Australian Government

Department of Health

MSAC Application 1646

Whole genome sequencing of antimicrobial-resistant pathogens

This application form is to be completed for new and amended requests for public funding (including but not limited to the Medicare Benefits Schedule (MBS)). It describes the detailed information that the Australian Government Department of Health requires to determine whether a proposed medical service is suitable.

Please use this template, along with the associated Application Form Guidelines to prepare your application. Please complete all questions that are applicable to the proposed service, providing relevant information only. Applications not completed in full will not be accepted.

Should you require any further assistance, departmental staff are available through the Health Technology Assessment Team (HTA Team) on the contact numbers and email below to discuss the application form, or any other component of the Medical Services Advisory Committee process.

Email: hta@health.gov.au
Website: www.msac.gov.au

PART 1 – APPLICANT DETAILS

1. **Applicant details (primary and alternative contacts)**

Corporation / partnership details (where relevant):

Corporation name: The Royal College of Pathologists of Australasia

ABN: 52 000 173 231

Business trading name: The Royal College of Pathologists of Australasia

Primary contact name: REDACTED

Alternative contact numbers

Business: REDACTED

Mobile: REDACTED

Email: REDACTED

Alternative contact name: REDACTED

Alternative contact numbers

Business:

Mobile: REDACTED

Email: REDACTED

2. **(a) Are you a lobbyist acting on behalf of an Applicant?**

☐ Yes
☒ No

(b) **If yes, are you listed on the Register of Lobbyists?**

☐ Yes
☐ No

PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

3. Application title

Whole genome sequencing of antimicrobial-resistant pathogens

4. Provide a succinct description of the medical condition relevant to the proposed service (no more than 150 words – further information will be requested at Part F of the Application Form)

Antimicrobial resistance, also referred to as antibiotic resistance, is defined as the ability of a microorganism to reproduce in the presence of a specific antimicrobial compound (Balloux et al 2018). Of particular concern is the emergence of multiple drug resistant pathogens associated with the widespread use of antibiotics and high-density clinical care that are capable of causing outbreaks and epidemics (Holden et al 2013). Whole genome sequencing (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'[a]) in order to guide a patient's treatment and/or the chemoprophylaxis of close contacts (Balloux et al 2018; Cabibbe & Cirillo 2016).

The literature describes the use of WGS to determine and characterise resistance in numerous clinically relevant pathogens including, but not limited to: *Campylobacter* spp.; *Escherichia coli; Klebsiella pneumoniae; Enterobacter cloacae; Pseudomonas aeruginosa; Bacteroides* spp[b].; *Salmonella* spp.; *Staphylococcus aureus; Streptococcus pneumoniae; Neisseria gonorrhoeae; Acinetobacter baumannii; Clostridium difficile* and *Plasmodium falciparum.* The most common reported use of WGS for the determination of resistance; however, is for the pathogen *Mycobacterium tuberculosis* (TB) Given the extensive list of potential pathogens and their associated clinical conditions, this application will focus on *Mycobacterium tuberculosis* as an exemplar of how WGS provides rapid and accurate characterisation of antimicrobial resistance.

5. Provide a succinct description of the proposed medical service (no more than 150 words – further information will be requested at Part 6 of the Application Form)

Sequencing and analysis of the complete nucleotide sequence of the microbial genome (bacterial, mycobacterial, fungal, viral or parasitic) of an isolate or to characterise an organism from a patient for the purpose of determining the antibiotic resistance markers (resistome) of the isolate to guide the patient's treatment and/or chemoprophylaxis of close contacts. WGS usually involves 'shotgun' sequencing of short reads that are either assembled *de novo* or mapped onto a high-quality reference genome (Balloux et al 2018). Genome-wide analysis can identify changes conferring resistance to standard of care antibiotics as well as newer antimicrobials for which established phenotypic susceptibility testing guidelines or protocols are not available.

6. (a) Is this a request for MBS funding?

☒ Yes
☐ No

(b) If yes, is the medical service(s) proposed to be covered under an existing MBS item number(s) or is a new MBS item(s) being sought altogether?

☐ Amendment to existing MBS item(s)
☒ New MBS item(s)

(c) If an amendment to an existing item(s) is being sought, please list the relevant MBS item number(s) that are to be amended to include the proposed medical service:

N/A

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[a] The sum of the detected AMR genes in a sequenced isolate is referred to as the resistome Balloux, F., Bronstad Brynildsrud, O. et al (2018). 'From Theory to Practice: Translating Whole-Genome Sequencing (WGS) into the Clinic', *Trends Microbiol,* 26 (12), 1035-1048.
[b] spp = several species

(d) If an amendment to an existing item(s) is being sought, what is the nature of the amendment(s)?

i. ☐ An amendment to the way the service is clinically delivered under the existing item(s)
ii. ☐ An amendment to the patient population under the existing item(s)
iii. ☐ An amendment to the schedule fee of the existing item(s)
iv. ☐ An amendment to the time and complexity of an existing item(s)
v. ☐ Access to an existing item(s) by a different health practitioner group
vi. ☐ Minor amendments to the item descriptor that does not affect how the service is delivered
vii. ☐ An amendment to an existing specific single consultation item
viii. ☐ An amendment to an existing global consultation item(s)
ix. ☐ Other (please describe below):

(e) If a new item(s) is being requested, what is the nature of the change to the MBS being sought?

i. ☐ A new item which also seeks to allow access to the MBS for a specific health practitioner group
ii. ☒ A new item that is proposing a way of clinically delivering a service that is new to the MBS (in terms of new technology and / or population)
iii. ☐ A new item for a specific single consultation item
iv. ☐ A new item for a global consultation item(s)

(f) Is the proposed service seeking public funding other than the MBS?

☐ Yes
☒ No

(g) If yes, please advise:

7. What is the type of service:

☐ Therapeutic medical service
☒ Investigative medical service
☐ Single consultation medical service
☐ Global consultation medical service
☐ Allied health service
☐ Co-dependent technology
☐ Hybrid health technology

8. For investigative services, advise the specific purpose of performing the service *(which could be one or more of the following)*:

i. ☐ To be used as a screening tool in asymptomatic populations
ii. ☒ Assists in establishing a diagnosis in symptomatic patients
iii. ☒ Provides information about prognosis
iv. ☒ Identifies a patient as suitable for therapy by predicting a variation in the effect of the therapy
v. ☐ Monitors a patient over time to assess treatment response and guide subsequent treatment decisions
vi. ☐ A service that tests for heritable mutations in clinically affected individuals to make a genetic diagnosis and thus estimate their variation in (predisposition for) future risk of further disease and, when also appropriate, cascade testing of family members of those individuals who test positive for one or more relevant mutations, to make a genetic diagnosis and thus estimate each family member's variation in (predisposition for) future risk of developing the clinical disease.

9. Does your service rely on another medical product to achieve or to enhance its intended effect?

☐ Pharmaceutical / Biological
☐ Prosthesis or device
☒ No

10. (a) If the proposed service has a pharmaceutical component to it, is it already covered under an existing Pharmaceutical Benefits Scheme (PBS) listing?

☐ Yes
☐ No

(b) **If yes, please list the relevant PBS item code(s):**

N/A

(c) **If no, is an application (submission) in the process of being considered by the Pharmaceutical Benefits Advisory Committee (PBAC)?**

☐ Yes (please provide PBAC submission item number below)
☐ No

N/A

(d) **If you are seeking both MBS and PBS listing, what is the trade name and generic name of the pharmaceutical?**

Trade name: N/A
Generic name: N/A

11. **(a) If the proposed service is dependent on the use of a prosthesis, is it already included on the Prostheses List?**

☐ Yes
☐ No
N/A

(b) **If yes, please provide the following information (where relevant):**

Billing code(s):
Trade name of prostheses:
Clinical name of prostheses:
Other device components delivered as part of the service:

(c) **If no, is an application in the process of being considered by a Clinical Advisory Group or the Prostheses List Advisory Committee (PLAC)?**

☐ Yes
☒ No

(d) **Are there any other sponsor(s) and / or manufacturer(s) that have a similar prosthesis or device component in the Australian market place which this application is relevant to?**

N/A
☐ Yes
☐ No

(e) **If yes, please provide the name(s) of the sponsor(s) and / or manufacturer(s):**

12. **Please identify any single and / or multi-use consumables delivered as part of the service?**

Single use consumables: laboratory consumables
Multi-use consumables: Nil

PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

The National Association of Testing Authorities (NATA) and the Royal College of Pathologists Australasia (RCPA) oversee the regulation of WGS for clinical purposes. Laboratories require accreditation by a joint NATA/RCPA process to ISO 15189, and specifically accredited to provide genetic testing via WGS. This accreditation process covers the technical aspects of the laboratory sequencing, analysis pipelines, curation (or interpretation) of results and production of the report to a clinical standard. This allows any accredited laboratory to provide equivalent variant analysis services to a minimum standard. There are no requirements for use of specific manufacturer's reagents, equipment or analysis pipelines.[c]

It should be noted that few pathology providers in Australia are/will be accredited to conduct genome sequencing and pathogen genome analysis in the near future. Testing is likely to be restricted to a few centres of excellence, with one or two laboratories accredited in each state to provide testing.

