



Australian Government

Department of Health

Ratified PICO Confirmation

Application 1646

**Whole genome sequencing of antimicrobial-
resistant pathogens**

This PICO confirmation to guide the assessment of whole genome sequencing (WGS) of antimicrobial-resistant pathogens is presented in five separate indications, representing five proposed Medicare Benefit Schedule (MBS) items. Although the intervention (WGS of the pathogen) is the same for each indication, the exemplar case for each indication is different. The exemplar cases have been selected by the applicant, in consultation with the Department, to illustrate a clinical scenario in which the intervention would be utilised and where evidence for the intervention exists.

For clarity and ease of reading, each indication is presented in turn in this PICO confirmation, with the proposed item descriptors followed by the PICO criteria and clinical algorithm for each exemplar case. Other than the tuberculosis example, the exemplar cases were not included in the original applicant submission. This means that limited information about the indication, and the comparator, for these cases was presented. The information about these exemplar cases that is included in this PICO confirmation has been found by the assessment group; however, it is recognised that the clinical implications may not have been correctly interpreted from the algorithms provided, and feedback or correction on these is welcome.

The five proposed indications and their respective exemplars are shown in Table 1.

Table 1 Proposed indications and their exemplars and location in this PICO confirmation

No.	Indication	Exemplar	Page no.
1	Mycobacteria	Tuberculosis	3
2	Primary antimicrobial-resistant bacterial infection	Carbapenem-resistant enterobacterales	12
3	Recurring or resistant bacterial infection	<i>H. pylori</i>	20
4	Primary viral infection	HIV	27
5	Recurring or resistant viral infection	Cytomegalovirus	36

A single section on the proposed economic evaluation approach is provided on page 35.

It should be noted by the PICO Advisory Sub-committee (PASC) that each of these five indications will need to be treated separately in the assessment, requiring individual clinical assessments (e.g. five separate systematic reviews) and individual cost effectiveness assessments (e.g. five separate economic models). This will need to be factored into the time and resources allocated to the assessment.

Indication 1: Mycobacteria - exemplar case Tuberculosis

Summary of PICO/PPICO for exemplar case

The suggested exemplar case for mycobacteria is tuberculosis (TB); the PPICO criteria for assessing the use of WGS in identifying microbial-resistant pathogens in TB can be found in Table 2.

Table 2 PPICO criteria for assessing WGS in identifying microbial-resistant pathogens in TB

Component	Description
Patients	Patients with diagnosed tuberculosis, who have begun empiric treatment for susceptible or resistant TB based on history and results from GeneXpert
Prior tests	Diagnostic test for tuberculosis, including resistance to rifampicin to guide early empiric treatment
Intervention	Whole genome sequencing of the mycobacterial pathogen, to determine and characterise antimicrobial resistance
Comparator	Phenotypical susceptibility testing
Outcomes	<p>Diagnostic performance:</p> <ul style="list-style-type: none"> Analytical sensitivity and specificity Likelihood ratios Rate of repeat testing required Time taken to achieve confirmed result <p>Safety:</p> <ul style="list-style-type: none"> Harms resulting from misdiagnosis Harms resulting from delayed diagnosis Improved antimicrobial stewardship (how to measure?) Rates of morbidity and mortality <p>Clinical effectiveness:</p> <ul style="list-style-type: none"> Change in management Quality of life (QoL) Length of hospital stay <p>Clinical validity</p> <ul style="list-style-type: none"> Clinical sensitivity and specificity PPV, NPV <p>Cost effectiveness</p>

Population

The population of interest is patients who have been diagnosed with tuberculosis (TB). Patients suspected of TB will undergo standard diagnostic testing, which in Australia is undertaken in Australian TB reference laboratories. Diagnostic tests involve conventional testing and polymerase chain reaction (PCR) testing using the GeneXpert® System (Cepheid, Sunnyvale, CA, USA), which not only detects the presence of mycobacteria, but also identifies resistance to Rifampicin, as a marker for multidrug-resistant TB. Patients can then begin treatment.

The incidence and prevalence of TB in Australia is low, and the majority of cases occur in people born overseas who have migrated from high-prevalence countries such as India, Vietnam, the Philippines, China and Nepal (Bright, Denholm et al. 2020). However it remains a public health issue for Aboriginal and Torres Strait Islander people in central and northern regions of Australia (Health Protection Policy Branch. 2019).

There were 1438 TB notifications in Australia in 2018, a rate of 5.8 per 100 000 population (Bright, Denholm et al. 2020). This number was consistent with the preceding three years. Of these notifications, 1369 were new cases and 64 were relapse cases. Of the notifications in 2018, 12% were identified as having resistance to at least one first-line anti-TB agent, whilst 2% were multi-drug resistant TB and <1% were extensively drug resistant (Bright, Denholm et al. 2020).

It should be noted that WGS may need to be undertaken more than once in a single patient, where treatment has failed. In these cases it is possible that resistance has developed to a previously susceptible drug, commonly due to non-adherence to the treatment regimen. In these cases, WGS can be undertaken a second time to inform a new treatment strategy. The number of cases that may require a second WGS test is expected to be very small; fewer than 2% of the population with TB. Clinical advice suggested that because this group is so small, and there is unlikely to be any evidence informing a clinical or economic assessment, no separate PICO criteria were required. In practice, this group can be treated in the same way as a new case of TB, and there are no proposed limits to the number of times the WGS item can be used for a single patient.

Rationale

The mycobacterium that causes TB has been selected as an exemplar case for this assessment as WGS has been widely used in global health settings to identify anti-microbial resistance in this condition. Whilst it is recognised that it is not a particularly prevalent pathogen in Australia, it is difficult to treat and antimicrobial resistance is a particular problem in this disease.

TB is generally treated within TB reference centres in Australia.

Prior test

Prior testing for the population includes diagnosis of TB. In most cases in Australia, this is undertaken at TB reference laboratories which use the GeneXpert® System (Cepheid, Sunnyvale, CA, USA) which not only detects the presence of mycobacteria, but also identifies resistance to Rifampicin, as a marker for multidrug-resistant TB.

Intervention

The intervention is whole genome sequencing (WGS). WGS provides rapid and simultaneous screening of all clinically-relevant mutations in close to real-time to predict a pathogen's full resistance profile to multiple drugs (the 'resistome'¹) in order to guide a patient's treatment and/or the chemoprophylaxis of close contacts (Cabibbe and Cirillo 2016, Balloux, Bronstad-Brynildsrud et al. 2018). For indication 1, the intervention involves the 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.

The key advantage of WGS for identifying the resistance profile is its speed compared to conventional drug susceptibility testing. Time is crucial in identifying any antimicrobial resistance, so that any inappropriate treatment can be halted and appropriate treatment initiated. Inappropriate treatment contributes to antimicrobial resistance, further impacting on the health of individuals and populations. It should be noted however, that time to grow the initial culture remains the same, whether WGS or phenotypic testing is used.

In Australia, WGS is available at laboratories who have joint National Association of Testing Authorities (NATA) and Royal College of Pathologists Australasia (RCPA) accreditation, and who are specifically accredited to provide genetic testing via WGS. There are few pathology providers with this accreditation currently, and clinical advice states that testing is likely to remain restricted to a few centres of excellence, with only one or two laboratories in each state to provide testing. It should be noted, however, that the number of laboratories who will be equipped and accredited to undertake WGS is likely to increase in the future; this may have an impact on uptake of the proposed items.

For the mycobacteria exemplar, WGS is currently undertaken at the TB reference laboratories located in public tertiary hospital settings.

Rationale

WGS is proposed as an intervention relatively early in the diagnostic and treatment phase of TB, however it is not expected to replace initial diagnosis using GeneXpert. Clinical advice suggests it is highly unlikely that WGS will be conducted immediately upon diagnosis.

PASC noted that the WGS strategy (for this and other indications within this PICO) relies heavily on the availability of good quality genetic databases being used to infer resistance from the reported genetic sequences.

¹ The sum of the detected AMR genes in a sequenced isolate is referred to as the resistome. Balloux, F., O. Bronstad Brynildsrud, L. van Dorp, L. P. Shaw, H. Chen, K. A. Harris, H. Wang and V. Eldholm (2018). "From Theory to Practice: Translating Whole-Genome Sequencing (WGS) into the Clinic." *Trends Microbiol* **26**(12): 1035-1048.

PASC noted that where the genetic basis of drug resistance is unknown, resistance can only be determined using phenotypic testing, and considered WGS would be an add-on test in most scenarios.

Comparator

The comparator is phenotypic susceptibility testing. Phenotypic analysis of bacterial susceptibility to antimicrobial agents is relatively straightforward and relies on well-proven methods, such as agar and broth microdilution (the latter being the reference standard) or disc diffusion, followed by interpretation according to agreed guidelines (Ellington, Ekelund et al. 2017). In addition, there are automated methods that can be used for standard bacterial pathogens; the aforementioned GeneXpert is one of these.

However, antimicrobial susceptibility testing (AST) is time consuming, with long turnaround times for slow-growing organisms such as mycobacteria. The results of a full AST workup can take several weeks, leading to difficult drug treatment decisions, the opportunity for further resistance to arise if inadequate regimens are prescribed, and potential patient exposure to unnecessary drugs and side effects during the interim period (Witney, Gould et al. 2015).

The applicant states that the proposed service will operate in addition to current testing, replacing some, but not all of the current methods. It is noted that genomic resistance prediction may need to be supplemented with standard phenotypic testing into the near future, especially for those antimicrobials for which the genetic basis of resistance is not yet fully known. There is no estimate of what proportion of WGS tests would replace standard testing and what proportion would be additional.

