeing how well it can grow with, and without, each drug.

Every living organism is made up of genes, and together all the genes in an organism are called its genome. Whole genome sequencing is a technique where all the genes of the pathogen are looked at, and mutations that are known to result in drug resistance can be identified. Whole genome sequencing therefore allows experts to work out which medications will work most effectively to kill the pathogen infecting each specific patient.

MSAC considered that there are no safety issues, and that whole genome sequencing of tuberculosis gave faster and more accurate results compared to the testing currently used. This means that patients can get the most effective treatment sooner, and there may be savings on hospital and drug costs if patients can be discharged home sooner.

MSAC also considered that the cost to the MBS of publicly funding whole genome sequencing for *M. tuberculosis* complex would be modest.

MSAC's advice to the Commonwealth Minister for Health

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC supported whole genome sequencing of *Mycobacterium tuberculosis* complex, both at the time that tuberculosis is diagnosed and if the infection comes back (recurs). The proposed testing is safe and more effective than current drug susceptibility testing, is probably cost-effective and would have a modest financial impact.

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

MSAC noted that this is an application from the Royal College of Pathologists of Australasia (RCPA) requesting MBS listing of pathogen WGS for five indications for antimicrobial drug susceptibility testing (DST). MSAC noted that PASC had advised that the mycobacterial indication should be assessed first, and the exemplar for this indication is patients diagnosed with tuberculosis (TB). MSAC noted ESC's advice that the DCAR had narrowed the exemplar to TB caused specifically by *Mycobacterium tuberculosis*, but that the evidence was relevant to patients with MTBC infections.

Currently, usual care in patients with an MTBC infection uses phenotypic antimicrobial drug susceptibility testing (pDST; the comparator), which can take several weeks. MSAC noted the clinical management algorithm, where the WGS test is proposed as an additional test for people diagnosed with mycobacterial infections. The purpose of the test is to detect and characterise antimicrobial resistance in the pathogen genome so that appropriate treatment can be provided.

MSAC supported the changes to the MBS item descriptor proposed by ESC and the applicant, as shown in Table 1.

Table 1 MSAC's supported MBS item descriptor

Category 3 – Pathology Services – Group 3 Microbiology
<p>MBS item XXXX</p> <p>Sequencing and analysis of the whole mycobacterial genome of <i>Mycobacterium tuberculosis complex (MTBC)</i> from an isolate or nucleic acid extract obtained at the time of:</p> <ul style="list-style-type: none"> a) initial diagnosis and commencement of initial empiric therapy, or b) following disease relapse recurrence of symptoms or failure to respond to treatment within the expected timeframe, <p>to speciate the organism accurately and for the purpose of genome-wide determination of the antimicrobial resistance markers (resistome) of the isolate to individualise the patient's treatment after initial empiric therapy.</p> <p>Applicable once at initial diagnosis and once per episode of disease relapse recurrence.</p> <p>Fee: \$120.00 \$150.00 Benefit: 75% = \$90.00 \$112.50 85% = \$102.00 \$127.50</p>

Deletions in strikethrough, ESC's additions in green, the applicant's additions in the pre-MSAC response in red.

MSAC noted that the fee originally proposed by the applicant was \$120, but that in the pre-MSAC response the applicant raised its proposed fee to \$150. MSAC questioned whether even this remained too low compared to the cost of providing WGS, which one public laboratory provides at \$214 on a bottom-up costing basis. However, MSAC also considered that an advantage of keeping the fee relatively low would be to reduce the number of laboratories that can offer the test based on throughput and economies of scale. Thus, MSAC accepted the applicant's revised fee of \$150.

MSAC noted that there are no safety issues associated with the test itself, but that WGS may result in slightly superior safety overall, given the faster return of test results and a switch to appropriate treatment earlier, thereby avoiding adverse effects of inappropriate treatment.

MSAC noted that a linked evidence approach was used to evaluate the clinical effectiveness of the test, because no direct evidence was available.

MSAC noted that for most patients their resistance results from WGS and phenotypic testing are likely to be the same, however, there is a small proportion of patients in whom one test will provide additional information important to treatment decisions (and information from both tests is used to inform treatment). There is some limited evidence that WGS has superior sensitivity, although slightly reduced specificity.

MSAC noted that, although it is assumed that turnaround time (TAT) to results is quicker for WGS, this is not always the case due to practical and logistical limitations with reference laboratories in Australia, resulting in variation in TAT between labs. MSAC considered the 5 day shorter TAT for WGS compared to pDST to be a modest difference, though it considered that the TAT of WGS will likely improve further in the future.

MSAC noted that there is a lack of evidence about how WGS testing changes patient management or improves their outcomes. However, as Australian guidelines recommend personalised treatment regimens based on susceptibility testing, and evidence shows that the number of effective drugs a patient receives has a significant influence on survival (i.e. patients should receive at least three antibiotics that the organism is susceptible to), MSAC considered it reasonable to assume that receiving resistance results earlier will enable earlier appropriate treatment and better patient outcomes.

MSAC noted that a cost-effectiveness analysis was presented for the addition of WGS to pDST compared to pDST testing alone, to identify resistance in isolates from patients diagnosed with TB. MSAC noted that the incremental cost per additional case with pathogen resistance correctly diagnosed is \$4,551.05. MSAC considered that expressing the ICER in terms of the incremental cost per additional pathogen resistance correctly diagnosed was appropriate, given the limited

evidence to support how testing improves outcomes and the assumption that all patients in Australia would eventually receive treatment appropriate for their resistance profile. MSAC noted the incremental cost was driven primarily by the proposed cost of the test, with a reduction in costs due to earlier adjustments to appropriate treatment regimens (i.e. less inappropriate treatment costs are incurred). This reduction in costs was due to both improved accuracy and reduced TAT. MSAC considered it reasonable to expect that the addition of WGS results in improved identification of drug resistance, and that early confirmation of resistance will result in an early treatment modification and reduction in the duration of hospital treatment, with resulting cost-offsets.

MSAC noted that at a fee of \$120, the net financial impact to the MBS is \$158,886 in Year 1 and \$170,970 in Year 5.

MSAC recommended that this listing be reviewed after two years. MSAC noted that the Netherlands had initially adopted TB WGS in addition to pDST, but after a time WGS replaced pDST. MSAC considered that the same may eventually take place in Australia, though at present testing relies on pDST, so advised it did not recommend ceasing or sunseting public funding for pDST at present. MSAC considered it would also be interesting to assess the concordance of WGS and pDST data if possible.

MSAC noted that TB is a relatively rare disease in Australia, and that while the majority of TB infections in Australia occur in people born overseas, amongst Australian-born people TB occurs at higher rates in Aboriginal and Torres Strait Islander populations than in the non-indigenous population (3.6 and 0.8 per 100,000 population respectively). MSAC considered that publicly funding WGS testing may benefit high-risk communities and remote hotspots the most. MSAC noted the paucity of TB WGS data from Aboriginal and Torres Strait Islander populations and considered that a further benefit of supporting this testing would be that it may provide more information on TB WGS in Aboriginal and Torres Strait Islander populations. MSAC noted consultation feedback from the National Aboriginal Community Controlled Health Organisation (NACCHO) that indigeneity data in pathology tests and results are poor at present, and also noted that there is not a registry at the national level that includes indigeneity data as the Jurisdictions conduct contact tracing. MSAC considered that better data could be gathered for Aboriginal and Torres Strait Islander populations if indigeneity data were collected. MSAC considered it was unlikely to be possible to collect indigeneity data as part of laboratory request processes or in MBS data, but considered that because tuberculosis is a notifiable disease, the notification to public health authorities may be a more appropriate mechanism to collect indigeneity data.

MSAC considered there are also other benefits of WGS in MTBC not captured by the economic evaluation, including improved antimicrobial stewardship (i.e. reducing development of antimicrobial resistance), and distinguishing between relapse and re-infection.

MSAC noted that PASC had supported tuberculosis being the first of the five proposed indications for pathogen WGS to undergo assessment, though that the applicant's pre-MSAC response stated the evidence base only exists at present for tuberculosis. MSAC agreed with the applicant that the current evidence base is insufficient for the other indications, and advised that assessment of the remaining indications commence when a suitable evidence base has developed.

4. Background

MSAC has not previously considered pathogen WGS for DST in patients with mycobacterial infection.

In 2009 MSAC considered an application for genotypic resistance testing for antiretroviral resistance in patients with confirmed HIV infection (MSAC 1127). MSAC supported public funding, and MBS item 69380 was listed on 1 July 2011.

5. Prerequisites to implementation of any funding advice

There are a number of commercial tests already approved by the TGA for WGS that would be suitable for DST. Any test that is not approved by the TGA is considered an in-house in vitro device (IVD) and subject to regulation in accordance with the TGA's IVD regulatory framework. Testing would be delivered only in NATA Accredited Pathology Laboratories (as defined by the MBS Pathology services table), which meet biosafety requirements for Australian mycobacteriology laboratories outlined in the Australian/New Zealand Standard 2243.3: 2010 Safety in laboratories – Microbiological aspects and containment facilities.