Note: A non-commercial IVD is required to be regulated but not to be listed on the ARTG: testing using an IVD would be delivered only by Approved Practising Pathologists in NATA Accredited Pathology Laboratories (as defined in MBS Pathology table) by referral only by registered Medical Practitioners (non-pathologists) in line with other tests in the MBS Pathology Table.

13. **(a) If the proposed medical service involves the use of a medical device, in-vitro diagnostic test, pharmaceutical product, radioactive tracer or any other type of therapeutic good, please provide the following details:**

    Type of therapeutic good: In-vitro diagnostic test
    Manufacturer's name: N/A
    Sponsor's name: N/A

    (b) Is the medical device classified by the TGA as either a Class III or Active Implantable Medical Device (AIMD) against the TGA regulatory scheme for devices?

    ☒ Class III
    ☐ AIMD
    ☐ N/A

14. **(a) Is the therapeutic good to be used in the service exempt from the regulatory requirements of the *Therapeutic Goods Act 1989*?**

    ☐ Yes
    ☒ No

    (b) If no, has it been listed or registered or included in the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)?

    ☐ Yes (if yes, please provide details below)
    ☒ No

15. **If the therapeutic good has not been listed, registered or included in the ARTG, is the therapeutic good in the process of being considered for inclusion by the TGA?**

    ☐ Yes
    ☒ No

16. **If the therapeutic good is not in the process of being considered for listing, registration or inclusion by the TGA, is an application to the TGA being prepared?**

    ☐ Yes (please provide details below)
    ☒ No

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[c] https://www.rcpa.edu.au/Library/Practising-Pathology/NPAACSupCertMods/Docs/MicroHBCertMod.aspx

PART 4 – SUMMARY OF EVIDENCE

17. **Provide an overview of all key journal articles or research published in the public domain related to the proposed service that is for your application (limiting these to the English language only).** *Please do not attach full text articles, this is just intended to be a summary.*

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
Mycobacterium tuberculosis					
1	Clinical utility Cohort study China	Prediction of Treatment Outcomes for Multidrug-Resistant Tuberculosis by Whole-Genome Sequencing (He et al 2020)	A total of 123 patients with MDR-TB were enrolled consecutively. Conventional phenotypic and genotypic, using WGS, drug sensitivity testing was performed using culture isolates. Patients were followed for 2-years to determine treatment outcomes.	https://www.ijidonline.com/article/S1201-9712(20)30260-5/fulltext	2020
2	Clinical utility and diagnostic accuracy Cohort study Tanzania	Whole genome sequencing of *Mycobacterium tuberculosis* isolates and clinical outcomes of patients treated for multidrug-resistant tuberculosis in Tanzania (Katale et al 2020)	Treatment outcomes and a comparison of mutations, detected by Xpert and WGS with phenotypic DST of *M. tuberculosis* isolates, in 57 (66%) and 30 (34%) patients with drug resistant and susceptible TB, respectively.	https://pubmed.ncbi.nlm.nih.gov/32085703/	2020
3	Diagnostic accuracy Level III-2 – comparative, non-blinded, non-randomised study United Kingdom	Prediction of Susceptibility to First-Line Tuberculosis Drugs by DNA Sequencing (Allix-Béguec et al 2018)	A total of 10,209 isolates from 16 countries across 6 continents were analysed using WGS and phenotypic drug-susceptibility testing. Resistance or susceptibility to the first-line antituberculosis drugs isoniazid, rifampin, ethambutol, and pyrazinamide was ascertained.	https://pubmed.ncbi.nlm.nih.gov/30280646/	2018

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
4	Clinical utility Level III-2 – comparative, non-blinded, non-randomised study United Kingdom	Clinical Application of Whole-Genome Sequencing To Inform Treatment for Multidrug-Resistant Tuberculosis Cases (Witney et al 2015)	WGS and Drug Susceptibility Testing was performed on 16 isolates from six patients with suspected XDR-TB. In several cases the speed of generation and the comprehensive nature of the WGS data were useful for informing clinical decisions.	https://jcm.asm.org/content/53/5/1473	2015
5	Clinical utility Level III-2 – comparative, non-blinded, non-randomised study USA	Comprehensive Whole-Genome Sequencing and Reporting of Drug Resistance Profiles on Clinical Cases of Mycobacterium tuberculosis in New York State (Shea et al 2017)	WGS was assessed using 608 MTBC isolates, with 146 isolates during the validation period and 462 prospective samples. Concordance with culture-based DST and turnaround time were reported. Species identification by WGS was 99% accurate. Concordance between drug resistance profiles generated by WGS and culture-based DST was 96% for 8 drugs, with an average resistance-predictive value of 93% and susceptible-predictive value of 96%. WGS assay has replaced 7 molecular assays and resulted in resistance profiles being reported to physicians an average of 9 days sooner compared to DST for 1st line drugs and 32days sooner for 2nd-line drugs.	https://jcm.asm.org/content/55/6/1871	2017

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
6	Clinical utility Level III-2 – comparative, non-blinded, non-randomised study United Kingdom	Direct Whole-Genome Sequencing of Sputum Accurately Identifies Drug-Resistant Mycobacterium tuberculosis Faster than MGIT Culture Sequencing (Doyle et al 2018)	43 *M. tuberculosis* samples underwent WGS and time to antimicrobial resistance profile and concordance were compared with Xpert MTB/RIF and phenotypic resistance testing from cultures. Antibiotic susceptibility could be predicted from WGS of sputum within 5 days of sample receipt and up to 24 days earlier than WGS from MGIT culture and up to 31 days earlier than phenotypic testing. Direct sputum results could be reduced to 3 days with faster hybridisation and if only regions encoding drug resistance are sequenced. This improved turnaround time enables prompt appropriate treatment with associated patient and health service benefits.	https://jcm.asm.org/content/56/8/e00666-18	2018
7	Systematic review Diagnostic accuracy	Whole genome sequencing of Mycobacterium tuberculosis for detection of drug resistance: a systematic review (Papaventsis et al 2017)	The sensitivity, specificity, PPV and NPV of WGS using phenotypic Drug Susceptibility Testing (DST) methods as a gold standard were determined. Evidence indicates that analytical performance characteristics of WGS for the detection of resistance to the 2 most important 1st line drugs is high with pooled sensitivity and specificity values of 98% and 98% for rifampicin and 97% and 93% for isoniazid, respectively.	https://www.sciencedirect.com/science/article/pii/S1198743X16303950	2017

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
8	Diagnostic accuracy Level III-2 – comparative, non-blinded, non-randomised study India	Elucidation of drug resistance mutations in Mycobacterium tuberculosis isolates from North India by whole-genome sequencing (Sethi et al 2019)	33 *M. tuberculosis* isolates were subjected to phenotypic drug susceptibility testing and WGS. WGS of isolates allowed the detection of drug resistance to all drugs in a single test in addition to providing information on the evolution of drug-resistant TB.	https://www.sciencedirect.com/science/article/pii/S2213716519301298	2019
9	Diagnostic accuracy Retrospective Level III-2 – comparative, non-blinded, non-randomised study New Zealand	Utility of whole genome sequencing for multidrug resistant Mycobacterium tuberculosis isolates in a reference TB laboratory in New Zealand (Basu et al 2018)	38 multidrug resistant *M.tuberculosis* isolates phenotyped by culture-based DST and genotyped (Cepheid Xpert® MTB/RIF test). Genotyping failed to identify 12 MDR-TB isolates (28%) and underwent WGS. WGS was 100% concordant with phenotyping but gave additional information on drug resistance.	http://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2018/vol-131-no-148714-december-2018/7764	2018
10	Diagnostic accuracy Retrospective Level III-2 – comparative, non-blinded, non-randomised study	Genome-wide analysis of multi- and extensively drug-resistant Mycobacterium tuberculosis (Coll et al 2018)	Characterisation of the genetic determinants of resistance to anti-TB using a genome-wide association study (GWAS) of 6,465 *M tuberculosis* clinical isolates from more than 30 countries. Phenotypic analysis found that 31.2% of isolates were resistant to at least one drug, with 15.1% MDR-TB and 4.3% categorised as XDR-TB.	https://www.nature.com/articles/s41588-017-0029-0	2018