Currently, AST for mycobacteria is listed on the MBS under three item numbers; these are shown in Table 3.

Table 3 MBS items in use for comparator (phenotypic susceptibility testing)

MBS item and use	Financial year			
	16/17	17/18	18/19	19/20
MBS item 69324: microscopy and culture for mycobacteria, 1 specimen, including pathogen identification and antibiotic susceptibility testing	35 777	37 009	38 013	37 361
MBS item 69327: microscopy and culture for mycobacteria, 2 specimens, including pathogen identification and antibiotic susceptibility testing	4993	5525	5938	6141
MBS item 69330: microscopy and culture for mycobacteria, 3 specimens, including pathogen identification and antibiotic susceptibility testing	8424	9360	9204	9391

PASC noted that WGS is currently already undertaken at TB reference laboratories in Australia and is almost routine for new cases of TB. The WGS is complementary to the phenotypic testing undertaken, as the resistance of all relevant genes is not known. Thus, the testing is additional to phenotypic testing.

Outcomes

Patient relevant

Safety:

- Harms resulting from misdiagnosis
- Harms resulting from delayed diagnosis
- Improved antimicrobial stewardship
- Rates of morbidity and mortality

Effectiveness:

- Change in management
- Symptom improvement
- Rates of cure /relapse
- Quality of life

Clinical validity:

- Clinical sensitivity and specificity
- PPV, NPV

Analytical validity:

- Analytical sensitivity and specificity
- Likelihood ratios
- Rate of repeat testing required
- Time taken to achieve confirmed result

Healthcare system

- Length of hospital stay
- Medication usage

Cost effectiveness

PASC noted that a key benefit of adding WGS for TB is shortening the window of infectiousness for people with transmissible disease, and the potential cost offsets from, for example, obviating years of therapy for multi-drug-resistant TB for each case prevented.

[Current and proposed clinical management algorithm for indication 1 exemplar](#)

The applicant provided a clinical algorithm that showed both existing and proposed algorithms in one diagram, which was subsequently amended based on PASC advice to indicate that WGS is additional to phenotypic testing.

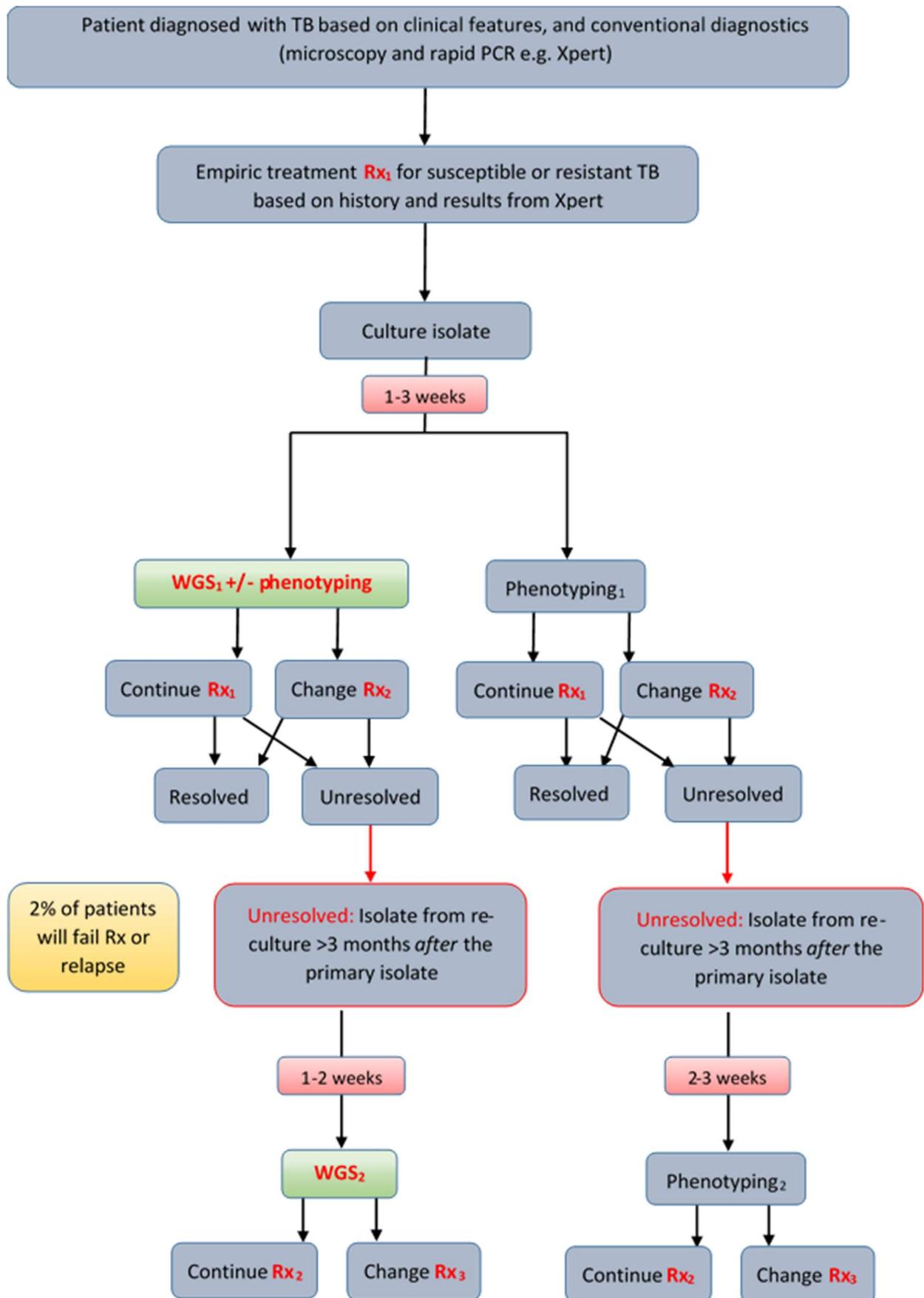


Figure 1 Current and proposed clinical algorithm for identification of antimicrobial resistance in tuberculosis

Proposed item descriptor

The proposed item descriptor for Indication 1 is in Table .

Table 4 Proposed item descriptor for mycobacteria

Category 6 (Pathology Services) – Group P3 Microbiology
Proposed item descriptor: 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

PASC noted that TB is often identified in rural and remote locations with no specialist services, and is ordered by GPs, and so advised that requestors of the item should not be limited to specialists.

Indication 2: Primary bacterial infection - exemplar case Enterobacterales

Summary of PICO/PPICO for exemplar case for Indication 2: primary bacterial infection

The suggested exemplar case for primary bacterial infection is carbapenem-resistant enterobacterales; the PPICO criteria for assessing the use of WGS in identifying antimicrobial-resistant pathogens in carbapenem-resistant enterobacterales can be found in Table 4.

Table 4 PPICO criteria for assessing WGS in identifying microbial-resistant pathogens in carbapenem-resistant enterobacterales

Component	Description
Patients	Patients with diagnosed carbapenem-resistant phenotype of an enterobacterales
Prior tests	Diagnostic test for enterobacterales, with phenotypic susceptibility testing to identify carbapenem-resistance or carbapenemase production
Intervention	Whole genome sequencing of the enterobacterales pathogen, to determine and characterise antimicrobial resistance
Comparator	Phenotypical susceptibility testing
Outcomes	<p>Diagnostic performance:</p> <ul style="list-style-type: none"> Analytical sensitivity and specificity Likelihood ratios Rate of repeat testing required Time taken to achieve confirmed result <p>Safety:</p> <ul style="list-style-type: none"> Harms resulting from misdiagnosis Harms resulting from delayed diagnosis Improved antimicrobial stewardship (how to measure?) Rates of morbidity and mortality <p>Clinical effectiveness:</p> <ul style="list-style-type: none"> Change in management QoL Length of hospital stay <p>Clinical validity</p> <ul style="list-style-type: none"> Clinical sensitivity and specificity PPV, NPV <p>Cost effectiveness</p>

PICO or PPICO rationale for therapeutic and investigative medical services only

Population

The population of interest is patients who have been diagnosed with a carbapenem-resistant or carbapenemase-producing enterobacterales. This group of patients will have already undergone diagnosis and phenotypic susceptibility testing to identify if their pathogen is carbapenem-resistant or carbapenemase-producing, which has implications for the treatments available. At present, further testing to identify resistance in other genes is then undertaken to identify appropriate treatments. Although testing is intended to guide initial therapy, in this exemplar case, empiric therapy begins before test results are available.

Enterobacterales is an order of gammaproteobacteria, and the family enterobacteriaceae are the pathogens of interest for this item. Enterobacteriaceae are some of the most important pathogens in human history, responsible for diseases of public health importance, such as *Salmonella*, *Shigella* and *Escherichia coli* (Jenkins, Rentenaar et al. 2017). Although certain species are part of the normal flora of humans, many are associated with diarrhoeal and extra-intestinal diseases.

The applicant reports that there were 877 cases of carbapenem-resistant enterobacterales in 2019, a figure derived from active surveillance (CARalert).

Rationale

The selection of a population with carbapenem-resistant or carbapenemase-producing enterobacterales as the exemplar case is based on clinical advice from the applicant, and because it is likely to have evidence.