Interpretation of results would be provided by an approved practising pathologist or suitably qualified medical scientist. The five Australian TB reference laboratories, based within public tertiary hospital settings, all have the appropriate accreditations.

6. Proposal for public funding

A new MBS item is sought for public funding of WGS of mycobacteria for the purposes of drug susceptibility testing (Table 2). No items are currently on the MBS for genomic testing of mycobacteria. The most commonly occurring type of mycobacteria to be tested is *M. tuberculosis*.

Patients with TB infections are often identified in rural and remote locations with no specialist services, and tests to diagnose and characterise TB are ordered by general practitioners. PASC therefore proposed that requestors of the item should not be limited to hospital specialists.

The key proposed advantage of WGS for identifying the resistance profile is its speed (shorter turnaround time) compared to conventional phenotypic drug susceptibility testing.

Table 2 PICO's proposed MBS item

Category 3 – Pathology Services – Group 3 Microbiology	
MBS item XXXX	
Sequencing and analysis of the whole mycobacterial genome of an isolate or nucleic acid extract obtained at the time of initial diagnosis to speciate the organism accurately and for the purpose of genome-wide determination of the antimicrobial resistance markers (resistome) of the isolate to individualise the patient's treatment after initial empiric therapy.	
Fee: \$120.00	Benefit: 75% = \$90.00 85% = \$102.00

Source: 1646 PICO

7. Population

The proposed patient population are those diagnosed with mycobacterial infection. The most common type of mycobacterium identified in humans is *M. tuberculosis*, responsible for causing the vast majority of cases of TB. For this reason, the exemplar for this indication is patients with TB specifically caused by *M. tuberculosis*. Other facilitated types of mycobacterial infections include:

- the remainder of the *M. tuberculosis* complex (MTBC; e.g. *M. bovis*, *M. africanum* and *M. canetti*), which also cause TB;
- Non-tuberculosis mycobacteria (NTM), which includes all mycobacteria not associated with TB or leprosy (e.g. *M. abscessus*, *M. avium-intracellulare*; *M. kansasii*, *M. scrofulaceum*, *M. fortuitum*, *M. marinum*, *M. chelonae* or *M. ulcerans*.); and
- *M. leprae* complex (*M. leprae* or *M. lepromatosis*) responsible for leprosy.

Although the applicants do not expect that pathogen WGS will be used to test patients with NTM or *M. leprae* complex infections in the near future, the item descriptor is non-specific to MTBC. Information regarding the different mycobacteria have therefore been provided.

In 2018, 1,259 new or relapsed cases of TB were confirmed to have mycobacteria (5-6 per 100,000¹). The incidence of clinically significant NTM in 2000 was 1.8 per 100,000², and the incidence of *M. leprae* is 0-0.1 per 100,000¹.

It is estimated that 2% of patients with TB fail to respond to either initial or subsequent treatment (n=25), and would be retested due to persistence of symptoms. In addition, a small number of patients would be identified with other types of mycobacterial infection. The applicants therefore estimate that approximately 1,300 patients per year would be eligible for the proposed MBS item.

For those with MTBC and NTM, WGS is performed on culture, after diagnosis of TB and confirmation of mycobacteria and initial classification of rifampicin-resistance by GeneXpert. WGS is performed at the same time as phenotypic DST. In most laboratories, the results of WGS are available before pDST results, which allows earlier amendments to the treatment regimen, if required. For those with leprosy, *M. leprae* complex cannot be cultured outside of animal models, and current methods of DST use polymerase chain reaction (PCR) methods.

8. Comparator

For those with MTBC, the PASC-ratified comparator is pDST, which analyses the bacterial susceptibility of antimicrobial agents. It is MBS-listed (items 69324, 69327 and 69330), and uses well-proven methods, such as agar and broth microdilution or disc diffusion, followed by interpretation according to agreed guidelines. However, pDST is time consuming, with long turnaround times for slow-growing organisms such as mycobacteria. The results of a full pDST workup for first-line antibiotics can take several weeks, and if resistance is identified, classification of second-line or third line antibiotics takes even longer. In the interim, patients are treated empirically based on the phenotype and GeneXpert platform test result. The GeneXpert *M. tuberculosis*/rifampicin (MTB/RIF) assay is a rapid test for TB (returning results within 2 hours), that confirms the presence of *M. tuberculosis*, and tests whether the isolate is susceptible to rifampicin, one of the first-line treatments for TB.

Note that the term used to describe the comparator is pDST – contrasting with DST, which is used to describe the overall process and could be performed using: pDST alone, pDST and WGS, or WGS alone.

The PASC-ratified PICO confirmation did not describe the comparator for those with NTM or leprosy. For NTM, the relevant comparator would also be pDST, as per MTBC.

Phenotypic DST is not possible on *M. leprae* complex, as it cannot be cultured. The comparator is therefore direct sequencing of clinical samples using PCR-based methods. This is not currently

¹ (Health Protection Policy Branch. 2019)

² Haverkort, F (2003), 'National atypical mycobacteria survey, 2000', *Clin Infect Dis*, **27**(2): 180-189.

funded on the MBS. There is no evidence comparing the clinical utility of PCR versus WGS in this population. It is unclear whether WGS methods would replace PCR methods in the future, if available for *M. leprae* complex.

9. Summary of public consultation input

Prior to ESC consideration (and subsequent to PASC), consultation feedback was received from 2 organisations, both of which were overall supportive of the proposed intervention:

- Australian Commission on Safety and Quality in Health Care (ACSQHC)
- Thoracic Society of Australia and New Zealand (TSANZ)

Note that post-PASC consultation feedback largely addressed the PICO, which included five separate disease indications (each with an exemplar indication), though the 1646 DCAR examines only the first of these.

A key point raised in comments from the ACSQHC was that the evidence for pathogens other than *M. tuberculosis* is less clear. As such, it considered that the generic proposed MBS item descriptor is not justified. The ACSQHC advised that the request should be refined to ensure that apart from HIV, the claim for use of WGS for other species is not considered to be supported or warranted at this time, and specific conditions for use should be applied and for the selected pathogens: *M. tuberculosis*, *Helicobacter*, and cytomegalovirus (CMV).

Comments highlighted the importance of WGS of antimicrobial-resistant pathogens in enabling targeted antimicrobial treatment, guiding appropriate initial therapeutic choices in a more timely manner, and ensuring better antimicrobial stewardship. TSANZ emphasised that treatment of resistant pathogens without WGS may place patients at risk of a multidrug resistant TB and render the treatment ineffective or impossible. Both organisations expressed that MBS funding of this intervention would provide patients with equitable access to early identification and appropriate targeted treatment of drug resistant strains, therefore reducing community transmission by improving outbreak detection and prevention.

The ACSQHC believed that there are no disadvantages in the utilisation of WGS, however, noted the possibility of a potential risk of its excessive use by clinicians for diseases or indications where the specific benefits of WGS over current technologies are limited, or absent, given the generic nature of the use proposed in the application form (bacterial, mycobacterial, fungal or parasitic). TSANZ was also concerned that WGS may be expensive and require expert interpretation. TSANZ also noted that there is a risk of failure for WGS to identify a phenotypic drug resistant strain if the causative gene variant is not contained in the databases utilised. However, the condition is likely to be identified in the fullness of time with treatment failure, as is it is with the current diagnostic algorithms.

Consultation feedback from both organisations supported the proposed population. TSANZ supported the intervention and proposed item descriptors, though the ACSQHC, while overall supportive of the proposed intervention, did not support the non-specific use of WGS.

TSANZ agreed that phenotypic drug sensitivity testing (DST) by culture is an appropriate comparator. Further, TSANZ considered that there is still a need for the capacity for DST to be conducted (at least by reference laboratories), as the proposal has described that new resistance will continue to arise for which the genetic mutation has yet to be described, or is not included in the genetic resistance database consulted. TSANZ advised that diagnostic reports of pathogen WGS should include a comment to highlight this limitation.

TSANZ agreed with the clinical claim that WGS is likely to be non-inferior to DST, and the ACSQHC commented that only TB was discussed yet the clinical claim is much broader.

10. Characteristics of the evidence base

Overall, there was relatively limited evidence for every component of the assessment report, with the exception of concordance between WGS and pDST, and information on the turnaround time for WGS and pDST. However, a single study with low risk of bias for a relatively applicable population was identified reporting on the accuracy of WGS and pDST separately, compared to a reference standard of information from the two types of tests combined. A small but highly applicable study from New South Wales was identified on the turnaround time of both tests, with international data to support the direction of effect. The evidence was most limited when it came to how the addition of WGS impacts the management of patients. One or two small case series (the amount of overlap is unclear) in a highly select group of patients from London suspected of having extensively drug resistant TB (XDR-TB, defined as multi-drug resistant TB (MDR-TB) strains that are resistant to fluoroquinolones and second-line injectable drugs), reported on the impact of WGS on management. Two articles from one institution in Germany (with a possible overlap of patients) retrospectively documented what management for MDR-TB (defined as TB resistant to isoniazid and rifampicin) patients would occur based only on WGS or pDST (i.e. providing a within-patient retrospective cohort study). The likely impact of the addition of WGS on the management of patients in Australia has therefore had to be hypothesised using treatment guidelines. The evidence supporting the use of drugs consistent with what their DST results say they should be susceptible to is consistent, and likely applicable to the small proportion of patients in whom WGS would alter treatment. A summary of the key features of the evidence is shown in Table 3.