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
11.	Diagnostic accuracy Level III-2 – comparative, non-blinded, non-randomised study Germany	What Is Resistance? Impact of Phenotypic versus Molecular Drug Resistance Testing on Therapy for Multi- and Extensively Drug-Resistant Tuberculosis (Heyckendorf et al 2018)	The utility of genotypic DST assays with phenotypic DST (pDST) using Bactec 960 MGIT or Löwenstein-Jensen to construct M/XDR-TB treatment regimens for a cohort of 25 consecutive M/XDR-TB patients and 15 possible anti-TB drugs was compared. The average agreement in the number of drugs prescribed in genotypic regimens ranged from just 49% (95% CI [39, 59%]) for Xpert and 63% [56, 70%] for LPAs to 93% [88 to 98%] for WGS.	https://pubmed.ncbi.nlm.nih.gov/29133554/	2018
12	Diagnostic accuracy Level III-2 – comparative, non-blinded, non-randomised study United Kingdom	Whole-genome sequencing for prediction of Mycobacterium tuberculosis drug susceptibility and resistance: a retrospective cohort study (Walker et al 2015) Included in (Papaventsis et al 2017)	Phenotypic drug-susceptibility testing at reference laboratories on 3,651 *M tuberculosis* samples from UK, Sierra Leone, South Africa, Germany, and Uzbekistan. 2,099 samples underwent WGS as a training set. 120 training-set mutations were characterised as resistance determining, and 772 as benign. Using these mutations, 89·2% of the validation-set phenotypes with a mean 92·3% sensitivity and 98·4% specificity could be predicted.	https://www.sciencedirect.com/science/article/pii/S1473309915000626	2015
13.	Diagnostic accuracy Level III-2 – comparative, non-blinded, non-randomised study Russia, United Kingdom	Evolution and transmission of drug-resistant tuberculosis in a Russian population (Casali et al 2014) Included in (Papaventsis et al 2017)	2,348 patients with pulmonary disease and culture-proven tuberculosis underwent susceptibility testing to 1st and 2nd line drugs and WGS. Concordance, sensitivity and specificity rates not reported.	https://www.nature.com/articles/ng.2878	2014

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
14.	Diagnostic accuracy Level III-2 – comparative, non-blinded, non-randomised study United Kingdom	Rapid, comprehensive, and affordable mycobacterial diagnosis with whole-genome sequencing: a prospective study (Pankhurst et al 2016) Excluded from (Papaventsis et al 2017)	356 phenotype specimens were submitted. In 326 (94%) cases, both Hain and WGS assays identified a single species, of which 3 (1%) were discordant. Two species were identified in 9 (3%) of cases, of which 8 (89%) were discordant for one of the species. WGS predictions were concordant with routine results in 322 (93%) of 345 specimens. Hain and WGS assays identified MTBC in 168 (52%) of 322 concordant specimens. Of the discordant isolates, 3 (13%) of 23 were MTBC cases identified by the reference lab alone, 3 (13%) were MTBC cases identified by WGS alone, and two (9%) were identified in a co-infection by either WGS or the reference laboratory (but not both). In a further 6 (26%) MTBC cases (identified by the reference laboratory), WGS failed. MTBC was identified with 95% sensitivity and 98% specificity.	https://www.sciencedirect.com/science/article/pii/S221326001500466X	2016
Other pathogens					
15.	Diagnostic accuracy Level III-2 – comparative, non-blinded, non-randomised study USA	Comparative Whole Genome Sequencing of Community-Associated Methicillin-Resistant Staphylococcus aureus Sequence Type 8 from Primary Care Clinics in a Texas Community (Lee et al 2015)	WGS was used to determine resistance in 13 clinical community-associated -MRSA isolates recovered from patients presenting with skin and soft tissue infections from 9 primary care clinics. There was complete concordance between genotypic evidence for antimicrobial resistance and the phenotypically derived antibiogram.	https://accpjournals.onlinelibrary.wiley.com/doi/abs/10.1002/phar.1536	2015

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
16.	Diagnostic accuracy Level III-2 – comparative, non-blinded, non-randomised study United Kingdom	A genomic portrait of the emergence, evolution, and global spread of a methicillin-resistant Staphylococcus aureus pandemic (Holden et al 2013)	WGS was used to determine resistance in 193 *Staphylococcus aureus* isolates both from hospital and community settings. Results were compared to susceptibility to antibiotics tested by standardized broth microdilution method and phenotypic resistance was defined by applying minimum inhibitory concentration.	https://genome.cshlp.org/content/23/4/653	2013
17.	Diagnostic accuracy Level III-2 – comparative, non-blinded, non-randomised study United Kingdom	Prediction of Staphylococcus aureus antimicrobial resistance by whole-genome sequencing (Gordon et al 2014)	The whole genomes of 501 unrelated Staphylococcus aureus isolates were sequenced, and the assembled genomes interrogated for a panel of known resistance determinants. Results were compared with phenotypic susceptibility testing for 12 commonly used antimicrobial agents performed by the routine clinical laboratory. In the validation set, the overall sensitivity and specificity of the genomic prediction method were 0.97 (95% CI [0.95, 0.98]) and 0.99 (95% CI [0.99, 1]), respectively, compared to standard susceptibility testing methods. The very major error rate was 0.5%, and the major error rate was 0.7%. WGS was as sensitive and specific as routine antimicrobial susceptibility testing methods. .	https://jcm.asm.org/content/jcm/52/4/1182.full.pdf	2014

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
18.	Diagnostic accuracy Level III-2 – comparative, non-blinded, non-randomised study United Kingdom	Rapid Whole-Genome Sequencing for Investigation of a Neonatal MRSA Outbreak (Koser et al 2012)	Isolates from a putative methicillin-resistant *staphylococcus aureus* outbreak in a neonatal intensive care unit (7 patients with MRSA carriage that were believed to be part of the NICU outbreak and 7 patients not thought to be associated with the outbreak) underwent WGS. Results were compared to MRSA detected in blood cultures and swabs used to screen for MRSA colonisation with the use of an automated system and plating onto selective medium, respectively. Antimicrobial susceptibility testing was performed with the use of a disk-diffusion method.	https://www.nejm.org/doi/full/10.1056/NEJMoa1109910	2012
19.	Diagnostic accuracy Level III-2 – comparative, non-blinded, non-randomised study Canada	Whole-genome phylogenomic heterogeneity of *Neisseria gonorrhoeae* isolates with decreased cephalosporin susceptibility collected in Canada between 1989 and 2013 (Demczuk et al 2015)	WGS was used to determine resistance in 169 *N. gonorrhoeae* isolates collected between 1989 and 2013 from across Canada and 10 international reference strains. Results were compared to antimicrobial susceptibility to spectinomycin, ceftriaxone, erythromycin, penicillin, tetracycline, azithromycin, cefixime and ciprofloxacin determined using the agar dilution method.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4290921/pdf/zjm191.pdf	2015

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
20.	Diagnostic accuracy Level III-2 – comparative, non-blinded, non-randomised study USA/ Canada	The Resistome of *Pseudomonas aeruginosa* in Relationship to Phenotypic Susceptibility (Kos et al 2015)	The concordance between phenotypic AST and WGS-based resistance prediction for *P. aeruginosa* or *A. baumannii.* Phenotypic susceptibility data for meropenem, levofloxacin and amikacin to the genome sequences of 390 clinical isolates of P. aeruginosa. The sensitivity and specificity for genotypic inference of meropenem and levofloxacin resistance were 91% and 94%, respectively. A genotypic marker for amikacin resistance was identified for only 60% of the amikacin non-susceptible isolates. In addition, 30 of 283 amikacin susceptible isolates were found to harbour genes associated with amikacin resistance.	https://aac.asm.org/content/59/1/427.full	2015
21	Diagnostic accuracy Level III-2 – comparative, non-blinded, non-randomised study USA	SISPA-Seq for rapid whole genome surveys of bacterial isolates (Wright et al 2015)	Evaluated the performance of SISPA (Sequence-Independent, Single-Primer Amplification) combined with next-generation sequencing (SISPA-Seq) of 75 clinical isolates of *Acinetobacter baumannii*.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5556377/	2015

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
22	Diagnostic accuracy Level III-2 – comparative, non-blinded, non-randomised study United Kingdom	Predicting antimicrobial susceptibilities for Escherichia coli and Klebsiella pneumoniae isolates using whole genomic sequence data (Stoesser et al 2013)	74 *E. coli* and 69 *K. pneumoniae* bacteraemia isolates were sequenced. Resistance phenotypes were predicted from genomic sequences using BLASTn-based comparisons of *de novo*-assembled contigs with a study database of 100 known resistance-associated loci. Predictions were made for 7 commonly used antimicrobials: amoxicillin, co-amoxiclav, ceftriaxone, ceftazidime, ciprofloxacin, gentamicin and meropenem. Comparisons were made with phenotypic results obtained in duplicate by broth dilution. The sensitivity of genome-based resistance prediction across all antibiotics for both species was 96% and the specificity was 97%.	https://academic.oup.com/jac/article/68/10/2234/715609	2013

MDR-TB = multi-drug resistant TB, XDR-TB = extensively drug-resistant TB

Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.