Prior test

Prior testing for the population includes diagnosis of carbapenem-resistant or carbapenemase-producing enterobacterales. This involves standard diagnostic testing and phenotypic susceptibility testing to identify carbapenem resistance.

Intervention

The intervention is WGS of the whole Enterobacteriaceae genome for the purpose of genome-wide determination of the antimicrobial susceptibility of the isolate in order to guide initial antimicrobial therapy.

As per Indication 1, testing would only occur in a NATA-accredited laboratory, with RCPA accreditation for providing genetic testing via WGS.

Rationale

WGS is proposed as an intervention to further explore the resistome in patients with known resistance to carbapenem, or that produce the carbapenemase enzyme. Its benefit is speed compared to usual phenotypic susceptibility testing.

Comparator

The comparator is phenotypic susceptibility testing. Phenotypic analysis of bacterial susceptibility to antimicrobial agents is relatively straightforward and relies on well-proven methods, such as agar and broth microdilution (the latter being the reference standard) or disc diffusion, followed by interpretation according to agreed guidelines (Ellington, Ekelund et al. 2017). In addition, there are automated methods that can be used for standard bacterial pathogens; the aforementioned GeneXpert is one of these.

Antimicrobial susceptibility testing (AST) for fast-growing and not fastidious organisms such as enterobacterales is not overly time consuming, with turnaround time approximately 48 hours.

The applicant states that the proposed service will operate in addition to current testing, replacing some, but not all of the current methods. It is noted that genomic resistance prediction may need to be supplemented with standard phenotypic testing into the near future, especially for those antimicrobials for which the genetic basis of resistance is not yet fully known. There is no estimate of how many WGS tests would replace standard testing and how many would be additional.

Currently, AST for enterobacterales is listed as MBS item 69345. The use of this item over the last four years is shown in Table 5.

Table 5 MBS items in use for comparator (phenotypic susceptibility testing) in enterobacterales

MBS item and use	16/17	17/18	18/19	19/20
MBS item 69345 culture: and microscopy without concentration techniques of faeces for faecal pathogens including pathogen identification and antibiotic susceptibility testing	592 962	608 653	593 628	579 826

Outcomes

Patient relevant

Safety:

- Harms resulting from misdiagnosis
- Harms resulting from delayed diagnosis
- Improved antimicrobial stewardship
- Rates of morbidity and mortality

Effectiveness:

- Change in management
- Symptom improvement
- Rates of cure /relapse
- Quality of life

Clinical validity:

- Clinical sensitivity and specificity
- PPV, NPV

Analytical validity:

- Analytical sensitivity and specificity
- Likelihood ratios
- Rate of repeat testing required
- Time taken to achieve confirmed result

Healthcare system

- Length of hospital stay
- Medication usage

Cost effectiveness

[Current and proposed clinical management algorithm for indication 2 exemplar](#)

The applicant provided a clinical algorithm that showed both existing and proposed pathways in one diagram; this was modified based on clinical input at the pre-PASC meeting. It is shown in Figure 2.

PASC noted that there is some discussion about where WGS could sit within the clinical algorithm; and considered, as it is important that the population is those with carbapenem resistance, phenotypic testing needs to be undertaken as the prior test and advised WGS is correctly placed within the algorithm following a diagnosis with carbapenem-resistant or carbapenemase-producing enterobacterales. PASC noted that WGS could be used earlier in the clinical pathway in the future, especially as this is a field where many new treatments are being developed. However, for the purposes of the assessment, WGS will be treated as a follow-up test, as described in the clinical algorithm.

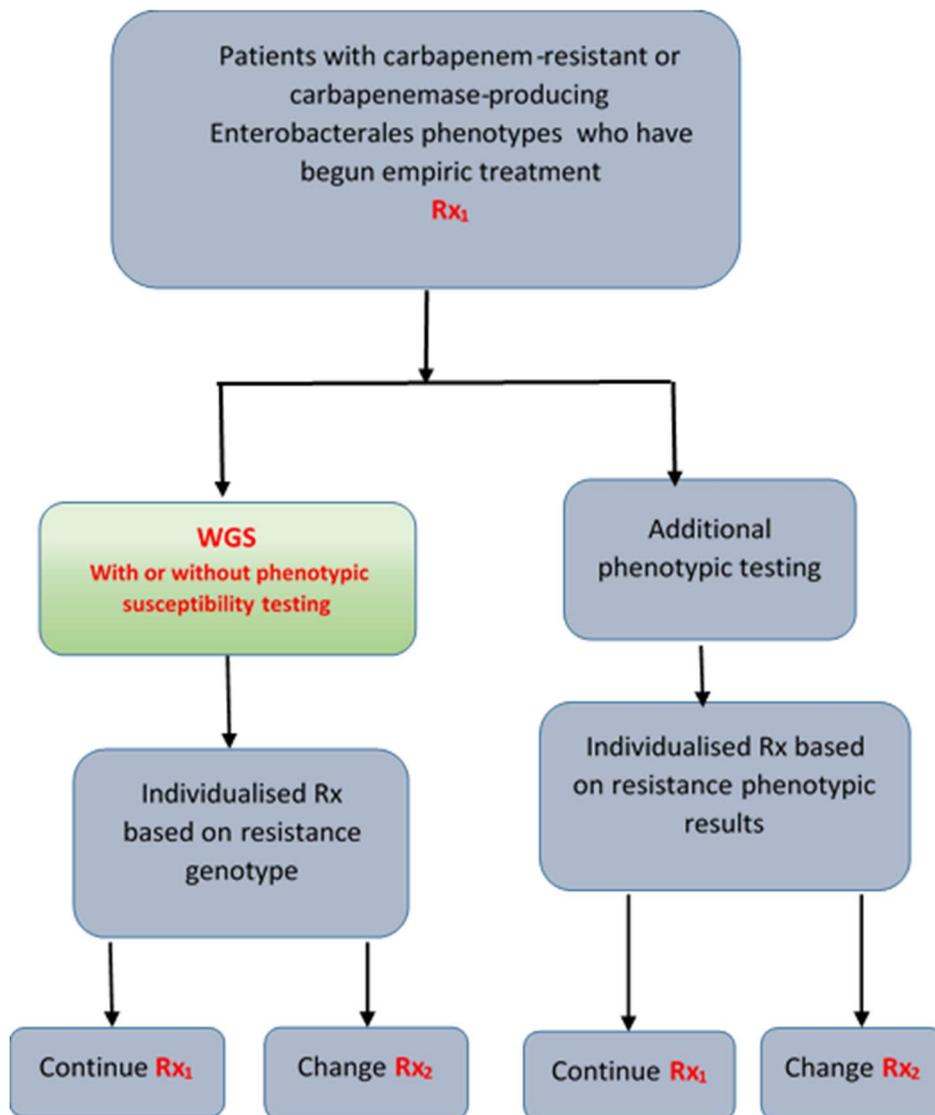


Figure 2 Current and proposed clinical algorithm for identification of antimicrobial resistance in carbapenem-resistant enterobacteriales primary infections

Proposed item descriptor

The proposed item descriptor for Indication 2 is in Table .

Table 7 Proposed item descriptor for primary bacterial infection

Category 6 (Pathology Services) – Group P3 Microbiology
Proposed item descriptor: Sequencing and analysis of the whole bacterial genome of an isolate from a primary infection of a patient, where the infection has been confirmed by phenotypic susceptibility testing to be antimicrobial-resistant, for the purpose of genome-wide determination of the antimicrobial susceptibility of the isolate in order to guide initial antimicrobial therapy, requested by a specialist or consultant physician. Fee: \$120

PASC advised that only specialists be allowed to order the WGS. PASC also considered that WGS should be used after diagnosis with a carbapenem-resistant or carbapenemase-producing enterobacterales, in the case of the exemplar for Indication 2. Thus, the item descriptor will read:

Sequencing and analysis of the whole bacterial genome of an isolate from a primary infection of a patient, where the infection has been confirmed by phenotypic susceptibility testing to be antimicrobial-resistant, for the purpose of genome-wide determination of the antimicrobial susceptibility of the isolate in order to guide initial antimicrobial therapy, requested by a specialist or consultant physician.

Indication 3: Recurrent or persistent bacterial infection - exemplar case *H. pylori*

Summary of PICO/PPICO for exemplar case for Indication 3: *H. pylori*

The suggested exemplar case for recurrent or persistent bacterial infection is *Helicobacter pylori*; the PPICO criteria for assessing the use of WGS in identifying microbial-resistant pathogens in *H. pylori* can be found in Table 8.

Table 6 PPICO criteria for assessing WGS in identifying microbial-resistant pathogens in *H. pylori*

Component	Description
Patients	Patients with diagnosed <i>H. pylori</i> infection who have failed first-line therapy or who have experienced subsequent treatment failure
Prior tests	Diagnostic test for <i>H. pylori</i> based on antigen, biopsy or breath test
Intervention	Whole genome sequencing of the <i>H. pylori</i> pathogen, to determine and characterise antimicrobial resistance
Comparator	Phenotypical susceptibility testing
Outcomes	<p>Diagnostic performance:</p> <ul style="list-style-type: none"> Analytical sensitivity and specificity Likelihood ratios Rate of repeat testing required Time taken to achieve confirmed result <p>Safety:</p> <ul style="list-style-type: none"> Harms resulting from misdiagnosis Harms resulting from delayed diagnosis Improved antimicrobial stewardship (how to measure?) Rates of morbidity and mortality <p>Clinical effectiveness:</p> <ul style="list-style-type: none"> Change in management QoL Length of hospital stay <p>Clinical validity</p> <ul style="list-style-type: none"> Clinical sensitivity and specificity PPV, NPV <p>Cost effectiveness</p>

Population

The population of interest is patients with *H. pylori* who have failed first-line therapy, or have experienced subsequent treatment failure. Newly diagnosed patients in this group do not usually undergo routine antimicrobial susceptibility testing; it is only in cases of recurrent or persistent disease that resistance is explored.