Table 3 Key features of the included evidence

Criterion	Type of evidence supplied	Extent of evidence supplied	Overall risk of bias in evidence base
Accuracy and performance of the test (cross-sectional accuracy)	Accuracy of WGS vs pDST against a composite reference standard	☒ k=1 n=1098	Low risk of bias (QUADAS 2)
	Concordance studies of WGS vs pDST	☒ k=21 n=20,881	Moderate risk of bias (QUADAS 2)
Change in patient management	Evidence that WGS impacts timing of results	☒ k=8 n= 1993	Moderate risk of bias (SIGN cohort studies)
	Evidence that WGS impacts management	☒ k=1-2 n=6-12	Case series data with very limited applicability
Health outcomes	Evidence that treatment targeted to the infection's resistome is superior to treatment not targeted, or with fewer targeted therapies	☒ k=6 n=13,817	Moderate to high risk of bias (SIGN cohort studies/AMSTAR 2)

AMSTAR = assessing the methodological quality of systematic reviews; k=number of studies, n=number of patients; pDST = phenotypic drug susceptibility testing; QUADAS = quality of diagnostic accuracy studies; SIGN = Scottish Intercollegiate Guidelines Network; WGS = whole genome sequencing

11. Comparative safety

The addition of WGS testing itself has no safety impact compared to pDST alone, as it does not require any additional samples from the patient.

The downstream effects of WGS should result in slightly superior safety outcomes overall. The following comments regarding safety are based on data on the accuracy of WGS, and on assumptions regarding changes in management based on treatment guidelines, rather than direct evidence that WGS reduces adverse events. In patients whose infections do not have resistance-conferring variants to first-line treatments (and are therefore classified as pan-susceptible), WGS allows patients to stop ethambutol earlier, reducing the likelihood of any ethambutol-related side-effects. However, the absolute risk of adverse events occurring in the time period between when WGS results are provided, and pDST results are provided

(approximately 5 days³ for first-line antibiotics) is very low, so the likelihood that any adverse events are prevented is also low.

The assumption is made that an appropriate treatment regimen that a patient is likely to respond to will result in the same number of adverse events, regardless of whether the patient is on this regimen early versus late. However, use of an inappropriate treatment regimen would delay the starting of an appropriate regimen, which may result in a worsening of disease in the interval. Furthermore, the rate of adverse events incurred while the patient is on an inappropriate treatment regimen should be considered.

For patients in whom WGS detects resistance, it is expected that they will be switched to an appropriate treatment regimen (if switching is required) at an earlier time point than they would be if waiting for pDST results. This should also result in slightly superior safety results. The individuals impacted to the largest degree, are those in whom WGS detects resistance, who would otherwise be classified as susceptible by pDST. In the absence of WGS, these patients would likely stay on a treatment regimen which includes at least one drug they are unlikely to respond to, for a period of 3-4 months (until defined as not responding, and retested).

Given the lack of evidence regarding how WGS changes the management of patients, these statements are all highly uncertain.

12. Comparative effectiveness

No direct from test to health outcomes evidence was identified comparing the effectiveness of WGS plus pDST versus pDST alone.

A linked evidence assessment was therefore used, linking the accuracy of WGS versus pDST, data on the turnaround time of WGS and pDST, clinical guidelines to suggest how management of patients would likely change based on the accuracy and turnaround time, and data on how appropriate versus inappropriate treatment changes health outcomes. The incremental benefit of WGS can be inferred from these studies.

Accuracy

A single study was identified that compared the accuracy of WGS and pDST for determining resistance to first-line drugs against a composite reference standard of information from the two tests combined (Table 4). Jajou et al. (2019)⁴ performed a retrospective cohort study on patients with MTBC from the Netherlands (with a very similar rate of drug resistance to Australia). WGS detected more cases of resistance to rifampicin, isoniazid and ethambutol than pDST, with a slight loss of specificity. It is therefore logical that WGS ± pDST would be more accurate than pDST alone, although conflicting results between WGS and pDST can make it difficult to interpret the patients' resistome profile appropriately.⁵ WGS relies heavily on the availability of good quality genetic databases being used to infer resistance from the reported genetic sequences.

³ Lam et al. (2021). Value of routine whole genome sequencing for *Mycobacterium tuberculosis* drug resistance detection. *International Journal of Infectious Disease*, **113**: S48-S54.

⁴ Jajou et al. (2019). WGS more accurately predicts susceptibility of *Mycobacterium tuberculosis* to first-line drugs than phenotypic testing, *Journal of Antimicrobial Chemotherapy*, **74**(9): 2605-2616.

⁵ Personal communication via teleconference with Ms Lisa Shephard (SA Pathology) and Maria Globan (Victorian Infectious Diseases Reference Laboratory) on 14th September 2021.

Table 4 Accuracy of WGS and pDST predictions compared to composite reference standard (WGS plus pDST)

Study	Test	Drug	Sensitivity (%)	Specificity (%)	Australian prevalence ^a	Translated PPV (%)	Translated NPV (%)
(Jajou et al. 2019)	WGS	Rifampicin	96.9	99.7	2.3%	88.6	99.9
		Isoniazid	98	99.9	11.3%	99.2	99.7
		Ethambutol	94.1	99.6	1.9%	82.2	99.9
		Pyrazinamide ^b	85.1	98.8	4.5%	77.1	99.3
	pDST	Rifampicin	78.1	100	2.3%	100.0	99.5
		Isoniazid	93	100	11.3%	100.0	99.1
		Ethambutol	29.4	100	1.9%	100.0	98.6
		Pyrazinamide ^b	100	100	4.5%	100.0	100.0

^aPrevalence based on data from the Australian Mycobacterium Laboratory Reference Network, covering SA, VIC, and NT for 2020

^bReference standard was pDST (as recommended by World Health Organization)

NPV = negative predictive value; pDST = phenotypic drug susceptibility testing; PPV = positive predictive value; WGS = whole genome sequencing

Given the limited data on the accuracy of WGS and pDST, concordance data were also included. The most directly relevant data were by Lam et al. (2021), reporting on the concordance of WGS and pDST from 3 years of testing from the NSW mycobacteria reference laboratory (2016 to 2019). WGS and pDST were moderately concordant, with both tests providing additional information (Table 5). The vast majority of patients were susceptible to all first-line drugs, as determined by both WGS and pDST. WGS did identify 21 extra cases of resistance, which would have been missed in the absence of WGS. It is hypothesised that this corresponds to 19 patients⁶ out of 1107 patients tested. Therefore, from the Australian population data, 1.7 per cent of those tested for first-line drug resistance are likely to have significant benefit from the addition of WGS. Lam et al. (2021) did not report on the concordance of resistance to later-line drugs.

Table 5 Concordance data reported by Lam et al. (2021)

Drug	PPA (95%CI)	NPA (95%CI)	Resistant on both WGS and pDST	Resistant on WGS, susceptible on pDST	Susceptible on WGS, resistant on pDST	Susceptible on both WGS and pDST
Isoniazid	0.93 (0.88, 0.97)	0.90 (0.98, 1.00)	117	12	8	966
Rifampicin	1.00 (0.89, 1.00)	1.00 (1.00, 1.00)	31	0	0	1072
Ethambutol	1.00 (0.81, 1.00)	1.00 (0.99, 1.00)	18	3	0	1082
Pyrazinamide	0.86 (0.64, 0.97)	0.99 (0.98, 0.99)	18	6	3	1076

NPA = negative per cent agreement (equivalent to specificity); pDST = phenotypic drug susceptibility testing; PPA = positive per cent agreement (equivalent to sensitivity); WGS = whole genome sequencing

Data from all studies identified as providing concordance data synthesised per drug in a 2x2 format was meta-analysed to derive the positive percent agreement and negative percent agreement, and translated back into 2x2 data applicable to the prevalence of resistance in patients with TB in Australia (Table 6). Per 1000 patients tested, WGS would result in 77 additional cases of resistance to isoniazid, ethambutol or pyrazinamide being identified. It is assumed this corresponds to 70 patients (7%), with the number needed to test to identify one additional patient with resistance being 14.