**Provide high level information including population numbers and whether patients are being recruited or in post-recruitment, including providing the trial registration number to allow for tracking purposes.*

*** If the publication is a follow-up to an initial publication, please advise.*

18. **Identify yet to be published research that may have results available in the near future that could be relevant in the consideration of your application by MSAC (limiting these to the English language only).** *Please do not attach full text articles, this is just intended to be a summary.*

None identified

PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

19. **List all appropriate professional bodies / organisations representing the group(s) of health professionals who provide the service (please attach a statement of clinical relevance from each group nominated):**

    Royal College of Pathologists of Australasia (RCPA)

20. **List any professional bodies / organisations that may be impacted by this medical service (i.e. those who provide the comparator service):**

    It should be noted that the RCPA provides other services used in the diagnostic workup of patients suspected of having an antibiotic resistant infection.

    Other professional bodies:

    Royal Australasian College of General Practitioners

    Royal Australasian College of Physicians - Infectious Diseases

    Australian Commission on Safety and Quality in Health Care

    Australian Group on Antimicrobial Resistance

    National Antimicrobial Utilisation Surveillance Program (NAUSP)

    Australian Society for Biochemistry and Molecular Biology

    Australian Society for Antimicrobials

    Australian Society for Microbiology

21. **List the consumer organisations relevant to the proposed medical service (please attach a letter of support for each consumer organisation nominated):**

    Australian Respiratory Council

22. **List the relevant sponsor(s) and / or manufacturer(s) who produce similar products relevant to the proposed medical service:**

    N/A

23. **Nominate two experts who could be approached about the proposed medical service and the current clinical management of the service(s):**

    Name of expert 1: **REDACTED**

    Telephone number(s): **REDACTED**

    Email address: **REDACTED**

    Justification of expertise: **REDACTED** is an Infectious Disease Physician, Medical Microbiologist and NHMRC Early Career Fellow **REDACTED**. Research interests include a focus on multi-drug resistant gram-negative bacteria, including E. coli, Klebsiella and Enterobacter. Current research projects include:

    - Using whole-genome sequencing to characterise carbapenem-resistant Enterobacteriaceae from QLD (the CREATE-Q Study)
    - Whole-genome sequencing of ESBL-producing E. coli and Klebsiella spp. bloodstream isolates (MERINO Trial).

    Name of expert 2: **REDACTED**

    Telephone number(s): **REDACTED**

    Email address: **REDACTED**

Justification of expertise: REDACTED is a Clinical Microbiologist and Deputy Director of the Microbiological Diagnostic Unit Public Health Laboratory (MDU PHL). **REDACTED** is also a Laboratory Head in the Department of Microbiology and Immunology. REDACTED is involved in the delivery of specialist public health laboratory services, and in the diagnosis and surveillance of communicable diseases. **REDACTED** research interests include the molecular epidemiology and pathogenesis of infections caused by antimicrobial resistant pathogens, and the translation of genomic technologies to questions of public health importance.

Name of expert 3: **REDACTED**

Telephone number(s): **REDACTED**

Email address: **REDACTED**

Justification of expertise: NHMRC Career Development Fellow and Associate Professor in Respiratory Medicine at **REDACTED**, Sydney. Area Director of Tuberculosis Services, Sydney Local Health District. **REDACTED** heads several NHMRC-funded clinical trials and translational research studies relating to tuberculosis, lung disease and antimicrobial resistance. His research aims to develop new approaches TB control in high-prevalence settings.

Please note that the Department may also consult with other referrers, proceduralists and disease specialists to obtain their insight.

PART 6 – POPULATION (AND PRIOR TESTS), INTERVENTION, COMPARATOR, OUTCOME (PICO)

PART 6a – INFORMATION ABOUT THE PROPOSED POPULATION

24. Define the medical condition, including providing information on the natural history of the condition and a high-level summary of associated burden of disease in terms of both morbidity and mortality:

Antimicrobial resistance, also referred to as antibiotic resistance, is defined as the ability of a microorganism to reproduce in the presence of a specific antimicrobial compound (Balloux et al 2018). Inappropriate and overuse of antimicrobials contributes to the emergence of resistant bacteria. Infection with pathogens resistant to antimicrobials lead to prolonged or serious illness, escalation in therapy with associated healthcare costs, hospitalisation or death (ACSQHC 2018). Of particular concern is the emergence of multiple drug resistant pathogens associated with the widespread use of antibiotics and high-density clinical care that are capable of causing outbreaks and epidemics (Holden et al 2013).

Whole genome sequencing (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'[d]) in order to guide a patient's treatment and/or the chemoprophylaxis of close contacts (Balloux et al 2018; Cabibbe & Cirillo 2016). In Australia, antimicrobial stewardship (AMS) programs have been developed in response to widespread and increasing antimicrobial resistance. AMS are required by the National Safety and Quality Health Service (NSQHS) Preventing and Controlling Healthcare-Associated Infection Standard to promote optimal antimicrobial prescribing and preserve the effectiveness of antimicrobials currently available. AMS programs have been shown to reduce unnecessary and inappropriate use of antimicrobials, reduce patient morbidity and mortality, and reduce bacterial resistance rates and healthcare costs (ACSQHC 2018). In 2015 The Australian Government released the first National Antimicrobial Resistance Strategy to guide the response to the threat of antibiotic misuse and resistance. Objectives of this strategy include:

- Implement effective antimicrobial stewardship practices across human health and animal care settings to ensure the appropriate and judicious prescribing, dispensing and administering of antimicrobials;
- Improve infection prevention and control measures across human health and animal care settings to help prevent infections and the spread of resistance;
- Agree a national research agenda and promote investment in the discovery and development of new products and approaches to prevent, detect and contain antimicrobial resistance (Australian Government 2015).

Early availability of diagnostic test results is critically important for the management of patients with infection. Rapid diagnostics can have a significant effect on patient outcomes, optimising the use of antibiotics by reducing the time required to confirm or exclude a diagnosis and guiding appropriate antimicrobial treatment (ACSQHC 2018). As such, WGS for the rapid determination of antimicrobial resistance would perform a key AMS role within the national AMR strategy.

The volume of antimicrobial use in Australia is higher than in most comparator countries. In Australia in 2015, more than 30 million prescriptions were dispensed in the community and in Australian hospitals, on any given day in 2015, nearly 40% of inpatients were prescribed antimicrobials, with up to 25% being considered inappropriate and a further 25% were noncompliant with guidelines. Inappropriate antimicrobial use, including underuse, overuse, or inadequate use (wrong antimicrobial, wrong dose or wrong route of administration), is often ineffective and is associated with increased patient morbidity and

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[d] The sum of the detected AMR genes in a sequenced isolate is referred to as the resistome Balloux, F., Bronstad Brynildsrud, O. et al (2018). 'From Theory to Practice: Translating Whole-Genome Sequencing (WGS) into the Clinic', *Trends Microbiol,* 26 (12), 1035-1048.

mortality due to infection. Adverse events may include allergic reactions or toxicity, especially when used in conjunction with other medications. A more serious consequence of the use of broad-spectrum antimicrobials is susceptibility to infection by opportunistic pathogens such as *C. difficile* and fungal infections such as Candida (ACSQHC 2018).