H. pylori is a very common bacterium that lives in the stomach. It is present in around 15% of Australians, but only causes problems in about 1 in 5 of those infected (Sutton 2018). It is responsible for gastritis, which can lead to peptic ulcers and cancer; around 1200 Australians die from gastric adenocarcinoma each year. *H. pylori* has been found to cause around 90% of these cancers. As with other bacterial infections, antimicrobial resistance is a growing problem in treating *H. pylori*, with most patients requiring a combination of antimicrobials, and other drugs, to clear the infection (Sutton 2018).

The Australian Institute of Health and Welfare (AIHW) reports that the prevalence of *H. pylori* is decreasing over time in Australia, but groups including older age groups, Indigenous Australians, people with socioeconomic disadvantage and people born in high prevalence countries have a higher prevalence (AIHW. 2020).

Rationale

The selection of a population with resistant or recurrent *H. pylori* s as the exemplar case is based on clinical advice from the applicant, and because it is likely to have evidence.

Prior test (investigative services only - if prior tests are to be included)

Prior testing for the population includes diagnosis of *H. pylori* infection based on antigen, biopsy or breath test. It should be noted that WGS and the comparator need to be undertaken on a biopsy specimen, so if treatment fails and it is deemed necessary to examine antimicrobial resistance, a first or repeat biopsy (if initial diagnosis based on biopsy) would need to be undertaken.

PASC noted that defining 'failed treatment' in this population is difficult, and patients can have a failure of therapy after a second round of treatment and may relapse or present for treatment again many months after their initial therapy. Thus, there should be no time requirements for treatment failure (for example, a certain number of weeks after treatment initiation).

Intervention

The intervention is whole genome sequencing of the bacterial genome of an isolate, for the purpose of determining the antimicrobial resistance markers present (i.e. the resistome), to guide the patient's treatment in cases of recurrent/persistent disease.

As per the other indications, testing would only occur in a NATA- and RCPA-accredited laboratory.

Rationale

WGS is proposed as an intervention to explore the resistome in patients with recurrent or persistent *H. pylori*. Its benefit is speed compared to usual phenotypic susceptibility testing. In addition, clinical advice suggests that phenotypic susceptibility testing for this pathogen varies according to the laboratory; WGS enables the whole resistome to be identified in a single test.

Comparator

The comparator is phenotypic susceptibility testing. Phenotypic analysis of bacterial susceptibility to antimicrobial agents is relatively straightforward and relies on well-proven methods, such as agar and broth microdilution (the latter being the reference standard) or disc diffusion, followed by interpretation according to agreed guidelines (Ellington, Ekelund et al. 2017).

However, antimicrobial susceptibility testing (AST) is time consuming, with turnaround time for *H. pylori* typically 10-14 days. The results of a full AST workup can take several weeks, leading to difficult drug treatment decisions, the opportunity for further resistance to arise if inadequate regimens are prescribed, and potential patient exposure to unnecessary drugs and side effects during the interim period (Witney, Gould et al. 2015).

The applicant states that the proposed service will operate in addition to current testing, replacing some, but not all of the current methods. It is noted that genomic resistance prediction may need to be supplemented with standard phenotypic testing into the near future, especially for those antimicrobials for which the genetic basis of resistance is not yet fully known. There is no estimate of how many WGS tests would replace standard testing and how many would be additional. Clinical advice suggests phenotypic testing is problematic in this group due to differences in the panels of drugs for susceptibility that different laboratories use. As WGS can give a genome-wide view, it is predicted that WGS may become the gold standard test for this condition. This may mean that it forms a replacement test for phenotypic susceptibility testing, rather than being additional.

Currently, AST for bacteria is listed on the MBS under one item:

MBS item 69321: microscopy and culture of biopsy specimens including pathogen identification and antibiotic susceptibility testing

This item is broad and does not specifically relate to *H. pylori*, so usage numbers have not been provided.

Outcomes

Patient relevant

Safety:

- Harms resulting from misdiagnosis
- Harms resulting from delayed diagnosis
- Improved antimicrobial stewardship
- Rates of morbidity and mortality

Effectiveness:

- Change in management
- Symptom improvement
- Rates of cure /relapse
- Quality of life

Clinical validity:

- Clinical sensitivity and specificity
- PPV, NPV

Analytical validity:

- Analytical sensitivity and specificity
- Likelihood ratios
- Rate of repeat testing required
- Time taken to achieve confirmed result

Healthcare system

- Length of hospital stay
- Medication usage

Cost effectiveness

Current and proposed clinical management algorithm for indication 3 exemplar

The applicant has provided a clinical algorithm that showed both existing and proposed pathways in one diagram; this was modified based on clinical input at the pre-PASC meeting. It is shown in Figure 3.

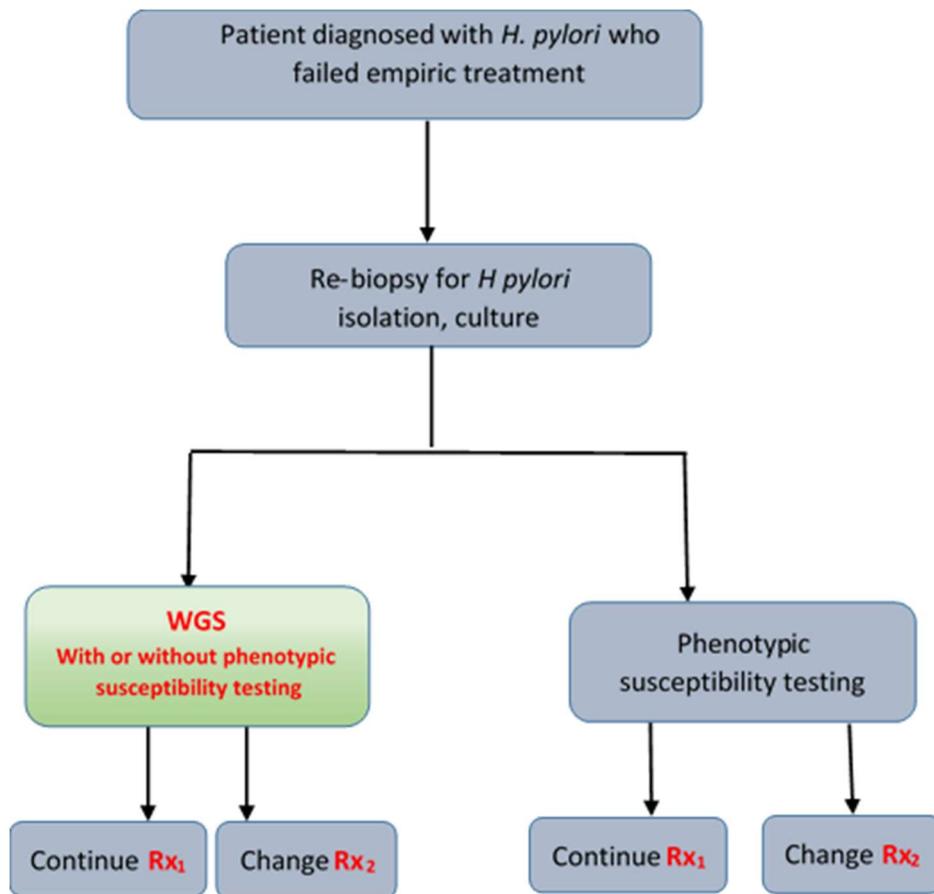


Figure 3 current and proposed clinical algorithm for identification of antimicrobial resistance in *H. pylori*

Proposed item descriptor

The proposed item descriptor for Indication 3 is in Table 9.

Table 9 Proposed item descriptor for recurrent or persistent bacterial infection

Category 6 (Pathology Services) – Group P3 Microbiology
Proposed item descriptor: Sequencing and analysis of the whole bacterial genome of an isolate for the purpose of genome-wide determination of the antimicrobial resistance markers (resistome) of the isolate to guide the patient’s treatment in cases of recurrent/persistent disease, requested by a specialist or consultant physician. If repeated, must be at an interval of not less than 12 months from previous [this item number]. Fee: \$120

PASC advised that only specialists be allowed to order the WGS. Thus, the item descriptor will read:

Sequencing and analysis of the whole bacterial genome of an isolate for the purpose of genome-wide determination of the antimicrobial resistance markers (resistome) of the isolate to guide the patient’s treatment in cases of recurrent/persistent disease, requested by a specialist or consultant physician.

PASC also noted that a limit of once per year for this test was appropriate.

Indication 4: Primary viral infection - exemplar case human immunodeficiency virus (HIV)

Summary of PICO/PPICO for exemplar case for Indication 4: HIV

The suggested exemplar case for primary viral infections is HIV; the PPICO criteria for assessing the use of WGS in identifying antiretroviral-resistant HIV can be found in Table 7.