⁶ Based on data from Jajou et al 2019, who reported that 57 isolates had 63 discrepancies in their MGIT and WGS results (5 discrepant for multiple drugs and 52 isolates for one drug)

Table 6 Summary of concordance studies between WGS and pDST for first-line drugs (applying SA, NT and Vic prevalence of resistance)

Drug	K	PPA (95%CI)	NPA (95%CI)	Results per 1000 patients tested			
				Resistant on both WGS and pDST	Resistant on WGS, susceptible on pDST	Susceptible on WGS, resistant on pDST	Susceptible on both WGS and pDST
Isoniazid	21	0.95 (0.91, 0.97)	0.98 (0.95, 0.99)	108 (104 to 111)	18 (9 to 44)	6 (3 to 10)	868 (842 to 877)
Rifampicin	20	0.98 (0.96, 0.99)	0.98 (0.96, 0.99)	27 (27 to 28)	19 (10 to 39)	1 (0 to 1)	953 (933 to 962)
Ethambutol	20	0.91 (0.84, 0.95)	0.95 (0.89, 0.98)	15 (14 to 16)	49 (20 to 108)	2 (1 to 3)	934 (875 to 963)
Pyrazinamide	13	0.85 (0.74, 0.92)	0.99 (0.97, 1.00)	17 (15 to 18)	10 (0 to 29)	3 (2 to 5)	970 (951 to 980)

K = number of studies; NPA = negative percent agreement (specificity); NT = Northern Territory; pDST = phenotypic drug susceptibility testing; PPA = positive percent agreement (sensitivity); SA = South Australian; Vic = Victorian; WGS = whole genome sequencing

Up to 10 per cent of patients who had their mycobacterial infection tested for resistance to second- or later-line drugs had isolates with resistance-conferring variants to at least one antibiotic (103/1000 for ethionamide), which was not detected by pDST (Table 7). However, from South Australian data, none of the 5/75 (6.7%) patients whose infection had ethionamide resistance-conferring variants would be considered for this treatment (as they were all likely to respond to at least three first-line drugs). The clinical impact of this discordance is therefore negligible.

Table 7 Summary of concordance studies between WGS and pDST for later-line drugs (applying SA prevalence of resistance)

Drug	K	PPA (95%CI)	NPA (95%CI)	Results per 1000 patients tested			
				Resistant on both WGS and pDST	Resistant on WGS, susceptible on pDST	Susceptible on WGS, resistant on pDST	Susceptible on both WGS and pDST
Amikacin	13	0.82 (0.60, 0.94)	1.00 (0.98, 1.00)	1 to 8 (1 to 9)	0 (0 to 20)	0 to 2 (0 to 4)	990 to 999 (970 to 999)
Capreomycin	4	0.92 (0.80, 0.97)	1.00 (0.94, 1.00)	1 to 9 (1 to 10)	0 (0 to 60)	0 to 1 (0 to 2)	990 to 999 (931 to 999)
Ethionamide	4	0.70 (0.51, 0.84)	0.89 (0.79, 0.94)	47 (34 to 56)	103 (56 to 196)	20 (11 to 33)	830 (737 to 877)
Kanamycin	9	0.92 (0.45, 0.99)	0.99 (0.96, 1.00)	1 to 9 (0 to 10)	10 (0 to 40)	0 to 1 (0 to 5)	980 to 989 (950 to 999)
Levofloxacin	7	0.87 (0.75, 0.94)	0.99 (0.93, 1.00)	35 (30 to 38)	10 (0 to 67)	5 (2 to 10)	950 (893 to 960)
Moxifloxacin	8	0.82 (0.66, 0.91)	0.96 (0.89, 0.98)	33 (26 to 36)	38 (19 to 106)	7 (4 to 14)	922 (854 to 941)

Drug	K	PPA (95%CI)	NPA (95%CI)	Results per 1000 patients tested			
				Resistant on both WGS and pDST	Resistant on WGS, susceptible on pDST	Susceptible on WGS, resistant on pDST	Susceptible on both WGS and pDST
All fluoro-quinolones	4	0.89 (0.70, 0.96)	1.00 (0.87, 1.00)	36 (28 to 38)	4 (2 to 12)	0 (0 to 125)	960 (835 to 960)

K = number of studies; NPA = negative percent agreement (specificity); pDST = phenotypic drug susceptibility testing; PPA = positive percent agreement (sensitivity); SA = South Australian; WGS = whole genome sequencing

Note: where no patients tested within SA dataset had resistance to the particular drug, a range of possible values has been included for prevalence, from 0.1 to 1%.

Change in management

Despite the majority of patients' infections having the same antimicrobial resistance results based on WGS and pDST, the use of WGS is proposed by the applicants to result in a change in management, due to the faster average turnaround of WGS results compared to pDST.

NSW data on 32 isolates from Martinez et al. (2016)⁷ reported that WGS results had a median turnaround time of 11 days, compared to pDST, which took a median of 16 days. Personal communication with the authors stated that their WGS results are now being turned around within 8-10 days⁸. Although not all laboratories in Australia are currently equipped to turnaround WGS results as fast as NSW, the expectation is that in the near future, the other reference laboratories will have similar in-house capacity⁹. Slightly longer turnaround times have been reported in the international literature, with mean turnaround times for WGS ranging from 3 to a mean 15 days, whereas turnaround time for pDST ranged from 13 to 24 days for first-line drugs, and 21 to 47 days for second-line drugs (Table 8).

Table 8 Turnaround times for WGS and pDST

Study	Country	N	Mean WGS turnaround time	Mean pDST turnaround time
He et al. (2020)	China	123	7 days (range not stated)	Liquid media: 10 days (range 4 to 13) Solid media: 30 days (range 26 to 32)
Shea et al. (2017)	US	294	15 days	First-line: 24 days Second-line: 47 days
Tafess et al. (2020)	HK / Ethiopia	163	MiSeq: 4 days MinION: 3 days	First-line: 13 days Second-line: 21 days
van Beek et al. (2010)	Finland	211	5 days (range 3 to 7)	19 days (range 10 to 50)
Study	Country		Median WGS turnaround time	Median pDST turnaround time
Martinez et al. (2016)	Australia	32	11 days	16 days
Olaru et al. (2018)	UK	92	8 days	22 days
Pankhurst et al. (2016)	Multiple	356	31 days (IQR 21, 60)	25 days (IQR 14, 32)
Quan et al. (2018)	UK	722	20 days (IQR 15, 31)	21 days (IQR 15, 29)

HK = Hong Kong; IQR = inter-quartile range; pDST = phenotypic drug susceptibility testing; UK = United Kingdom; US = United States of America; WGS = whole genome sequencing

⁷ Martinez et al. (2016). Whole-genome sequencing of *Mycobacterium tuberculosis* for rapid diagnostics: feasibility of a decentralised model. *The Lancet Respiratory Medicine*, **4**(4): e13-e14.

⁸ Email from Prof Vitali Sintchenko (NSW Health Pathology) received 30 August 2021.

⁹ Personal communication via teleconference with Ms Lisa Shephard (SA Pathology) and Maria Globan (Victorian Infectious Diseases Reference Laboratory) on 14 September 2021.

Although the change in management resulting from WGS for patients whose isolates are pan-susceptible is expected to be minimal¹⁰, the more drugs a patient's isolate is resistant to, the larger the benefit is likely to be from using WGS.

The only evidence documenting how WGS likely altered management (compared to what patients would have received in the absence of WGS) was one or two small case series of suspected XDR-TB patients from London (Arnold et al. 2016; Witney, A, Gould & al 2015). In this highly selected group, WGS resulted in 2/6 patients being treated with a different regimen than they would have received based on pDST alone. A further 2/6 patients (33%) were treated for MDR-TB rather than XDR-TB, earlier than they would have been if they had waited for pDST results. Cases of suspected XDR-TB are rare in Australia (<1% of TB cases). The applicability of this evidence is therefore very low.

A further two articles reported on what treatments would be recommended, based on a standardised treatment algorithm in patients with rifampicin-resistant TB (RR-TB), MDR-TB or XDR-TB (Grobbe et al. 2021; Heyckendorf et al. 2018). The two articles were from the same reference laboratory in Germany, and it is unknown to what extent the samples overlap. Only Grobbe et al. (2021) provided per-patient data, and they reported that use of WGS would result in an identical regimen to pDST in only 54 per cent of cases. They also reported that 4 per cent of patients would receive a drug they had pDST-classified resistance to, based solely on WGS. It can therefore be inferred that if information from both WGS and pDST were combined, that this would result in 42 per cent of patients with RR-TB or MDR-TB receiving a different treatment from the addition of WGS than they would with pDST results alone. Bright et al. report that <1 per cent of cases of TB in Australia have mono-resistance to rifampicin, and 2 per cent have MDR-TB. The proportion of patients in whom WGS is expected to alter the treatment regimen (rather than the timing of any alterations) is therefore very small.