Australian standards recommend hospital antibiograms[e] consider six important 'signal resistances' (S), which have been supplemented by other isolates with resistances that need to be reported to the National Alert System for Critical Antimicrobial Resistances (CARAlert):

- Methicillin-resistant S. aureus or MRSA (S), and vancomycin-, linezolid- or daptomycin-resistant *S. aureus* (CAR)
- Vancomycin-intermediate and vancomycin resistant *S. aureus* (S)
- Multidrug-resistant *Mycobacterium tuberculosis* (CAR)
- Vancomycin-resistant *enterococci* (S), linezolid-non-susceptible species (CAR)
- Carbapenemase-producing *Enterobacteriaceae* (CPE) and other carbapenemase-producing gram-negative organisms (S), carbapenemase-producing or ribosomal methylase–producing *Enterobacteriaceae* (CAR)
- *Streptococcus pneumoniae* with a penicillin minimum inhibitory concentration ≥0.06 mg/L (S)
- *Enterobacteriaceae* that are resistant to third- or later-generation cephalosporins (S)
- Ceftriaxone- or azithromycin-non-susceptible *Neisseria gonorrhoeae* (CAR)
- Ceftriaxone-non-susceptible *Salmonella* species (CAR)
- Multidrug-resistant *Shigella* species (CAR)
- *Streptococcus pyogenes* with reduced susceptibility to (benzyl) penicillin (CAR) (ACSQHC 2018).

The literature describes the use of WGS to determine and characterise resistance in numerous clinically relevant pathogens including, but not limited to: *Campylobacter spp.; Escherichia coli; Klebsiella pneumonia; Enterobacter cloacae; Mycobacterium tuberculosis, Pseudomonas aeruginosa; Bacteroides sppf.; Salmonella spp.; Staphylococcus aureus; Streptococcus pneumonia; Neisseria gonorrhoeae; Acinetobacter baumannii; Clostridium difficile* and *Plasmodium falciparum.* The third Australian report on antimicrobial use and resistance in human health summarises the priority organisms and their AMR prevalence in Australia from 2014-2017 (Table 4.2, page 109) (ACSQHC 2019). A breakdown of the number of cases of resistance can be accessed in the AURA supplementary data.[g] However, given the extensive list of potential pathogens and their associated clinical conditions, this application will focus on *Mycobacterium tuberculosis* as an exemplar of how WGS can be used to characterise antimicrobial resistance. *M. tuberculosis* may not be the most prevalent pathogen in Australia, but it is the most commonly reported use of WGS for the determination of resistance in the literature.

M. tuberculosis is a bacterium that causes tuberculosis (TB), which most commonly presents as lung disease and is the leading infectious cause of death worldwide. TB is contagious, transmitted by airborne droplets produced by infected people with pulmonary or respiratory tract TB when coughing or sneezing. TB can remain dormant for long periods as latent tuberculosis with most infected people remaining asymptomatic; however, if the immune system is challenged and immunity wanes, it can reactivate, causing active disease (Health Protection Policy Branch 2019; ACSQHC 2019). A chronic cough, haemoptysis, weight loss, low-grade fever, and night sweats are some of the most common physical symptoms in pulmonary TB. In secondary disease, tissue reaction and hypersensitivity are more severe, and patients usually form cavities in the upper portion of the lungs. Pulmonary or systemic dissemination of the tubercles may be seen in active disease, and this may manifest as miliary TB characterised by millet shaped lesions on chest x-ray. Disseminated TB may also be visible in the spine, the central nervous system, or the bowel. Outcomes are poorer in the elderly, infants and young children and in immunosuppressed individuals. In addition, patients with radiological evidence of extensive spread, those who experience delays in receiving treatment and those who have severely compromised respiratory function that requires mechanical ventilation also fare poorly. Without treatment mortality rate for tuberculosis is more than 50% (Adigun & Singh 2019).

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[e] Antibiograms are tables of antimicrobial susceptibilities compiled according to a certain set of standards.
[f] spp = several species
[g] https://www.safetyandquality.gov.au/sites/default/files/2019-06/AURA-2019-Data-supplementary-report.pdf

Although TB is a major public health issue in many countries, Australia has relatively low rates of disease, with the majority of notified cases (85%) occurring in people born overseas who have migrated from high-prevalence countries (ACSQHC 2019). In addition, TB remains a public health issue particularly for Aboriginal and Torres Strait Islander people in the central and northern regions of Australia (Health Protection Policy Branch 2019).

There were 1,364 notifiable cases of TB reported nationally in 2016 (5.6 cases per 100,000 population) with numbers increasing slightly in 2017 to 1,434 notifiable cases (5.8 cases per 100,000 population). Of these, 1,031 cases in 2016 and 1,056 cases in 2017 had positive laboratory cultures and susceptibility test results.

Multidrug-resistant (MDR) *Mycobacterium tuberculosis* complex (MTBC) strains represent a major threat for tuberculosis (TB) control. Treatment of MDR-TB patients is long and less effective, resulting in a significant number of treatment failures. The development of further resistances leads to extensively drug-resistant (XDR) variants (Merker et al 2013). The clinical management of XDR-TB is difficult and lengthy, impacting significantly on health care resources. Ineffective treatments amplify the problem, which in turn increases the risk of transmission to the wider population. Most TB drugs are associated with side effects, and patient care in an isolation unit may be required during the early months while the patient is still infectious (Witney et al 2015).

M. tuberculosis is not susceptible to most conventional antibacterial agents and usually requires treatment with the specially designed antimycobacterial agents: isoniazid, rifampicin, ethambutol and pyrazinamide. Rates of resistance to these first-line treatments are summarised in Table 1, with actual number of 2017 cases for Australia summarised in Table 2 (AURA supplementary data). Combinations of antimycobacterial agents are required for treatment because resistance to any of them can emerge during treatment (ACSQHC 2019). For pan-susceptible TB treatment consists the four first-line drugs (isoniazid, rifampicin, pyrazinamide, and ethambutol) given for 2 months followed by isoniazid and rifampicin alone for an additional 4 months. Therapeutic advances include the development of new drugs, bedaquiline and delamanid, and the use of high-dose rifampicin and the addition or substitution of fluoroquinolones in the regimen (Furin et al 2019). The standard treatment period is a minimum of six months; however, longer courses of treatment are needed for resistant strains. Strains resistant to isoniazid and rifampicin, with or without resistance to the other two first-line agents, are considered to be multidrug-resistant tuberculosis (MDR-TB). If these strains are also resistant to fluoroquinolones and at least one injectable agent (amikacin, capreomycin, kanamycin), they are categorised as extensively drug-resistant tuberculosis (XDR-TB). Treatment success is significantly lower, and costs are significantly higher, for MDR-TB, and even more so for XDR-TB (ACSQHC 2019). World-wide, drug-resistant forms of tuberculosis are on track to be responsible for a quarter of deaths due to antimicrobial resistance (Furin et al 2019).

Table 1   Summary of antimicrobial resistance for the high-priority organism, Mycobacterium tuberculosis, 2014–2017 in Australia (ACSQHC 2019)

Organism	Important microbials for treatment	% resistant 2014	% resistant 2015	% resistant 2016	% resistant 2017
Mycobacterium tuberculosis	Ethambutol	1.2	0.9	1.5	0.7
Setting: Community	Isoniazid	8.5	10.7	9.4	8.9
Main type of infection: Pulmonary	Pyrazinamide	2.1	2.7	2.1	1.5
tuberculosis, extra-pulmonary	Rifampicin	2.4	3.8	2.8	2.2
tuberculosis	Multidrug-resistant	1.7	3.0	2.4	2.0

Table 2   Mycobacterium tuberculosis resistance to first-line antimycobacterial agents (ACSQHC 2019)

Isolates and resistance patterns	2017
Total TB cases notified to NNDSS	1,446
Total number of laboratory isolates	1,066

Isolates and resistance patterns	2017
Fully susceptible	945
Resistant to isoniazid only	69
Resistant to rifampicin only	2
Resistant to isoniazid and rifampicin (susceptible to ethambutol and pyrazinamide)	11
Resistant to isoniazid, rifampicin and ethambutol (susceptible to pyrazinamide)	6
Resistant to isoniazid, rifampicin and pyrazinamide (susceptible to ethambutol)	3
Resistant to isoniazid, rifampicin, ethambutol and pyrazinamide	1
Total MDR strains	21
Percentage of all laboratory isolates that are MDR-TB	2.0
XDR-TB (resistant to at least isoniazid and rifampicin, plus fluoroquinolone and an injectable agent)	0

25. **Specify any characteristics of patients with the medical condition, or suspected of, who are proposed to be eligible for the proposed medical service, including any details of how a patient would be investigated, managed and referred within the Australian health care system in the lead up to being considered eligible for the service:**

Patients presenting with a persistent bacterial infection that is known to be associated with antimicrobial resistance (e.g. TB). For some pathogens, WGS will be conducted only when patients fail to respond to first-line antimicrobial treatment options. However, infection with a serious pathogen such as TB, WGS would be conducted *prior* to commencement of treatment rather than waiting for treatment failure, and in so doing, better inform clinical decision-making and deliver appropriate and effective treatment to patients.