Table 7 PPICO criteria for assessing WGS in identifying microbial-resistant pathogens in HIV

Component	Description
Patients	Patients diagnosed with HIV based on clinical features and viral load in the peripheral blood
Prior tests	Diagnostic test for HIV, based on clinical assessment, including blood viral or antibody testing
Intervention	Whole genome sequencing of the HIV pathogen, to determine and characterise antiretroviral resistance
Comparator	Sequencing multiple PCR products
Outcomes	<p>Diagnostic performance:</p> <ul style="list-style-type: none"> Analytical sensitivity and specificity Likelihood ratios Rate of repeat testing required Time taken to achieve confirmed result <p>Safety:</p> <ul style="list-style-type: none"> Harms resulting from misdiagnosis Harms resulting from delayed diagnosis Improved antimicrobial stewardship (how to measure?) Rates of morbidity and mortality <p>Clinical effectiveness:</p> <ul style="list-style-type: none"> Change in management QoL Length of hospital stay <p>Clinical validity</p> <ul style="list-style-type: none"> Clinical sensitivity and specificity PPV, NPV <p>Cost effectiveness</p>

Population

The population of interest are patients with clinically diagnosed human immunodeficiency virus (HIV) primary infection. HIV is transmitted through body fluids, and has multiple stages of progression in the host, ultimately leading to a breakdown of the immune system in the form of acquired immunodeficiency syndrome (AIDS). HIV is diagnosed on the basis of clinical features such as flu-like symptoms, and HIV viral load on blood examination. Data from the Australian Federation of AIDS Organisations (AFAO) estimated that there were 29,045 people with HIV in Australia in 2019, and a further 3,020 people are estimated to be unaware that they have a HIV infection. A decrease in infection rates has been seen over the past 6 years. Although uptake of post- and pre-exposure prophylaxis (PrEP) have brought infection rates down in recent years, the continuation of PrEP uptake depends on carefully communicated messaging to targeted groups.²

HIV infections, when left untreated can develop into AIDS disease. The United Nations UNAIDS organisation³ published recent data for individual countries. Australian data from 2019 are given in Table 8. UNAIDS reported that in 2019 an estimated 29,000 adults and children were living with HIV (95%CI 21,000 to 39,000), 86.2% of which were adult men (25,000; 95%CI 18,000 to 33,000). The prevalence of HIV in adults aged 15 to 49 years was 0.1% (95%CI <0.1% to 0.2%), while the incidence in this age group was 0.063 per 1000 population (95%CI 0.04 to 0.11). In 2019, there were <1000 new infections in adults and children (range <500 to 1400), and fewer than 100 AIDS-related deaths.

UNAIDS also reported statistics on the uptake of antiretroviral therapy (ART) (Table 8). In 2019, approximately 83% (95%CI 60% - 100%) of people living with HIV were on ART. This proportion equates to 23,808 adults aged 15 years and over, and 15 children who were receiving ART in that year.

Table 8 HIV and AIDS estimates in Australia for 2019 (UNAIDS)

Statistic description	Estimate [95%CI]
People living with HIV (all ages)	29,000 [21,000 – 38,000]
Prevalence of HIV (age 15 to 49 years)	0.1% [<0.1% – 0.2%]
New HIV infections (all ages)	<1000 [<500 – 1400]
HIV incidence per 1000 population (age 15 to 49 years)	0.06 [0.04 – 0.11]
Deaths due to AIDS (all ages)	<100 [<100- <200]
Proportion of people living with HIV receiving ART (all ages)	83% [60% - 100%]
Adults (≥15 years) receiving ART	23,808
Children (<15 years) receiving ART	15

² <https://www.afao.org.au/about-hiv/hiv-statistics/>

³ <https://www.unaids.org/en/regionscountries/countries/australia>

Rationale

The selection of a population newly diagnosed HIV infection as the exemplar case is based on clinical advice from the applicant, and because it is likely to have evidence.

Resistance to HIV treatments is an important consideration in Australia, where all people with HIV are offered treatment, and people who are at high risk of becoming infected with HIV also receive the same treatment as pre-exposure prophylaxis (The Kirby Institute. 2018). According to the Kirby Institute, more than 70% of people living with HIV were taking a combination of three or more antiviral drugs, with some patients using as many as six different drugs (The Kirby Institute. 2020). Long-term treatment and associated adherence issues have meant that drug resistant viruses have emerged, and can be transmitted (Pinto, Hawke et al. 2018). Transmitted drug resistance is well documented in countries where highly active antiretroviral therapy has been in use, including Australia. The most recent estimate of transmitted drug resistance in Australia is from a median sample year of 2013 (years sampled 2005-2015, paper published 2017), where the rate was 9.5% (Pinto, Hawke et al. 2018). Overall the rate of transmitted drug resistance does seem to have declined over time in Australia, however this is in contrast to other parts of the world such as North America (Pinto, Hawke et al. 2018).

Prior test

Clinical diagnosis of HIV is required before WGS testing is requested. In the early stage of HIV infection, symptoms and biological markers develop within the patients, enabling testing and diagnosis. Flu-like symptoms may be experienced as there is rapid multiplication and spread of the virus throughout the body. There are multiple HIV tests for diagnosis and monitoring, the choice of which depends on suspected stage of the disease, and whether it was recently acquired or long-term. Authors of a recent review (Parekh, Ou et al. 2018) say that the biological markers – HIV RNA, HIV antibodies, and CD4 cells appear at different stages in the disease course. Test applications for diagnosis include (i) the determination of patient serostatus (antibodies), (ii) distinguishing of recent from long-term infection (antibodies, p24 antigen, and viral load), and (iii) early infant diagnosis using RNA and DNA, (iv) staging and monitoring of disease progression (CD4). Test applications for monitoring include (v) identification and monitoring of treatment effectiveness or failure (viral load), and (vi) identification of drug resistance mutations for a specific ART regimen failure (RNA and DNA).

Rapid point of care (POC) testing has become increasingly common, and home-testing kits are available. POC tests use a finger prick or oral fluid, returning results within 10 to 20 minutes. Rapid tests detect HIV antibodies; however, it is recommended that a positive rapid test should be confirmed by laboratory testing.

Enzyme immunoassays (EIAs) are the standard approach to HIV testing. According to Parekh et al (2019) fourth generation EIA platforms use automated chemiluminescent microparticle technology to detect HIV-1 p24 antigen and antibodies to HIV (groups M, N, and O) and HIV-2. The simultaneous detection of antigen and antibodies shortens test turnaround time, and instruments can manage large sample throughput. Older or more recent EIA platforms are likely to be used across Australia.

Intervention

The intervention is whole genome sequencing of the viral genome of a nucleic acid extract from a primary viral infection of a patient for the purpose of guiding initial antiretroviral therapy.

This would only be performed in a NATA- and RCPA-accredited laboratory.

In this exemplar case, WGS would be offered soon after initial diagnosis, before any treatment is started.

Rationale

WGS is proposed as an intervention to explore the resistome in patients with newly diagnosed HIV infection. Its benefit is earlier and more sensitive detection of low-level antiretroviral resistance mutations (Pinto, Hawke et al. 2018).

PASC noted that currently, WGS is offered at the same time as phenotypic testing, so patients receive both tests. WGS is recommended in guidelines to identify resistant viral strains before treatment commences. In the context of listing this item on the MBS, this would most likely represent a cost shift from the states to the Commonwealth and would therefore represent an additional cost.

Comparator

In the comparator arm, empiric therapy (ART) is commenced on clinical diagnosis, prior to any analysis of viral nucleic acid sequence. While ART is successful in maintaining a low viral load, sequence analysis is not performed. If the viral load increases and remains elevated, then testing for drug resistance mutations is performed through the sequencing of viral DNA and RNA. Viruses are typically difficult to culture, and therefore are not usually suited to phenotypic testing. Viral DNA and RNA require special methods for preparation for testing.

Variations in viral genetic coding can lead to resistance and failure of empiric ART. Resistance mutations exist either within the initial viral infection, or as a result of subsequent mutation of the viral DNA. Currently, direct sequencing is performed to determine the mutations causing antiretroviral drug resistance, and to re-direct therapy (Parekh, Ou et al. 2018).

The identified comparator test is currently subsidised on the MBS under item 69380, as shown in Table 9.

Table 9 MBS items in use for comparator (genotypic testing) in HIV

MBS item and use	16/17	17/18	18/19	19/20
MBS item 69380: genotypic testing for HIV antiretroviral resistance in a patient with confirmed HIV infection if the patient's viral load is greater than 1,000 copies per ml at any of the following times: (a) at presentation; or (b) before antiretroviral therapy; or (c) when treatment with combination antiretroviral agents fails	474	459	399	335

Outcomes

Patient relevant

Safety:

- Harms resulting from misdiagnosis
- Harms resulting from delayed diagnosis
- Improved antimicrobial stewardship
- Rates of morbidity and mortality

Effectiveness:

- Change in management
- Symptom improvement
- Rates of cure /relapse
- Quality of life

Clinical validity:

- Clinical sensitivity and specificity
- PPV, NPV

Analytical validity:

- Analytical sensitivity and specificity
- Likelihood ratios
- Rate of repeat testing required
- Time taken to achieve confirmed result

Healthcare system

- Length of hospital stay
- Medication usage

Cost effectiveness

Rationale

The outcomes are appropriate. In this case, the comparator is undertaken after empiric antiviral treatment has begun.

[Current and proposed clinical management algorithm for indication 4 exemplar](#)

The applicant provided a clinical algorithm that showed both existing and proposed pathways in one diagram; this was modified based on clinical input at the pre-PASC meeting. It is shown in Figure 4.