Table 9 Comparison of treatment regimens recommended based on WGS compared to pDST

Study	Population	Concordance with regimen recommended based on pDST
(Heyckendorf et al. 2018)	25 patients with MDR-TB or XDR-TB	93% (95%CI 88, 98) agreement in individual drugs selected No drugs recommended using WGS for which pDST showed resistance. Differences occurred to due to WGS detecting more ethambutol resistance than pDST
(Grobbe et al. 2021)	70 patients with RR-TB or MDR-TB	84.9% (248/292 gDST-based treatment decisions) concordant with MGIT 54.3% (38/70) of patients would have received identical drug regimens with WGS and pDST. When variants of unknown significance were conservatively classified as resistance-conferring, only 3/929 cases (1% of drugs), and 3/70 (4.3%) of patients would have received a drug that they had pDST-resistance to.

gDST = genomic drug susceptibility testing (i.e. WGS); MDR = multidrug resistant; MGIT = mycobacteria growth indicator tube; pDST = phenotypic drug susceptibility testing; RR = rifampicin-resistant; TB = tuberculosis; WGS = whole genome sequencing; XDR = extensively multidrug resistant

Impact of change in management on health outcomes

Australian guidelines recommend for patients without rifampicin resistance identified by GeneXpert, that initial empiric treatment be with all four first-line antibiotics. Fully susceptible TB can be treated with isoniazid and rifampicin for nine months. The addition of pyrazinamide for the first two months shortens the course of treatment to six months. Ethambutol has the lowest effectiveness of the first-line antibiotics, and is only part of the initial treatment strategy on the chance that the infection has resistance to one of other first-line drugs. On confirmation of pan-

¹⁰ Australian guidelines recommend that patients without rifampicin resistance start on all four first-line drugs at diagnosis. If pan-susceptibility is confirmed, then ethambutol may be ceased.

susceptibility, ethambutol treatment can be ceased. WGS is likely to result in this adjustment to treatment regimen happening earlier, and the expectation is that this would result in non-inferior effectiveness.

For patients with resistant infection, WGS is likely to 1) decrease the time to appropriate treatment; and 2) increase the number of drugs a person is treated with that are appropriate to their infection's resistome.

Only one study was identified that reported on how patient outcomes differ by time to appropriate treatment, though for GeneXpert MTB/RIF assay rather than WGS. The study by Ershova et al. (2020) prospectively followed up two cohorts of patients who were treated before and after the introduction of GeneXpert (Table 10). No significant difference in the proportion of patients who had a successful treatment outcome was reported (OR 0.60, 95%CI 0.23, 2.06), although the study was likely underpowered.

Table 10 Association between time to appropriate treatment and health outcomes

Study	Population	Outcome measure	pre-GeneXpert group	post-GeneXpert group	Difference
(Ershova et al. 2020)	53 patients with RR-TB	Time to appropriate treatment (second-line drugs)	Median: 37 days	Median: 11 days	HR: 2.06 (95%CI 1.09, 3.89) Log rank p=0.02
		Successful outcome (cured/completed treatment)	13/27 (48%)	15/26 (58%)	OR: 0.60 (95%CI 0.23, 2.06)
	252 patients with rifampicin-susceptible TB	Time to appropriate treatment (first-line drugs)	Median: 3 days	Median: 2 days	Log rank p=0.73
		Successful outcome (cured/completed treatment)	105/138 (76%)	94/114 (82%)	OR: 0.68 (95%CI 0.36, 1.26)

HR = hazard ratio; OR = odds ratio; RR-TB = rifampicin resistant tuberculosis; TB = tuberculosis

Three articles reported on the association between the number of likely effective drugs that patients with MDR-TB are treated with, and survival (Table 11) or treatment success (Table 12). Although the studies differed in their methodology and cut-offs used for their analyses, they were reasonably consistent that patients on a higher number of likely effective drugs, survived longer and had a higher chance of treatment success than those on fewer likely effective drugs. The addition of WGS is therefore likely superior to pDST alone, as it will detect more cases of resistance, which should result in a higher number of likely effective drugs being used in the treatment regimen, which is associated with superior survival.

Table 11 Association between number of effective drugs used and survival in patients with MDR-TB

Study	Population	Definition of appropriate treatment	Outcomes for appropriate treatment	Outcomes for inappropriate treatment	Comparison
(Drobniewski et al. 2002)	90 patients with MDR-TB	3 drugs susceptible to	n=62 Median survival: 2066 days (5.66 years) (95%CI 1336, 2515 days)	n=13 Median survival: 599 days (1.64 years) (95%CI 190, 969 days)	Multivariate log-rank test, Cox proportional hazards model $\chi^2=0.0001$, RR=0.056 (95%CI 0.01, 0.23)
(Turett et al. 1995)	34 HIV-infected patients with MDR-TB	≥ 2 drugs susceptible to for ≥ 2 weeks	Overall response: 17/22 Cumulative probability of survival: 82% at 6 months and 12 months	Overall response: 0/12 Median survival 16 days	$p < 0.001$
		≥ 2 drugs susceptible to within 4 weeks of diagnosis	Overall response: 14/21 Cumulative probability of survival: 71% at 6 months, 65% at 12 months	Overall response: 2/13 Median survival: 19 days	$p = 0.02$

HIV = human immunodeficiency virus; MDR-TB = multidrug resistant tuberculosis; RR = relative risk

Table 12 Association between number of effective drugs used and treatment success (cure or treatment completion) in patients with MDR-TB

Study	Population	No. of likely effective drugs in intensive phase	N	Success versus fail/relapse/death aOR (95%CI)	
(Ahuja et al. 2012)	9153 patients with MDR-TB	0-2	227	1.0 (reference)	
		3	250	1.7 (1.2, 2.4)	
		4	542	2.7 (1.9, 3.9)	
		5	900	2.8 (1.7, 4.6)	
		6+	977	2.1 (1.4, 3.1)	
		No. of likely effective drugs in continuation phase	N	Success versus fail/relapse/death aOR (95%CI)	
		0-2	531	1.0 (reference)	
		3	635	5.7 (3.4, 9.7)	
		4	663	5.7 (3.2, 10.0)	
		5+	608	7.0 (5.1, 9.7)	

aOR =adjusted odds ratio (adjusted for age, sex, human immunodeficiency virus, past TB treatment, past MDR-TB treatment (treatment for more than 1 month with 2 or more second-line drugs) and extent of disease; MDR-TB = multidrug resistant TB

Impact of WGS on transmission of infection to other people

No data were found on the impact of WGS on reducing transmission of TB. Prior to the availability of WGS, the relatedness of cases was determined using 24-locus mycobacterium interspersed repetitive unit (MIRU-24) genotyping. Gurjav et al. (2016) retrospectively assessed all cases with culture confirmed *M. tuberculosis* from NSW between 2009 and 2013, where demographic and MIRU-24 data were available. From MIRU-24, it was estimated that up to 12.8 per cent of cases were clustered (having the same strain as another case) and may be from recent transmission. However, when WGS was used for single nucleotide

polymorphism (SNP) analysis of the four largest MIRU-24 clusters (accounting for 71.8% of clustered cases in NSW), only a single case of local transmission (reduced from 26 to 1) was identified. Local transmission of TB within Australia is therefore rare. This is supported by reports of reproduction numbers (R numbers) for TB well below 1 in developed countries, such as 0.55 in the USA and 0.26 in the Netherlands (Ma et al., 2018).

Transmission is most likely to occur prior to diagnosis and initiation of effective treatment. Cases that are potentially infectious (such as those with sputum smear positive, pulmonary TB) are recommended to isolate. If social circumstances in the home do not allow the person to isolate, then hospitalisation (in a negative pressure room) is recommended until discharge criteria are met (a reduction or absence of cough, reduced smear burden or smear negativity, assured treatment and an appropriate discharge plan) (Communicable Disease Network Australia 2015). Although there will be a small number of patients in whom the use of WGS results in faster initiation of effective treatment, the target population are those already diagnosed, and who should be isolating until they show signs of improvement. The likelihood of transmission occurring within the window of time between WGS results are returned, and when pDST results are returned, is therefore negligible.

Clinical claim

Overall (for all patients tested):

The use of WGS in addition to pDST results in superior effectiveness compared with pDST alone.

The use of WGS in addition to pDST results in superior safety compared with pDST alone.

13. Economic evaluation

The clinical evaluation suggested that the use of WGS in addition to pDST results in superior effectiveness and safety compared to pDST alone. Based on this a cost-effectiveness analysis is presented to assess the effectiveness of adding WGS to pDST. A summary of the economic evaluation is presented in Table 13.

Table 13 Summary of the economic evaluation

Component	Description
Perspective	Health care system perspective
Population	Those who are diagnosed with TB and confirmed to have <i>M. tuberculosis</i>
Prior testing	Diagnostic tests for TB, including resistance to rifampicin to guide early empiric treatment and detection of mycobacteria. This includes sputum microscopy, chest x-ray and GeneXpert
Comparator	pDST
Type(s) of analysis	Cost-effectiveness analysis
Outcomes	<ul style="list-style-type: none"> - Correct diagnosis after initial DST^a - Early identification of resistance - Early confirmation of true status^b
Time horizon	Time to treatment decision appropriate to resistance profile of the isolate (less than one year)
Computational method	Decision tree analysis
Generation of the base-case	<p>Modelled</p> <p>Given that the addition of WGS has varying effects (i.e. improved accuracy, reduced test turnaround time), these are incorporated into the base-case analysis in a stepped manner to allow the impact of each of these on the base-case to be discerned:</p> <ul style="list-style-type: none"> - Step 1: Improved accuracy - Step 2: Improved accuracy + Early identification and no hospital costs - Step 3: Improved accuracy + Early identification with hospital costs
Software	Microsoft Excel

DST = drug susceptibility testing; *M. tuberculosis* = *Mycobacterium tuberculosis*; pDST = phenotypic drug susceptibility testing; TB = tuberculosis; WGS = whole genome sequencing

^a First pDST is initial DST in pDST arm (comparator arm), first WGS+pDST is the initial DST in WGS+pDST arm (intervention arm)

^b While early identification of resistance measures impact only in drug resistant cases, early confirmation of true status also includes pan-susceptible case who benefit from early discontinuation of ethambutol

The model takes the form of a decision tree analysis. Patients enter the model after being diagnosed with TB and initiating empiric treatment based on the results of prior testing. As both treatment and the benefits of WGS vary according to the resistance profile of the isolate, patients entering the model are split into four categories depending on the status of their pathogen; pan-susceptible, mono-resistant (non-rif; other than rifampicin), rifampicin mono-resistant and multi-drug resistant (MDR). MDR patients are further categorised into two groups based on resistance to other second-line drugs.