26. **Define and summarise the current clinical management pathway *before* patients would be eligible for the proposed medical service (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway up to this point):**

The current clinical algorithm is described in Figure 1. Using conventional antimicrobial susceptibility testing methods is time consuming, with a turnaround time of several weeks for results. Treatment usually commences in this lag time, providing the opportunity for further resistance to arise if inappropriate drug regimens are prescribed in addition to potentially exposing patients to unnecessary drugs and side effects during this waiting period.
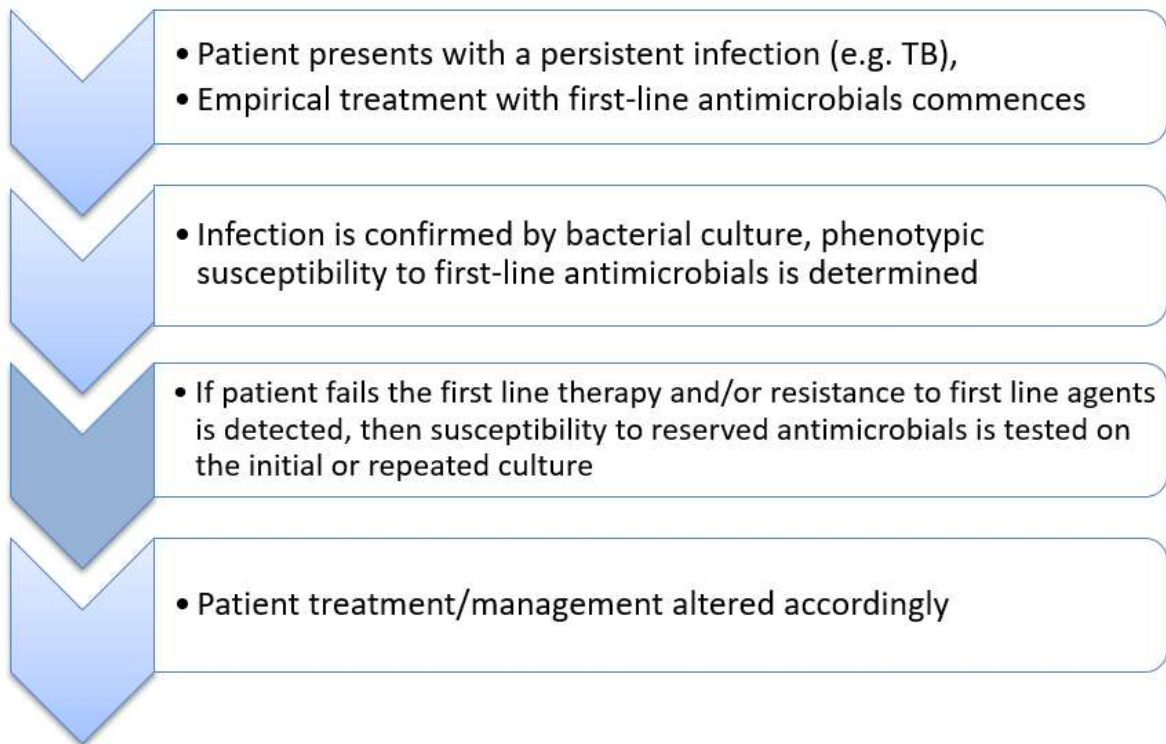
- Patient presents with a persistent infection (e.g. TB),
- Empirical treatment with first-line antimicrobials commences

- Infection is confirmed by bacterial culture, phenotypic susceptibility to first-line antimicrobials is determined

- If patient fails the first line therapy and/or resistance to first line agents is detected, then susceptibility to reserved antimicrobials is tested on the initial or repeated culture

- Patient treatment/management altered accordingly

Figure 1   *The current clinical algorithm using conventional drug susceptibility culture methods*

PART 6b – INFORMATION ABOUT THE INTERVENTION

27. **Describe the key components and clinical steps involved in delivering the proposed medical service:**

    The clinical algorithm incorporating WGS is described in Figure 2.

    WGS is performed on genomic DNA samples extracted from clinical isolates to ensure the required high quality and quantity of DNA for library preparation and sequencing reaction steps (Cabibbe & Cirillo 2016). Genotypic antimicrobial resistance is detected by identifying resistance genes with nucleotide BLASTC 2.6.0 using default values against four widely used resistance gene databases: ARG-ANNOT[h], the Canadian Comprehensive Antibiotic Resistance Database (CARD[i]), ResFinder[j], and the National Database of Antibiotic Resistant Organisms (NDARO)[k] (Bogaerts et al 2019). WGS has potential to yield data about resistance genes or mutations present with the resultant data analysed to create a genotypically inferred antimicrobial resistance profile (or antibiogram) and to infer susceptibility (Ellington et al 2017).

    Genotypic testing for AMR genes is now widely used for different organisms harbouring certain resistance genes. An example of this is direct detection of *Staphylococcus aureus* genes and methicillin resistance from a positive blood culture broth (ACSQHC 2018).

    The turnaround time for WGS of *M. tuberculosis* is significantly faster 5 days (range 3-7 days) compared to that of traditional mycobacteria growth indicator tube (MGIT), which was estimated to be 19 days (range 10-50 days) for first-line drugs (van Beek et al 2019).
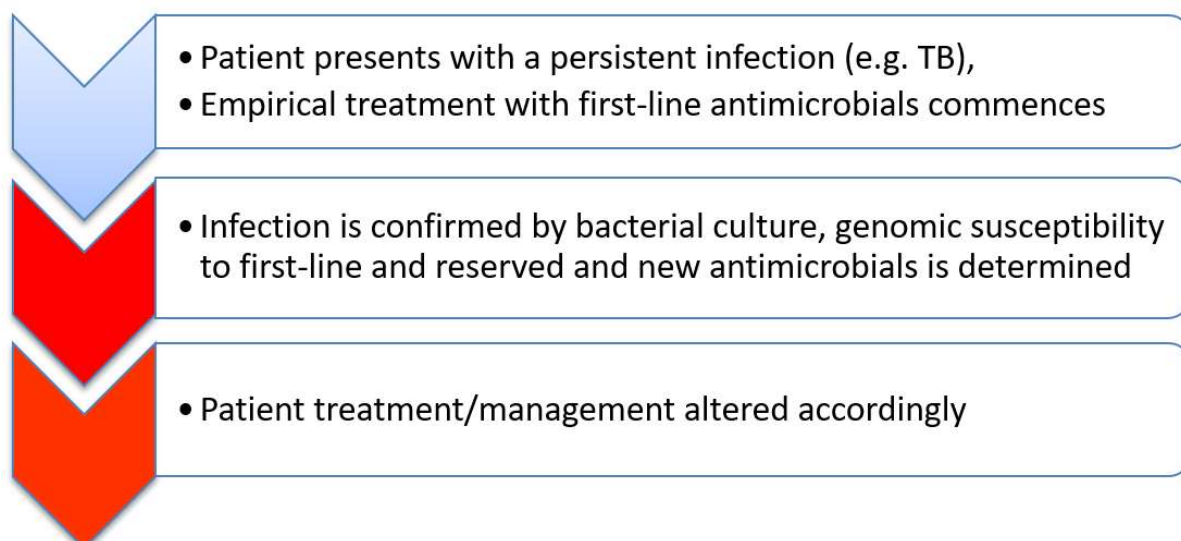

- Patient presents with a persistent infection (e.g. TB),
- Empirical treatment with first-line antimicrobials commences

- Infection is confirmed by bacterial culture, genomic susceptibility to first-line and reserved and new antimicrobials is determined

- Patient treatment/management altered accordingly

Figure 2   The clinical algorithm using WGS to identify antimicrobial resistance

28. **Does the proposed medical service include a registered trademark component with characteristics that distinguishes it from other similar health components?**

    N/A

29. **If the proposed medical service has a prosthesis or device component to it, does it involve a new approach towards managing a particular sub-group of the population with the specific medical condition?**

    N/A

30. **If applicable, are there any limitations on the provision of the proposed medical service delivered to the patient (i.e. accessibility, dosage, quantity, duration or frequency):**

    N/A

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[h] https://omictools.com/arg-annot-tool
[i] https://card.mcmaster.ca/
[j] https://omictools.com/resfinder-tool or www.genomicepidemiology.org
[k] https://www.ncbi.nlm.nih.gov/pathogens/antimicrobial-resistance/

31. **If applicable, identify any healthcare resources or other medical services that would need to be delivered <u>at the same time</u> as the proposed medical service:**

    N/A

32. **If applicable, advise which health professionals will primarily deliver the proposed service:**

    Testing would be provided by Approved Practising Pathologists in line with other tests on the MBS Pathology Table.