Currently, Australasian Society for HIV Medicine guidelines suggest that ART therapy is started as soon as possible in all patients; noting that genotypic drug resistance testing should be undertaken before a regimen is selected, but ART should be initiated as soon as possible, before test results are available if necessary. Expert advice to PASC indicated that resistance testing (either using WGS or PCR) is undertaken before therapy is initiated in the Australian clinical setting. (ASHM. 2021) Patients

are monitored at regular intervals to assess ongoing viral load. While viral load is suppressed, ART will continue. If viral load becomes elevated and sustained at high level, patients will undergo further testing. Direct sequencing of the viral DNA will be conducted to determine the resistome. Testing can take up to 1 to 2 weeks. The virus' resistome will guide the future treatment of the patient.

In the proposed management pathway, once patients are diagnosed with HIV they will undergo WGS. When the resistome is known, treatment will be chosen to target the likely susceptibility of the virus. Testing is likely to take 1 to 2 weeks. Monitoring of the viral load will be conducted on all patients. Further sequencing will only be required if the treatment ceases to be effective, to assess any additional resistance mutations that have arisen.

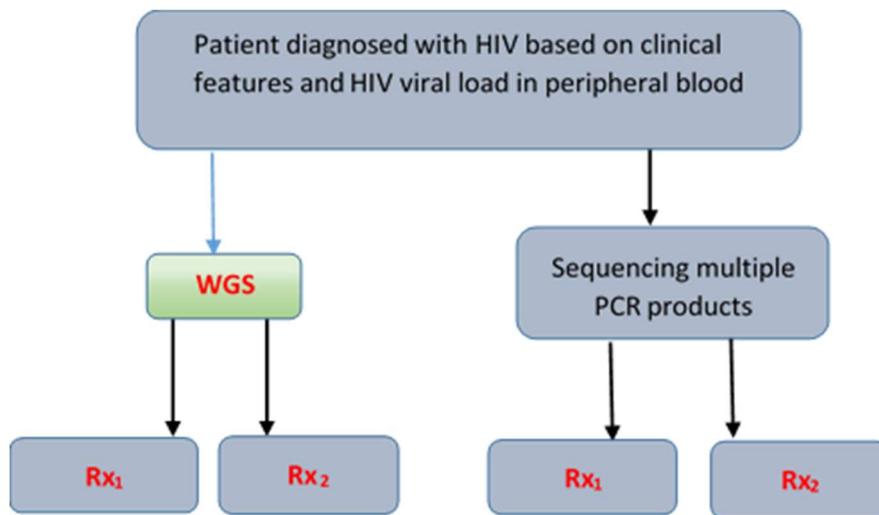


Figure 4 Current and proposed clinical algorithm for identification of antimicrobial resistance in HIV

PASC noted that anti-retroviral therapy (ART) takes place after PCR, not before. PASC further noted that Australasian Society for HIV Medicine resources recommend treatment is initiated as soon as possible, preferably after genotypic resistance testing, but prior to those results becoming available if necessary. Expert advice indicates that drug resistance testing is undertaken prior to initiating ART, to guide regimen selection – except where there was an urgent need for therapy, such as a very low T cell count.

This has been reflected in an altered clinical algorithm.

Proposed item descriptor

The proposed item descriptor for Indication 4 is in Table 10.

Table 10 Proposed item descriptor for primary viral infection

Category 6 (Pathology Services) – Group P3 Microbiology
Proposed item descriptor: Sequencing and analysis of the whole viral genome of a nucleic acid extract from a primary viral infection of a patient for the purpose of guiding initial antiretroviral therapy. Fee: \$120

PASC noted that many people with HIV are managed by their GPs and should not be excluded from use of this item, and so advised that its requestors should not be limited to specialists and consultant physicians.

Indication 5: Recurrent or persistent viral infection - exemplar case cytomegalovirus

Summary of PICO/PPICO for exemplar case for Indication 5: CMV

The suggested exemplar case for recurrent or persistent viral infections is cytomegalovirus (CMV); the PPICO criteria for assessing the use of WGS in identifying antiviral-resistant pathogens in CMV can be found in Table 11/7.

Table 11 PPICO criteria for assessing WGS in identifying antiviral-resistant pathogens in CMV

Component	Description
Patients	Patients with diagnosed cytomegalovirus who did not improve with empiric antiviral treatment or in whom disease recurred
Prior tests	Diagnostic test for CMV, testing of viral load to assess response to treatment
Intervention	Whole genome sequencing of the CMV pathogen, to determine and characterise antiviral resistance
Comparator	Sequencing multiple PCR products
Outcomes	<p>Diagnostic performance:</p> <ul style="list-style-type: none"> Analytical sensitivity and specificity Likelihood ratios Rate of repeat testing required Time taken to achieve confirmed result <p>Safety:</p> <ul style="list-style-type: none"> Harms resulting from misdiagnosis Harms resulting from delayed diagnosis Improved antimicrobial stewardship (how to measure?) Rates of morbidity and mortality <p>Clinical effectiveness:</p> <ul style="list-style-type: none"> Change in management QoL Length of hospital stay Outcomes in babies <p>Clinical validity</p> <ul style="list-style-type: none"> Clinical sensitivity and specificity PPV, NPV <p>Cost effectiveness</p>

Population

Cytomegalovirus (CMV) is a genus of the herpesviridae family, and the most common infectious cause (and second most common cause overall) of congenital malformation in Australia. CMV lies dormant after initial infection and becomes active in the body at time of compromised immunity such as organ transplant, chemotherapy and pregnancy. Vertical transmission of CMV is common, occurring between infected mother and unborn child, across the placenta, or after birth. Transmission can also occur between infectious children or adults and uninfected children through body fluids (saliva and urine) that is transferred with drink bottles, pacifiers and other utensils, or through poor hygiene at nappy changes (DoH 2019).

In addition to congenital malformations in babies, CMV is responsible for multi-organ disease after haematopoietic stem cell transplant (HSCT) in patients treated for blood cell malignancies. The incidence of CMV disease in HSCT patients has been around 10 to 40% of patients, however in a recent guideline publication, CMV incidence rates were reported between 2% and 3% in the placebo arm of prophylaxis trials (representing the natural history), and between 5% and 10% in real world practice. New transplant methods, such as graft versus host disease prophylaxis, are associated with a reduced frequency of CMV infection (Ljungman, de la Camara et al. 2019).

Estimates of prevalence of prior CMV infection are between 40% and 90% in adult women in Australia, with the highest prevalence occurring in lower socioeconomic backgrounds. Mother-to-child transmission rates are higher for primary infection than for non-primary infection (reactivation or reinfection) (30% – 35% versus 1% – 2%). It is estimated from global data that 400 children in Australia will be born with or develop CMV-related disease each year through primary or non-primary maternal infections (DoH 2019).

The risks to developing babies in utero affected by CMV include late miscarriage, hydrops, still birth and growth restriction. In addition, approximately 10% of babies with CMV will have symptoms including rash, microcephaly, and hepatosplenomegaly at birth. There are also risks of developing sensorineural hearing loss (35%), cognitive deficits (up to 60%) and other neurodevelopmental issues (epilepsy and cerebral palsy) or death (4%) (DoH 2019).

Rationale

The selection of a population with resistant or recurrent CMV as the exemplar case is based on clinical advice from the applicant, and because it is likely to have evidence.

Prior test

Failure of first-line therapy should be established before testing for resistant viral DNA mutations. Treatment failure should be established through biopsy or rising viral load.

CMV symptoms are generally non-specific in nature and serology testing is recommended to identify CMV-specific immunoglobulins IgM and IgG levels. The addition of testing IgG avidity, which measures the binding strength between the IgG antibodies and the virus, can improve the identification of primary and secondary maternal infections, and the timing of infection. The

International Congenital Cytomegalovirus Recommendations Group recommend testing in pregnant women with symptoms (fever, fatigue, or headache) that cannot be attributed to other infections when imaging findings are suggestive of fetal CMV infection (DoH 2019).

In HSCT recipients diagnosis of CMV pneumonia is hindered by the background viral shedding that is common in the airways. The following points are commended by a Clinical guidelines group in relation to diagnosis by DNA testing (Ljungman, de la Camara et al. 2019):

(1) a negative result in a DNA test for cytomegalovirus in the bronchoalveolar lavage (BAL) fluid has a negative predictive value close to 100% and is strong evidence against cytomegalovirus pneumonia;

(2) the positive predictive value of cytomegalovirus DNA detection in BAL fluid for cytomegalovirus pneumonia increases with higher viral DNA load in the BAL and with increasing underlying risk for cytomegalovirus disease in the tested patient (pretest probability); and

(3) a cut-off for viral DNA load in the BAL cannot be established because it can vary between patients, by how the BAL procedure and processing are done, by the assay used for DNA quantitation, and by the severity of symptoms.

Intervention

The intervention is whole genome sequencing of the viral genome in a nucleic acid extract from a viral infection of a patient for the purpose of guiding treatment in cases of recurrent or persistent disease.

This would only be performed in a NATA- and RCPA-accredited laboratory.

Rationale

WGS is proposed as an intervention to explore the resistome in patients with recurring or persistent CMV infection. Its benefit is speed and consistency compared to PCR testing.

Comparator

Guidelines recommend monitoring of response to empiric antiviral therapy using real-time PCR assays. PCR assays vary in the target genes amplified, the number of target genes, the nature of the probe, and the platform used for PCR, thus contributing to variation in outcomes. Commercial kits are recommended over individual laboratory-developed assays, to improve consistency. For an individual patient, the test assay should remain the same and contain the likely gene targets that would be implicated in failure of treatment (Ljungman, de la Camara et al. 2019).