It is considered that first and second-line drug testing occurs in parallel in both WGS and pDST arm. The model terminates at the point where patients are allocated an appropriate treatment regimen for their underlying resistance profile.

The key structural assumptions in the model are:

- Specificity of tests is assumed to be 100% in both the arms. Therefore, no false positives are considered in the model.
- Clinical decisions are based on whichever result is provided first. When WGS and pDST results are discordant, an isolate is confirmed to have drug resistance if the test result is positive on either of the tests.
- Time to appropriate treatment in false negatives is assumed to be 3-4 months from the start of empiric treatment. In the base-case it was considered that false negative cases in the pDST arm will be on inappropriate treatment for an additional 60 days compared to WGS+pDST arm.

- There was no evidence identified in the clinical evaluation to support a reduction in disease transmission due to the addition of WGS. Therefore, the analysis did not model the impact of WGS on disease transmission.
- It was assumed that only MDR-TB patients with second-line drug resistance were in hospital isolation at the time of testing in the base-case.

Key variables in the model are the accuracy of tests and test turnaround times. It is expected that the addition of WGS results in improved identification of drug resistance and early confirmation of resistance which further results in an early treatment modification and reduction in the duration of hospital isolation.

One study (Jajou et al. 2019) was identified comparing the accuracy of WGS and pDST with a composite reference standard for the first-line drugs. As this study came from the Netherlands and may have applicability issues to the Australian context, concordance data from an Australian study were also used, and translated into sensitivity/specificity using both tests combined as the reference standard (Lam et al. 2021). A comparison of accuracy estimates from both the studies is presented in Table 14.

Table 14 Comparison of the accuracy of WGS or pDST to a combined reference standard of WGS + pDST

Test	Drug	(Jajou et al. 2019)		(Lam et al. 2021)	
		Sensitivity (%)	Specificity (%)	Sensitivity (%) ^b	Specificity (%) ^b
WGS	Rifampicin	96.9	99.7	100.0	100.0
	Isoniazid	98.0	99.9	94.2	100.0
	Ethambutol	94.1	99.6	100.0	100.0
	Pyrazinamide	85.1 ^a	98.8 ^a	88.9	100.0
pDST	Rifampicin	78.1	100.0	100.0	100.0
	Isoniazid	93.0	100.0	91.2	100.0
	Ethambutol	29.4	100.0	85.7	100.0
	Pyrazinamide	100.0 ^a	100.0 ^a	77.8	100.0

pDST = phenotypic drug susceptibility testing; WGS = whole genome sequencing

^a Jajou et al. (2019) considered that pDST was the reference standard in determining the accuracy of pyrazinamide. Thus WGS was compared to pDST (not the composite reference standard of WGS + pDST), and pDST was associated with 100% test performance

^b Derived from the data given in the study

To reduce the complexity of the model, accuracy estimates of all non-rifampicin mono-resistances were combined into single group of mono-resistance estimate by weighing the individual accuracy estimates with the proportion of individual resistances. Accuracy for the group with MDR-TB (with isolates resistant to rifampicin and isoniazid only) is considered to be the same as accuracy of isoniazid resistance. Accuracy for the group with MDR-TB with second-line drug resistance was based on the concordance estimates of moxifloxacin. Derived accuracy estimates of WGS and pDST are presented in Table 15.

Table 15 Derived accuracy of WGS and pDST for each treatment group included in the base-case

	Mono-resistant	RIF mono-resistant	MDR-TB (RIF and INH only)	MDR-TB (RIF, INH and other second-line drugs)^a
WGS vs WGS plus pDST				
Sensitivity	94.0%	100.0%	94.2%	82.0%
Specificity	100.0%	100.0%	100.0%	100.0%
pDST vs WGS plus pDST				
Sensitivity	86.0%	100.0%	91.2%	100.0%
Specificity	100.0%	100.0%	100.0%	100.0%

INH = isoniazid; MDR = multi-drug resistance (resistant to isoniazid and rifampicin); pDST = phenotypic drug susceptibility testing; RIF = rifampicin; WGS = whole genome sequencing;

^a Concordance estimate of WGS based on meta-analysis

Turnaround times included in the base-case are based on an Australian study (Martinez et al. 2016) that reported turnaround times for WGS and pDST as 11 days and 16 days respectively. Based on this the difference in turnaround times is estimated to be 5 days in the base-case. Globally, mean turnaround time for WGS ranged from 3 to 15 days where as for pDST it was between 13 to 24 days. It is reported that in some of the laboratories in Australia, WGS results are delayed compared to pDST. The impact of variation in test turnaround times is assessed in a sensitivity analysis.

Incremental cost-effectiveness ratio (ICER) of the addition of WGS in a stepped manner is presented in Table 16, in terms of cost per additional pathogen resistance correctly diagnosed.

Table 16 Incremental cost-effectiveness of addition of WGS

	Intervention	Comparator	Increment	ICER
Step 1: Improved accuracy				
Cost	\$122.40	\$6.86	\$115.54	
Outcomes				
Correct diagnosis after initial DST	1.000	0.986	0.014	\$8,241.60
Step 2: Improved accuracy + reduced turnaround and no hospital costs				
Cost	\$122.70	\$42.25	\$80.45	
Outcomes				
Early identification of resistance	0.113	0.000	0.113	\$712.53
Early confirmation of true status	0.993	0.000	0.993	\$81.02
Correct diagnosis after initial DST	1.000	0.986	0.014	\$5,738.29
Step 3: Improved accuracy + reduced turnaround time with hospital costs				
Cost	\$126.35	\$62.55	\$63.80	
Outcomes				
Early identification of resistance	0.113	0.000	0.113	\$565.11
Early confirmation of true status	0.993	0.000	0.993	\$64.26
Correct diagnosis after initial DST	1.000	0.986	0.014	\$4,551.05

DST = drug susceptibility testing; ICER = incremental cost-effectiveness ratio

Cost of the intervention is the major contributor to incremental cost. With the addition of earlier treatment modification, the incremental cost decreased from \$115.54 to \$80.45 (30% decrease). This can be attributed to the higher inappropriate treatment costs in pDST arm due to delayed modification of the treatment that are offset by the addition of WGS. The incremental cost further reduces with the addition of costs associated with a reduction in hospital isolation. This is mainly due to the reduction in duration of hospital isolation among cases with MDR-TB with second-line drug resistance. The addition of WGS correctly identified the resistance in an additional 1.4% of isolates compared to pDST alone. Given the small incremental cost and small

incremental benefit of identifying additional resistant cases, the incremental cost of WGS per additional case with resistance identified is \$4,551.05.

Sensitivity analyses for the base-case scenario were conducted around a number of parameters included in the economic modelling (Table 17). The ICER is most sensitive to changes in the difference in test turnaround times and the proportion of cases with MDR-TB in hospital isolation at the time of testing. Addition of WGS is found to be cost saving when the difference in test turnaround time is more than 11 days. The intervention was also found to be cost saving when all cases with MDR-TB are assumed to be in hospital isolation at the time of testing.