33. **If applicable, advise whether the proposed medical service could be delegated or referred to another professional for delivery:**

    N/A

34. **If applicable, specify any proposed limitations on who might deliver the proposed medical service, or who might provide a referral for it:**

    Patients should be referred by a specialist, consultant physician or an accredited supervising pathologist.

35. **If applicable, advise what type of training or qualifications would be required to perform the proposed service, as well as any accreditation requirements to support service delivery:**

    Testing would be delivered only by NATA Accredited Pathology Laboratories (as defined in MBS Pathology table) by referral only by registered Medical Practitioners (non-pathologists) in line with other tests in the MBS Pathology Table. Interpretation of results would be provided by an approved practising pathologist or a suitably qualified medical scientist.

36. **(a) Indicate the proposed setting(s) in which the proposed medical service will be delivered (select <u>ALL</u> relevant settings):**

    ☐ Inpatient private hospital (admitted patient)
    ☐ Inpatient public hospital (admitted patient)
    ☐ Private outpatient clinic
    ☐ Public outpatient clinic
    ☐ Emergency Department
    ☐ Private consulting rooms - GP
    ☐ Private consulting rooms – specialist
    ☐ Private consulting rooms – other health practitioner (nurse or allied health)
    ☐ Private day surgery clinic (admitted patient)
    ☐ Private day surgery clinic (non-admitted patient)
    ☐ Public day surgery clinic (admitted patient)
    ☐ Public day surgery clinic (non-admitted patient)
    ☐ Residential aged care facility
    ☐ Patient's home
    ☒ Laboratory
    ☐ Other – please specify below

    (b) Where the proposed medical service is provided in more than one setting, please describe the rationale related to each:

    N/A

37. **Is the proposed medical service intended to be entirely rendered in Australia?**

    ☒ Yes
    ☐ No – please specify below

38. Nominate the appropriate comparator(s) for the proposed medical service, i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system (including identifying health care resources that are needed to be delivered at the same time as the comparator service):

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 et al 2017). However, antimicrobial susceptibility testing (AST) is time consuming, with long turnaround times. 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 et al 2015).

Broth dilution tests. One of the earliest AST methods was the macrobroth or tube-dilution method. This procedure involves preparing two-fold dilutions of antibiotics in a liquid growth medium dispensed in test tubes, which are inoculated with a standardised bacterial suspension. Following incubation, tubes are examined for visible bacterial growth, with the lowest concentration of antibiotic that prevented growth reported as a quantitative result: the minimal inhibitory concentration (MIC). Test tubes have been replaced with 96 well micro-dilution trays, which allow for approximately 12 antibiotics to be tested in a range of 8 two-fold dilutions in a single tray. Most laboratories purchase standard commercial pre-prepared trays; however, this may limit the number of drugs available for testing (Reller et al 2009).

Disc diffusion susceptibility method is performed by applying a bacterial inoculum to the surface of a large Mueller-Hinton agar plate. Commercially prepared, fixed concentration, paper antibiotic discs are placed on the inoculated agar surface. After incubation, the zones of growth inhibition around each of the antibiotic discs is measured, with the diameter of the zone being related to the susceptibility of the isolate and to the diffusion rate of the drug through the agar medium. Results are "qualitative" and are reported as a category of susceptibility (i.e. susceptible, intermediate, or resistant), rather than an MIC (Reller et al 2009).

In addition, there are automated methods that can be used for standard bacterial pathogens. For example, every Australian TB reference laboratory would use the GeneXpert® system (Cepheid Sunnyvale, CA, USA), which, in addition to detecting the presence of TB bacteria (diagnosis) also tests for resistance to Rifampicin as a marker for MDR-TB (Lange et al 2019).

In the case of TB, individualised treatment for MDR- or XDR-TB relies on phenotypic drug susceptibility testing (DST) for *M. tuberculosis*. The initiation of appropriate therapy is often delayed due to the rate-limiting step of culturing *Mycobacterium tuberculosis* from isolates, which has a slow growth rate (Heyckendorf et al 2018). Turnaround time for mycobacteria growth indicator tube was reported to be 19 days (range 10-50 days) for first-line drugs, compared to the more rapid turnaround time for WGS of 5 days (range 3-7 days) (van Beek et al 2019).

39. Does the medical service (that has been nominated as the comparator) have an existing MBS item number(s)?

☒ Yes (please list all relevant MBS item numbers below)
☐ No

MBS item number: 69303 (Group P3 – Microbiology)

Culture and (if performed) microscopy to detect pathogenic micro-organisms from nasal swabs, throat swabs, eye swabs and ear swabs (excluding swabs taken for epidemiological surveillance), including (if performed):
    (a) pathogen identification and antibiotic susceptibility testing; or
    (b) a service described in item 69300;
    specimens from 1 or more sites

Fee: $22.00 Benefit: 75% = $16.50 85% = $18.70

MBS item number: 69306 (Group P3 – Microbiology)

Microscopy and culture to detect pathogenic micro-organisms from skin or other superficial sites, including (if performed):
    (a) pathogen identification and antibiotic susceptibility testing; or
    (b) a service described in items 69300, 69303, 69312, 69318;
    1 or more tests on 1 or more specimens

    Fee: $33.75 Benefit: 75% = $25.35 85% = $28.70

MBS item number: 69312 (Group P3 – Microbiology)

Microscopy and culture to detect pathogenic micro-organisms from urethra, vagina, cervix or rectum (except for faecal pathogens), including (if performed):
    (a) pathogen identification and antibiotic susceptibility testing; or
    (b) a service described in items 69300, 69303, 69306 and 69318;
    1 or more tests on 1 or more specimens

    Fee: $33.75 Benefit: 75% = $25.35 85% = $28.70

MBS item number: 69318 (Group P3 – Microbiology)

Microscopy and culture to detect pathogenic micro-organisms from specimens of sputum (except when part of items 69324, 69327 and 69330), including (if performed):
    (a) pathogen identification and antibiotic susceptibility testing; or
    (b) a service described in items 69300, 69303, 69306 and 69312;
    1 or more tests on 1 or more specimens

    Fee: $33.75 Benefit: 75% = $25.35 85% = $28.70

MBS item number: 69321 (Group P3 – Microbiology)

Microscopy and culture of post-operative wounds, aspirates of body cavities, synovial fluid, CSF or operative or biopsy specimens, for the presence of pathogenic micro-organisms involving aerobic and anaerobic cultures and the use of different culture media, and including (if performed):
    (a) pathogen identification and antibiotic susceptibility testing; or
    (b) a service described in item 69300, 69303, 69306, 69312 or 69318;
    specimens from 1 or more sites

    Fee: $48.15 Benefit: 75% = $36.15 85% = $40.95

MBS item number: 69324 (Group P3 – Microbiology)

Microscopy (with appropriate stains) and culture for mycobacteria - 1 specimen of sputum, urine, or other body fluid or 1 operative or biopsy specimen, including (if performed):
    (a) microscopy and culture of other bacterial pathogens isolated as a result of this procedure; or
    (b) pathogen identification and antibiotic susceptibility testing;
    including a service mentioned in item 69300

    Fee: $43.00 Benefit: 75% = $32.25 85% = $36.55

MBS item number: 69327 (Group P3 – Microbiology)

Microscopy (with appropriate stains) and culture for mycobacteria - 2 specimens of sputum, urine, or other body fluid or 2 operative or biopsy specimens, including (if performed):
    (a) microscopy and culture of other bacterial pathogens isolated as a result of this procedure; or
    (b) pathogen identification and antibiotic susceptibility testing;
    including a service mentioned in item 69300

    Fee: $85.00 Benefit: 75% = $63.75 85% = $72.25

MBS item number: 69330 (Group P3 – Microbiology)

Microscopy (with appropriate stains) and culture for mycobacteria - 3 specimens of sputum, urine, or other body fluid or 3 operative or biopsy specimens, including (if performed):
    (a) microscopy and culture of other bacterial pathogens isolated as a result of this procedure; or

(b) pathogen identification and antibiotic susceptibility testing;
including a service mentioned in item 69300

Fee: $128.00 Benefit: 75% = $96.00 85% = $108.80

MBS item number: 69345 (Group P3 – Microbiology)

Culture and (if performed) microscopy without concentration techniques of faeces for faecal pathogens, using at least 2 selective or enrichment media and culture in at least 2 different atmospheres including (if performed):
(a) pathogen identification and antibiotic susceptibility testing; and
(b) the detection of clostridial toxins; and
(c) a service described in item 69300;
- 1 examination in any 7 day period

Fee: $52.90 Benefit: 75% = $39.70 85% = $45.00

MBS item number: 69354 (Group P3 – Microbiology)

Blood culture for pathogenic micro-organisms (other than viruses), including sub-cultures and (if performed):
(a) identification of any cultured pathogen; and
(b) necessary antibiotic susceptibility testing;
to a maximum of 3 sets of cultures -1 set of cultures
Fee: $30.75 Benefit: 75% = $23.10 85% = $26.15

40. **Define and summarise the current clinical management pathway/s that patients may follow *after* they receive the medical service that has been nominated as the comparator (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway that patients may follow from the point of receiving the comparator onwards, including health care resources):**

See Figure 1. The main difference with using conventional antimicrobial susceptibility testing methods is the time taken to obtain a result that can be used to guide clinical decision-making. Due to the long turnaround times required for the comparator methods, patients are likely to have commenced treatment, which may turn out to be inappropriate and harmful.