A comparator MBS item was not provided by the applicant for the CMV exemplar; to determine resistance markers using currently funded tests, real-time PCR and sequencing can be performed on prepared blood and other tissue samples. For comparison, quantitation of viral load is currently funded for the identification of HIV RNA load in plasma, serum or cerebrospinal fluid, and Hepatitis C virus (HCV) RNA load in plasma or serum. Item 69491 is for the nucleic acid amplification and HCV genotyping to evaluate patients for antiviral therapy of chronic HCV hepatitis; these items are described in Table 12.

Table 12 Similar MBS items for the comparator test for identifying resistance in CMV

MBS item	Use
69381	Quantitation of HIV viral RNA load in plasma or serum in the monitoring of antiretroviral therapy in a HIV sero-positive patient - 1 or more tests on 1 or more specimen Fee: \$180.25 Benefit: 75% \$135.20 85% \$153.25
69382	Quantitation of HIV viral RNA load in cerebrospinal fluid in a HIV sero-positive patient - 1 or more tests on 1 or more specimens Fee: \$180.25 Benefit: 75% \$135.20 85% \$153.25
96445	Detection of Hepatitis C viral RNA in a patient undertaking antiviral therapy for chronic HCV hepatitis (including a service described in item 69499) - 1 test. To a maximum of 4 of this item in a 12 month period Fee: \$92.20 Benefit: 75% \$69.15 85% \$78.40
69488	Quantitation of HCV RNA load in plasma or serum in: (a) the pre-treatment evaluation, of a patient with chronic HCV hepatitis, for antiviral therapy; or (b) the assessment of efficacy of antiviral therapy for such a patient (including a service in item 69499 or 69445) (Item is subject to rule 18 and 25) Fee: \$180.25 Benefit: 75% \$135.20 85% \$153.25
69491	Nucleic acid amplification and determination of Hepatitis C virus (HCV) genotype if the patient is HCV RNA positive and is being evaluated for antiviral therapy of chronic HCV hepatitis. Fee: \$204.80 Benefit: 75% \$153.60 85% \$174.10

Rationale

This is the appropriate comparator; however, there may be an alternate MBS item that is more relevant to this comparator that has not been identified.

Outcomes**Patient relevant****Safety:**

- Harms resulting from misdiagnosis
- Harms resulting from delayed diagnosis
- Improved antimicrobial stewardship
- Rates of morbidity and mortality

Effectiveness:

- Change in management
- Symptom improvement
- Rates of cure /relapse
- Quality of life
- Outcomes in babies

Clinical validity:

- Clinical sensitivity and specificity
- PPV, NPV

Analytical validity:

- Analytical sensitivity and specificity
- Likelihood ratios
- Rate of repeat testing required
- Time taken to achieve confirmed result

Healthcare system

- Length of hospital stay
- Medication usage

Cost effectiveness

Current and proposed clinical management algorithm for indication 5 exemplar

The applicant provided a clinical algorithm that showed both existing and proposed pathways in one diagram; this was modified based on clinical input at the pre-PASC meeting. It is shown in Figure 5.

Patients are diagnosed with CMV based on biopsy examination or clinical features and VMC viral load in the peripheral blood. Empiric antiviral therapy will be given on diagnosis and high viral load. If the patient condition recovers, no further testing is required. Under the current pathway, if the condition is reactivated or not controlled with empirical treatment (as measured by monitoring tests, which would reveal high viral load or evidence of CMV infection on biopsy), viral DNA sequence will be determined through real-time PCR assay and sequencing, targeted towards common mutations for antiviral drug resistance. Once resistance mutations are determined, directed antiviral therapy can be offered. Testing for resistance mutations can take 1 to 3 weeks.

In the proposed scenario, WGS would be performed in place of real-time PCR and sequencing. Once resistance mutations have been identified, directed antiviral therapy can be offered. Testing for resistance mutations is likely to take 1 to 2 weeks in the proposed pathway.

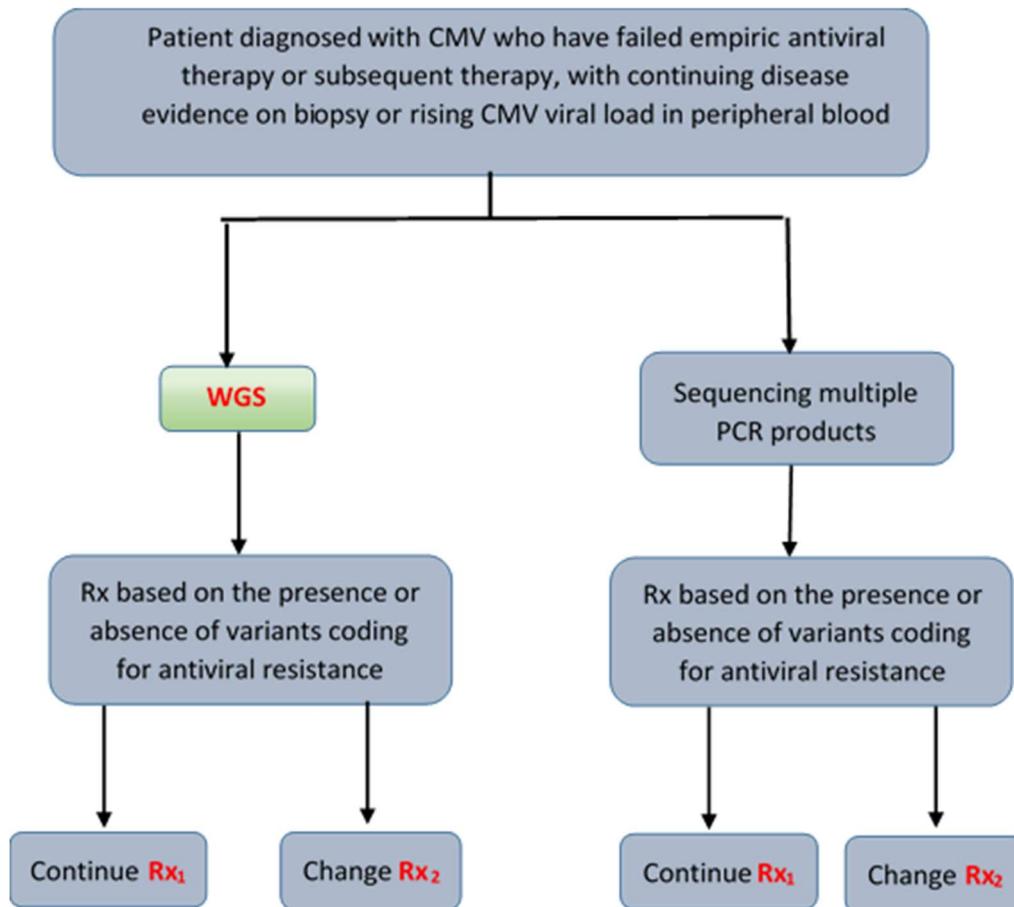


Figure 5 Current and proposed clinical algorithm for identification of microbial resistance in CMV

Proposed item descriptor

The proposed item descriptor for Indication 5 is in Table 16.

Table 13 Proposed item descriptor for recurrent or persistent viral infection

Category 6 (Pathology Services) – Group P3 Microbiology
Proposed item descriptor: Sequencing and analysis of the whole viral genome of a nucleic acid extract from a primary viral infection of a patient for the purpose of guiding treatment in cases of recurrent or persistent disease, requested by a specialist or consultant physician.
Fee: \$120

PASC advised that only specialists be allowed to order the WGS. Thus, the item descriptor will read:

Sequencing and analysis of the whole viral genome of a nucleic acid extract from a primary viral infection of a patient for the purpose of guiding treatment in cases of recurrent or persistent disease, requested by a specialist or consultant physician.

Proposed economic evaluation for all indications

The comparative clinical claim is for non-inferiority. Although the clinical advice was that WGS would be an additional test to AST, it is probably more likely that it will replace AST in most cases. Indeed, the application states:

“WGS will largely replace traditional diagnostic procedures for many microorganisms”

However, it is noted that WGS will need to be supplemented with AST into the near future.

As the number of laboratories that currently undertake WGS is limited and is likely to remain so in the short term, the applicant expects that uptake and usage of the service should remain relatively stable. However, it is likely that adoption of this technology will continue to expand, and as more laboratories become equipped and accredited to use WGS, then this may drive demand. This should be considered given the non-specific nature of the proposed items.

It should be noted that each indication will require an evaluation of cost effectiveness and an analysis of financials, meaning that there will be five separate economic analyses, including models.

PASC noted that the major issue for economic evaluation and financial impact for these items is estimating how many tests will be used; in particular, how many will be additional to existing tests and how many will replace existing tests. This remains unclear at this stage.

Consultation feedback

PASC noted that there had been no public feedback received on this PICO, but also noted that there were a further two weeks remaining (after the PASC meeting) before consultation closed.

Next steps

PASC recommended evaluating just one of the proposed indications – mycobacteria – in the first instance. This is due to the complexity of assessing the more generic items, and the workload associated with undertaking what would essentially be five DCARs. The TB exemplar is a sensible choice for the first assessment, as there is likely to be sufficient evidence given the widespread use of WGS for this indication around the world. It is also easier to estimate the usage for this indication as WGS would be additional in every case. Once this assessment is undertaken, feedback from MSAC and its sub-committees can inform assessments of the other exemplars.