Table 17 Sensitivity Analysis, Outcome: Correct diagnosis after initial DST

	Inc. cost	Inc. effect	ICER	% change
Base-case	\$63.80	0.014	\$4,551.05	
Source of sensitivity data [true positives/(true positives plus false negatives)] (Base-case: Lam study)				
Jajou (2019)	\$61.87	0.020	\$3,062.30	-33%
Difference in turnaround times (pDST compared to WGS) (Base-case: 5 days)				
0 days	\$115.54	0.014	\$8,241.60	81%
2 days	\$94.84	0.014	\$6,765.38	49%
7 days	\$43.11	0.014	\$3,074.82	-32%
10 days	\$12.06	0.014	\$860.49	-81%
11 days	\$1.72	0.014	\$122.38	-97%
12 days	-\$8.63	0.014	-\$615.73	-114%
Cases with MDR-TB in hospital isolation at the time of testing (Base-case: only MDR cases with other second-line resistance)				
58.5% of MDR-TB (R and I) and all MDR-TB (with second-line resistance)	-\$2.13	0.014	-\$151.66	-103%
No MDR-TB cases	\$80.45	0.014	\$5,738.29	26%
Time to appropriate treatment in false negative cases (Base-case: 60 days after pDST)				
75 days	\$62.54	0.014	\$4,460.71	-2%
90 days	\$61.27	0.014	\$4,370.38	-4%
Cost of WGS (Base-case: \$120)				
SA pathology cost - \$214	\$159.68	0.014	\$11,390.29	150%
Cost of pDST (Base-Case: MBS Item 69330: \$128)				
MBS Item: 69324: \$43	\$64.99	0.014	\$4,636.05	2%
MBS Item 69327: \$85	\$64.40	0.014	\$4,594.05	1%
Acquired resistance due to inappropriate treatment (Base-case: 0% of false negatives)				
2% of false negatives	\$50.54	0.014	\$3,604.89	-21%
Resistance to second-line drugs among cases with MDR-TB (Proportion of cases with MDR-TB resistant to clofazamine: 14.5%)				
Moxifloxacin: 7.3%	\$72.04	0.014	\$5,082.35	12%
Cycloserine: 9.1%	\$69.98	0.014	\$4,950.62	9%
Linezolid: 3.6%	\$76.28	0.014	\$5,350.87	18%
Proportion of type of resistances (Base-case: Average of 2015-18)				
2015	\$57.68	0.015	\$3,772.92	-17%
2016	\$64.94	0.015	\$4,473.73	-2%
2017	\$68.15	0.013	\$5,309.38	17%
2018	\$63.85	0.014	\$4,704.10	3%

DST = drug susceptibility testing; I = isoniazid; ICER = incremental cost-effectiveness ratio; MBS = Medicare Benefits Schedule; MDR-TB = multi-drug resistance tuberculosis; pDST = phenotypic drug susceptibility testing; R = rifampicin; SA = South Australian; WGS = whole genome sequencing

14. Financial/budgetary impacts

An epidemiological approach was used to estimate the financial implications of use of WGS of mycobacteria to identify drug-resistant pathogens. The primary sources of data used to calculate the financial impact of addition of WGS are: Australian population projections estimates (2022 to 2027) from the Australian Bureau of Statistics (ABS)¹¹ and annual TB disease notifications (Bright et al. 2020)¹².

The financial implications associated with addition of WGS to identify drug resistant pathogens are presented in Table 18.

Table 18 Net financial implications of whole genome sequencing of mycobacteria to the MBS

Parameter	2022	2023	2024	2024	2025	2026
Estimated use and cost of the proposed health technology						
Number of people eligible for whole genome sequencing	2,035	2,067	2,098	2,129	2,160	2,190
Number of people who receive whole genome sequencing	1,550	1,575	1,599	1,622	1,646	1,668
Number of services of whole genome sequencing (including 2% re-test rate)	1,581	1,606	1,631	1,655	1,679	1,702
Cost of whole genome sequencing (with appropriate copayments excluded)	\$161,279	\$163,815	\$166,319	\$168,783	\$171,208	\$173,582
Change in use and cost of other health technologies						
Change in use of phenotypic drug susceptibility testing (no. of services)	-22	-23	-23	-23	-24	-24
Net change in costs to the MBS (with appropriate copayments excluded)	-\$2,394	-\$2,502	-\$2,502	-\$2,502	-\$2,611	-\$2,611
Net financial impact to the MBS	\$158,886	\$161,312	\$163,817	\$166,280	\$168,596	\$170,970

MBS = Medicare benefits schedule

15. Other relevant information

WGS can provide additional information over pDST, which allows it to distinguish between relapse and reinfection, providing public health benefits such as tracking transmission, determining how closely related clusters are, helping to tell the direction of infection and finding possible missing links/additional cases of TB.

Given the low rate of relapse and community transmission within Australia, the impact of using WGS for these purposes is unclear. However, one article was identified that reported on WGS being used to investigate transmission dynamics between cases of MDR-TB in Papua New Guinea and Australia (Bainomugisa et al. 2019). WGS identified two separate episodes of MDR-TB transmission to Australian residents by the Torres Strait Protected Zone (TSPZ), which would not have been identified through conventional genotypic techniques. Four Australian citizens who resided or previously resided in the TSPZ were found to have MDR-TB, and MIRI-24 results suggested that they had the same MIRU profile (and may therefore have been considered to be a

¹¹ https://stat.data.abs.gov.au/Index.aspx?DatasetCode=POP_PROJ_2011# Accessed on 09 Nov 2021

¹² Bright et al. (2020). Tuberculosis notifications in Australia, 2015-2018. *Commun Dis Intell*, **44**: Oct 25.

single cluster). However, the additional depth of information provided by WGS (using the number of SNPs to infer transmission, with a threshold of 8 for direct transmission) suggested that while three of the Australian citizens formed a single cluster (with only 1 SNP difference), the fourth isolate was linked to another cluster from Papua New Guinea (with no SNP differences).

Rapid testing may be most beneficial in high-risk communities and remote hotspots. A genomic analysis of all culture-confirmed TB cases in the Top End of the Northern Territory from 1989-2020 found that over three quarters of clustered cases occurred outside urban Darwin, suggesting that TB control resources should continue to be directed to TB hotspot regions with focus on timely and complete case detection, contact tracing, and latent TB treatment (Meumann, 2021). Genomic sequencing was able to identify putative transmission links that had not been evident during contact tracing.

Beyond outbreak investigation, other potential benefits of WGS for DST in mycobacteria include reducing development of antimicrobial resistance, and distinguishing between relapse and re-infection with a different strain.

16. Key issues from ESC to MSAC

ESC key issue	ESC advice to MSAC
Clinical outcomes	While the service is likely to improve treatment adherence and clinical outcomes, there is only limited evidence from small case series linking WGS to changes in clinical outcomes. There are no data from Aboriginal and Torres Strait Islander populations.
ICER interpretation	The ICER is \$4,551 per additional pathogen resistance correctly diagnosed, which is difficult to interpret but in line with cost per additional proband detected in germline genetic tests previously supported by MSAC. The ICER may be conservative: if the difference in turnaround time (TAT) increases from 5 to 10 days, the ICER decreases to \$860 per additional pathogen resistance correctly diagnosed.
Turnaround time (TAT)	There is uncertainty over the estimated TAT, and TAT is likely to shorten over time. The effectiveness of WGS will be less if TATs are more similar between WGS and pDST. In practice, a shorter TAT is likely to have only a modest effect on patient management.
Economic model	<p>The decision tree used in the DCAR was an overly simple choice for infectious disease modelling, as it poorly addresses timing and transmission. A discrete event simulation model would be more suitable for the future in similar assessments for other organisms/disease indications.</p> <p>Nonetheless, the decision tree model is correct and valid. The model made many assumptions, which were appropriately explored in sensitivity analyses. That the model omitted disease transmission, however as a result has provided a more conservative estimate of cost-effectiveness.</p>
MBS item descriptor	<p>The item descriptor needs to be expanded from initial diagnoses only, to include testing at disease relapse, per the management algorithm. The frequency of testing should be restricted to prevent inappropriate usage.</p> <p>Rather than all mycobacterial infections, the item descriptor should be for patients with all MTBC infections. The exemplar as narrowed by the DCAR excluded the remainder of the MTBC, but the DCAR's evidence aligned with the applicant's target population.</p>
Proposed fee and breakdowns	The proposed fee of \$120 is reasonable based on benchmarking, though may be too low. No information was provided on the breakdown of costs (to include consumables, bioinformatics, data sharing, etc.), which would be helpful for MSAC to advise on the appropriate fee.
Wider benefits	WGS has important wider benefits that are difficult to quantify in economic modelling, including outbreak control, phylogenetics, contributions to variant libraries used in resistome analysis, and data sharing across jurisdictions.
Equity of access	Better access to testing for Aboriginal and Torres Strait Islander peoples must be addressed, as the incidence of TB in this group is currently higher than in non-indigenous Australians. Equitable access for patients in remote areas could be supported through decentralised testing laboratories, or funding for samples to be sent to state-based reference laboratories.

ESC discussion

ESC noted that this application from the Royal College of Pathologists of Australasia was for a new Medicare Benefits Schedule (MBS) item for whole genome sequencing of antimicrobial-resistant organisms. ESC noted that the original application requested MBS listing for WGS for a wide range of indications, and that this had been refined for the PICO into five indications (separate classes of infectious organism or disease) and their respective exemplar organisms, with all item descriptors describing the indication rather than the exemplar. ESC noted PASC had advised that the mycobacterial indication should be the first to undergo assessment, and that for this indication the exemplar is tuberculosis.