PASC advised that, upon ratification of the post-PASC PICO, the application to consider the mycobacteria indication can proceed to the Evaluation Sub-Committee (ESC) stage of the MSAC process.

PASC noted the applicant has elected to progress its application as a DCAR (Department-contracted assessment report).

Applicant Comments on the PICO Confirmation

Indication 1: Mycobacteria - exemplar case Tuberculosis

Comparator

The applicant advised that an initial diagnosis with GeneXpert can be performed directly on sputum or the positive culture with the result available in 90 minutes. Whole genome sequencing (WGS) ideally needs an isolate on solid media (which takes 2-3 weeks from specimen receipt) and then takes another 1-2 weeks to perform depending on the workload of the microbial genomics lab.

The applicant stated that WGS cannot currently replace GeneXpert.

As previously stated, the use of the current MBS phenotypic susceptibility testing item numbers to indicate the potential usage of WGS is highly misleading. These numbers support the statement above that WGS should not be used as a first-line diagnostic test, as they represent all patients suspected of having a mycobacterial infection, or those patients who undergo repeat testing (multiple presentations). WGS would only be conducted on those patients with a confirmed mycobacterial infection. In 2017, there were 1,434 notifiable cases of TB in Australia. Only these patients would undergo WGS, with a small fraction (2% or 28 patients) who may require re-testing with WGS.

Outcomes

The applicant agreed with comments by PASC.

Proposed item descriptor

The applicant agreed with comments by PASC.

Indication 2: Primary bacterial infection - exemplar case Enterobacterales

Prior test

The applicant advised that the first susceptibility testing for gram negative bacteria is always carbapenem-resistance, which is a major problem, with diminishing treatment options available.

Intervention

The applicant remarked that WGS could be conducted at same time as phenotyping in carbapenem-resistant patients; however, WGS cannot replace phenotyping.

New drugs are being developed to treat carbapenem-resistance; however, it is important to know which type of carbapenem-resistance the patient has. Unusual phenotypes are not picked up by standard PCR and require diagnosis by detailed genomics such as WGS.

Comparator

*The applicant remarked, as stated above, the use of this MBS item number to indicate the potential use of WGS in patients with an enterobacterales infection is **highly misleading**. WGS would only be used in patients diagnosed as being carbapenem-resistant. As stated above and in the original*

clinical algorithm supplied by the applicant, in 2019 there were only 877 cases of carbapenem-resistant enterobacterales detected in Australia, a figure derived from active surveillance (CARAlert).

Current and proposed clinical management algorithm for indication 2 exemplar

The applicant remarked that WGS could be conducted at same time as phenotyping in carbapenem-resistant patients; however, WGS cannot replace phenotyping.

Proposed item descriptor

The applicant agreed with comments by PASC.

Indication 3: Recurrent or persistent bacterial infection - exemplar case H. pylori

Population

The applicant stated that once patients are diagnosed with H pylori they commence empirical treatment immediately. With increasing rates of antimicrobial resistance comes increasing rates of therapy failure, which usually occurs within 2 weeks. The success of therapy should be checked at 6 weeks after diagnosis and commencement of treatment.

Intervention

The applicant agreed with comments by PASC.

Comparator

The applicant stated that the use of MBS item number 69380 in this case is appropriate.

Current and proposed clinical management algorithm for indication 4 exemplar

The applicant stated that it is appropriate to perform WGS immediately after a patient has been diagnosed with HIV in order to identify any potential resistance against empirical treatment.

Proposed item descriptor

The applicant agreed with PASC's comments.

Indication 4: Primary viral infection - exemplar case HIV

Comparator

The applicant stated that the use of MBS item number 69380 in this case is appropriate.

Current and proposed clinical management algorithm for indication 4 exemplar

The applicant stated that it is appropriate to perform WGS immediately after a patient has been diagnosed with HIV in order to identify any potential resistance against empirical treatment.

Proposed item descriptor

The applicant agreed with PASC's comments.

Indication 5: Recurrent or persistent viral infection - exemplar case cytomegalovirus

Comparator

The applicant stated that cytomegalovirus (CMV) viral load PCR is not covered by Medicare and is known as a non-rebatable test. [Private pathology](#) labs may charge \$120 per test

Next steps

The applicant agreed with PASC that the current evidence-base supports the use of WGS to determine and characterise resistance for the pathogen mycobacterium tuberculosis (TB). Although the four other exemplar cases described in the application and subsequent draft PICO are considered as equally important clinically, the evidence-base for these indications is not as mature as that for TB. Therefore, the College agrees that, in the first instance, the TB exemplar should be the only indication to undergo a DCAR at this point in time.

References

- AIHW. (2020). "Disparities in potentially preventable hospital admissions across Australia: Exploring the data." Retrieved 12 Mar, 2021, from <https://www.aihw.gov.au/reports/hpf/51/disparities-in-potentially-preventable-hospitalisations/contents/potentially-preventable-hospitalisations-condition>.
- ASHM. (2021). "Antiretroviral Guidelines." Retrieved 11 May, 2021, from <https://arv.ashm.org.au/>.
- Balloux, F., O. Bronstad-Brynildsrud, L. van Dorp, L. Shaw, H. Chen, K. Harris, H. Wang and V. Eldholm (2018). "From theory to practice: translating whole genome sequencing (WGS) into the clinic." *Trends Microbiol* **26**(12): 1035-1048.
- Balloux, F., O. Bronstad Brynildsrud, L. van Dorp, L. P. Shaw, H. Chen, K. A. Harris, H. Wang and V. Eldholm (2018). "From Theory to Practice: Translating Whole-Genome Sequencing (WGS) into the Clinic." *Trends Microbiol* **26**(12): 1035-1048.
- Bright, A., J. Denholm, C. Coulter, J. Waring and R. Stapledon (2020). "Tuberculosis notifications in Australia, 2015-2018." *Commun Dis Intell* (2018) **44**.
- Cabibbe, A. and D. Cirillo (2016). "Best approaches to drug resistance surveillance at the country level." *Int J Mycobacteriol* **5**: S40-S41.
- DoH (2019). "Cytomegalovirus." *Australian Government Department of Health*.
- Ellington, M., O. Ekelund and e. al (2017). "The role of whole genome sequencing in antimicrobial susceptibility testing of bacteria: report from the EUCAST Subcommittee." *Clin Microbiol Infect* **23**(1): 2-22.
- Ellington, M. J., O. Ekelund, F. M. Aarestrup, R. Canton, M. Doumith, C. Giske, H. Grundman, H. Hasman, M. T. G. Holden, K. L. Hopkins, J. Iredell, G. Kahlmeter, C. U. Koser, A. MacGowan, D. Mevius, M. Mulvey, T. Naas, T. Peto, J. M. Rolain, O. Samuelsen and N. Woodford (2017). "The role of whole genome sequencing in antimicrobial susceptibility testing of bacteria: report from the EUCAST Subcommittee." *Clin Microbiol Infect* **23**(1): 2-22.
- Health Protection Policy Branch. (2019). Australia's notifiable disease status, 2015: Annual report of the National Notifiable Diseases Surveillance System. D. o. Health. Canberra.
- Jenkins, C., R. J. Rentenaar, L. Landraud and S. Brisse (2017). Enterobacteriaceae. *Infectious Diseases*: 1565-1578.e1562.
- Ljungman, P., R. de la Camara, C. Robin, R. Crocchiolo, H. Einsele, J. A. Hill, P. Hubacek, D. Navarro, C. Cordonnier and K. N. Ward (2019). "Guidelines for the management of cytomegalovirus infection in patients with haematological malignancies and after stem cell transplantation from the 2017 European Conference on Infections in Leukaemia (ECIL 7)." *The Lancet Infectious Diseases* **19**(8): e260-e272.
- Parekh, B. S., C.-Y. Ou, P. N. Fonjongo, M. B. Kalou, E. Rottinghaus, A. Puren, H. Alexander, M. Hurlston Cox and J. N. Nkengasong (2018). "Diagnosis of Human Immunodeficiency Virus Infection." *Clinical microbiology reviews* **32**(1): e00064-00018.
- Pinto, A. N., K. Hawke, A. Castley, D. Chibo, G. Francesca Di, C. Cooper, S. Sawleshwarkar, A. Kelleher and D. E. Dwyer (2018). "HIV-1 subtype diversity, transmitted drug resistance and phylogenetics in Australia." *Future Virology* **13**(8): 575-575-584.
- Sutton, P. (2018). "Explainer: What is Helicobacter pylori?" *RACGP NewsGP* **27 Dec 2018**.

The Kirby Institute. (2018). Public health surveillance of transmitted HIV drug resistance and subtype- FAQs. Sydney, NSW, The Kirby Institute.

The Kirby Institute. (2020). Australian HIV Observational Database Annual Report 2020. Sydney, NSW, The Kirby Institute, UNSW. **20**.

Witney, A., K. Gould and e. al (2015). "Clinical application of whole-genome sequencing to inform treatment for multi-drug resistant tuberculosis cases." J Clin Microbiol **53**(5): 1473-1483.

Witney, A. A., K. A. Gould, A. Arnold, D. Coleman, R. Delgado, J. Dhillon, M. J. Pond, C. F. Pope, T. D. Planche, N. G. Stoker, C. A. Cosgrove, P. D. Butcher, T. S. Harrison and J. Hinds (2015). "Clinical application of whole-genome sequencing to inform treatment for multidrug-resistant tuberculosis cases." J Clin Microbiol **53**(5): 1473-1483.