ESC noted that the application is for patients who have already been diagnosed with TB using point-of-care tests (such as GeneXpert) that have started early empiric treatment for TB. ESC noted that the exemplar had been narrowed by the DCAR to TB caused specifically by *Mycobacterium tuberculosis*, but that TB can also be caused by other members of the *M. tuberculosis* complex (MTBC), such as *M. bovis* and *M. canetti*. ESC noted the pre-ESC response clarified the target population is primarily patients diagnosed with TB caused specifically by *M. tuberculosis*, the most common type of mycobacterial infection. ESC considered that the exemplar as defined by the DCAR had excluded the remainder of the MTBC, but that the DCAR's evidence aligned with the applicant's target population. The pre-ESC response also clarified that WGS will not be used in patients with *M. leprae* or non-tuberculosis mycobacteria (NTM) infection. ESC confirmed the total population eligible for testing is therefore patients with MTBC infection.

ESC noted that the applicant specified in its pre-ESC response that it intended use of WGS both after diagnosis and after initial therapy to refine drug therapy. ESC noted that resistance may develop after treatment is initiated, so testing is used to refine the therapy. ESC also noted that the proposed item descriptor does not suggest any restrictions on how many times WGS can be claimed. ESC considered that because TB is estimated to recur in 2% of patients, the item descriptor should be expanded to encompass testing in patients with recurrent disease. ESC also advised that it would be appropriate to restrict the frequency of testing, noting that TB typically resolves in 6 months or less, though in patients with extrapulmonary TB in hard-to-reach sites it may take 12 months or longer. A revised item descriptor is provided accordingly in Table 1.

Table 19 ESC's revised MBS item descriptor

Category 3 – Pathology Services – Group 3 Microbiology	
MBS item XXXX	
Sequencing and analysis of the whole mycobacterial genome of <i>Mycobacterium tuberculosis complex (MTBC)</i> from an isolate or nucleic acid extract obtained at the time of:	
<ul style="list-style-type: none"> a) initial diagnosis and commencement of initial empiric therapy, or b) following disease relapse, 	
to speciate the organism accurately and for the purpose of genome-wide determination of the antimicrobial resistance markers (resistome) of the isolate to individualise the patient's treatment after initial empiric therapy .	
Applicable once at initial diagnosis and once per episode of disease relapse.	
Fee: \$120.00	Benefit: 75% = \$90.00 85% = \$102.00

ESC's proposed changes from the item descriptor in the PICO: deletions are in strikethrough, and additions in green.

ESC noted that the proposed service will be performed in addition to MBS-funded phenotypic drug susceptibility testing (pDST). ESC noted that WGS is already routinely used by TB reference laboratories, where it is performed concurrently with traditional pDST, and a skilled workforce is required to interpret the results. ESC also noted that WGS may completely replace pDST in the future (as has happened in the Netherlands), but that laboratories would likely need to develop experience with WGS before dropping pDST.

ESC noted the proposed fee of \$120 aligns with some laboratories' fee to perform this service, however, ESC considered that this fee may be too low for smaller-throughout laboratories due to loss of economies of scale. ESC considered that it would be useful if the applicant provided a breakdown of the components of this costing, including consumables, bioinformatics, data sharing and analytic time, to help MSAC advise on the appropriate fee.

ESC noted consultation feedback was received from two organisations, who were overall supportive of the technology and most elements of the application. Both stakeholders expressed concern about the requirement for specialist workforce skills. ESC noted that feedback also mentioned the risk of leakage, and the lack of an external quality assurance (EQA) program. ESC noted the application did not address the risk of not identifying antibiotic-resistance sequences that are absent from the database used to interpret WGS results, and that one stakeholder had suggested that this limitation should be highlighted in WGS diagnostic reports. ESC noted that feedback also queried the use of testing for surveillance purposes, and the associated cost of data sharing, which the application did not address.

ESC noted that the vast majority of the TB infections in Australia occur in people born overseas, but that amongst Australian-born people TB occurs at higher rates in Aboriginal and Torres Strait Islander populations than in the non-indigenous population. ESC noted that a stated aim of this application is to make WGS more widely and equitably available, but that the DCAR had not found any data on use of TB WGS in Aboriginal and Torres Strait Islander Australian populations specifically. Given the higher incidence of TB and multidrug-resistant TB (MDR-TB) in Aboriginal and Torres Strait Islander Australian populations, ESC considered that this proposed service would preferentially benefit Aboriginal and Torres Strait Islander Australians. ESC further considered that equitable access for patients in remote areas could be supported through decentralised testing laboratories, or funding for samples to be sent to state-based reference laboratories. ESC noted uncertainty around how data are shared. ESC noted that the Australian Mycobacterium Reference Laboratory Network may be able to support data sharing.

ESC noted the applicant's non-inferiority claim overall for WGS, but that the Department-contracted Assessment Report (DCAR) had determined that adding WGS to pDST had superior clinical effectiveness and safety, compared to pDST alone. ESC noted that WGS can detect isolates that are reported as false negatives on pDST, and that WGS can accurately detect mutations associated with low-level resistance, which can be missed by pDST (Jajou et al. 2019).

ESC noted the main benefits of WGS compared to pDST were proposed to be the shorter turnaround time (TAT), better sensitivity and detection, changes to treatment regimes, distinguishing reinfection from relapse, and providing epidemiological data including whether an infection is nosocomial. The TAT for pDST is several weeks for slow-growing organisms such as mycobacteria, and WGS results were estimated to be more than five days faster (Martinez et al. 2016). ESC noted uncertainty around TAT in different settings, and that the pre-ESC response states WGS results are reported one week earlier than pDST. ESC considered that with a difference in TAT of approximately five days, any patient benefit is likely quite small. ESC considered the TATs to be uncertain and likely to shorten over time.

ESC noted the lack of evidence regarding how the availability of WGS changes the management of patients and their outcomes, as well as other uncertainties around clinical management, including:

- how results are managed and fit with public health (clusters, outbreaks and follow-up)
- coordination of clinical intervention
- availability of microbiologist/pathologist expertise and bioinformatic support.

ESC considered that safety may be superior for WGS because of earlier treatment modification, which improves adherence to a simpler drug regime and may result in reduced drug side effects. ESC noted that there may also be increased safety for the community by identifying and tracking outbreaks of antimicrobial-resistant TB (including within hospitals).

ESC noted that the economic evaluation used a decision-tree analysis, which it considered to be an overly simple model choice for infectious disease, as it poorly addresses timing of diagnosis, which is a key issue for this assessment, and also does not assess the potential to reduce disease transmission rate. ESC advised a discrete event simulation would be a more appropriate model type, and would be appropriate for subsequent assessments including those for the remaining four indications from the 1646 PICO. Nonetheless, ESC considered the decision tree model to be correct and valid: in a situation with a small population and limited data, the model makes sense and has been built sensibly. ESC considered that omitting disease transmission was unrealistic and transmission should have been included because there is evidence that TB spreads within hospitals – however as a result of omitting it, the model has provided a more conservative estimate of cost-effectiveness.

ESC noted the following assumptions and exclusions in the economic model:

- treatment failure for other reasons
- timing of appropriate treatment due to false negatives on pDST was assumed to be 60 days
- the side effects of inappropriate treatment were not included.

ESC considered that the cost-effectiveness measure “cost per additional correct diagnosis” is difficult to contextualise, leaving uncertainty as to the cost-effectiveness of the incremental cost-effectiveness ratio (ICER) of \$4,551 per additional correct diagnosis. However, ESC considered that this cost-effectiveness per correct additional diagnosis is broadly consistent with cost-effectiveness measured in terms of “cost per additional proband detected” in previous germline genetic testing supported by MSAC. ESC considered the ICER of \$4,551 to be conservative, and noted that if the difference in TAT between WGS and pDST doubles from 5 to 10 days, then the ICER drops to \$860 per additional correct diagnosis. ESC also noted that had disease transmission been included in the economic model, the ICER would be more favourable.

ESC noted that many wider benefits of WGS cannot be quantified in an economic model, including:

- distinguishing between relapse and re-infection to inform the focus of outbreak control activities, which includes increasing treatment adherence and contact tracing
- reducing development of antimicrobial resistance because of more judicious prescribing of regimens with less toxicity
- outbreak investigation – WGS assists in controlling an outbreak (there is weak evidence regarding TB). Cluster testing will be important in this public health secondary use for WGS data on pathogen resistance, along with phylogenetic analysis to establish transmission dynamics
- WGS contributes to libraries of known resistance genetic variants. ESC considered contributing to genetic databases to be important as this will improve WGS sensitivity
- data exchange between national and international jurisdictions. There are important implications for national and international epidemiology regarding nosocomial infections and outbreaks.

ESC considered the estimated financial impact to MBS to be small, at \$158,886 in year 1 and \$170,970 in year 5. ESC noted the sensitivity analysis showed the cost-effectiveness was most sensitive to the fee for WGS, which it considered may be too low. The DCAR also reported savings to the Pharmaceutical Benefits Scheme (PBS) for drugs, and hospital savings from reduced duration of isolation. ESC considered other MTBC species may be included in some estimates, but that hospitalisations are unlikely to affect the overall cost substantially. ESC considered that as TB is a notifiable disease, data on incidence in Australia are likely to be robust.

17. Applicant comments on MSAC's Public Summary Document

The applicant would like to express their delight in MSAC approving public funding for WGS, and would like to take this opportunity to thank the Department for its assistance throughout the assessment process for this complicated application.

18. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)