41. **(a) Will the proposed medical service be used in addition to, or instead of, the nominated comparator(s)?**

☒ In addition to (i.e. it is an add-on service)
☐ Instead of (i.e. it is a replacement or alternative)

(b) If instead of (i.e. alternative service), please outline the extent to which the current service/comparator is expected to be substituted:

It is expected that WGS will replace some, but not all, of the methods currently used to identify antimicrobial resistance, and that genomic resistance prediction may need to be supplemented with standard phenotypic testing into the near future, especially for those antibiotics for which the genetic basis of resistance is not yet (fully) known (Dunne et al 2017).

42. **Define and summarise how current clinical management pathways (from the point of service delivery onwards) are expected to change as a consequence of introducing the proposed medical service, including variation in health care resources (Refer to Question 39 as baseline):**

WGS will largely replace traditional diagnostic procedures for many microorganisms. Compared with traditional diagnostics, WGS allows the rapid identification and control of resistant pathogens and the ability to monitor emergence of new resistance mechanisms. Ideally, WGS to identify resistant pathogens would be conducted prior to commencement of treatment. Through rapid and simultaneous first-line and second-line drug susceptibility prediction, the experimental treatment of patients is minimised. In short, patients are screened for treatment with appropriate antimicrobials, reducing treatment times and length of hospital stays, in so doing, resulting in better patient outcomes, and saving health system resources.

43. Summarise the clinical claims for the proposed medical service against the appropriate comparator(s), in terms of consequences for health outcomes (comparative benefits and harms):

Culture-based tests are the principal investigations used to diagnose and guide treatment for most bacterial infections that are treated with antimicrobials. The proposed item can be applied to improve testing of high-burden persistent bacterial infections associated with prosthetic devices and recurrent/persistent disease.

Antibiotic resistance is a major medical problem and rapid and precise detection of (multi-) antibiotic resistance is increasingly important. Identification of microbial resistance enables individualised treatment regimens and results in improved patient outcomes (e.g. increased treatment success rates, reduced treatment times, reduced mortality rates etc). From a patient and health system perspective, more rapid identification of antibiotic resistance is required. Although current phenotypic methods are helpful, speed, especially for slowly growing organisms, is a limiting factor (Dunne et al 2017). WGS has demonstrated its diagnostic and public health worth in the rapid identification of microorganisms in cholera, tuberculosis, and *Escherichia coli* O104:H4 outbreaks (Koser et al 2012). WGS is also capable of providing resistance profiles for multiple drugs within a single analysis (He et al 2020). In addition, WGS provides a preparedness and futureproofing for emerging pathogens.

Another important future target for WGS is the identification of the major public health problem related primarily to health care: invasive methicillin-resistant *Staphylococcus aureus* (MRSA) infection, vancomycin-resistant *enterococci* and carbapenemase-producing *Enterobacteriaceae*. Data obtained from the use of WGS can be used to predict the risk of outbreaks and to control the spread of "super bugs", allowing the ability for the appropriate placement of patients within hospitals in order to protect them from exposure. MRSA infections are increasing over time and are associated with high rates of hospital-acquired cases of bacteraemia, lengthy and costly hospital stays, and high rates of mortality (Koser et al 2012).

Mycobacterium tuberculosis (TB)

WGS can be used to rapidly identify patients with a drug resistant strain of TB, ensuring patients receive the appropriate medication from the start of their treatment, shortening the infectious period, stopping the spread and reducing the prevalence of drug-resistant TB, in so doing, reducing hospital care costs (Public Health England 2017). Using the comparator test (microculture) a confirmatory diagnosis of TB may take up to a month, delaying treatment choices and allowing spread between cases, compared to testing and confirmatory results taking a week when WGS is used. WGS provides resistance predictions for first line drugs (isoniazid, rifampicin, ethambutol and pyrazinamide), aminoglycosides and fluoroquinolones, at the same time as determining species and strain relatedness (Public Health England 2017).

Note: In March 2017 Public Health England announced that WGS would be used to identify different strains of TB and to screen for resistance to first-line agents. WGS of positive Mycobacterium isolates was implemented by PHE's National Mycobacterial Reference Service to replace MIRU-VNTR[i] typing (Public Health England 2017).

44. Please advise if the overall clinical claim is for:

☐ Superiority
☒ Non-inferiority

The genome-wide high-resolution detection of resistance conferring mutations is non-inferior to currently used phenotypic techniques of testing but could be better standardised and harmonised across pathology providers and have higher reproducibility.

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[i] The UK National TB Strain Typing Service was established in 2010 to prospectively type TB isolates using 24 loci mycobacterial interspersed repetitive units -variable number tandem repeats (MIRU-VNTR)

45. Below, list the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be specifically measured in assessing the clinical claim of the proposed medical service versus the comparator:

Diagnostic performance

- Analytical sensitivity

- Analytical specificity

- Likelihood ratios

- Rate of repeat testing required

- Time taken to achieve confirmed result

Safety Outcomes:

- Physical and psychological harms resulting from misdiagnosis

- Physical and psychological harms of delayed diagnosis

- Improved antimicrobial stewardship

- Reductions in morbidity and mortality

Clinical Effectiveness Outcomes:

- Change in clinical management

- Health-related quality of life

- Length of hospital stay

Clinical validity

- Clinical sensitivity

- Clinical specificity

- Positive and negative predictive values

Cost-effectiveness

- Savings in health system resources

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

46. **Estimate the prevalence and/or incidence of the proposed population:**

    In 2014, the National Notifiable Diseases Surveillance System received 1,339 tuberculosis (TB) notifications, representing a rate of 5.7 per 100,000 population. Australia has achieved and maintained good tuberculosis (TB) control since the mid-1980s, sustaining a low annual TB incidence rate of approximately 5 to 6 cases per 100,000 population. The number of multi-drug resistant TB (MDR-TB) cases diagnosed in Australia is low by international standards, with approximately 1-2% of notifications per year being classified as MDR-TB. Australia's overseas-born population continued to represent the majority (86%) of TB notifications and Australia's Aboriginal and Torres Strait Islander population continue to record TB rates around 6 times higher than the Australian born non-Indigenous population. Whilst Australia has achieved excellent and sustained control of TB in Australia, sustained effort is still required to reduce rates further and contribute to the achievement of the World Health Organization's goal to end the global TB epidemic by 2035.

    There were 1,364 notifiable cases of TB reported nationally in 2016 (5.6 cases per 100,000 population) with numbers increasing slightly in 2017 to 1,434 notifiable cases (5.8 cases per 100,000 population). Of these, 1,031 cases in 2016 and 1,056 cases in 2017 had positive laboratory cultures and susceptibility test results (Toms et al 2017). AS MDR *M tuberculosis* represents a major threat for the control of TB, WGS will become the standard of care for all TB patients in order to prevent the development of extensively drug-resistant variants (Merker et al 2013). WGS of all TB patients will ultimately reduce the spread of MDR TB in the community, and in so doing, deliver cost-savings to the health system as treatment of MDR-TB is estimated to cost $60,000 per patient, per year.

47. **Estimate the number of times the proposed medical service(s) would be delivered to a patient per year:**

    WGS would only be performed once per treatment episode and would rarely be required to be repeated (1-2% of failure cases).

48. **How many years would the proposed medical service(s) be required for the patient?**

    N/A – episode dependent

49. **Estimate the projected number of patients who will utilise the proposed medical service(s) for the first full year:**

    It is difficult to estimate the number of WGS services that may be required to be conducted in any one year. Using the current MBS item numbers listed above are likely to give an over estimation of numbers as these items are used for diagnostic *and* susceptibility purposes. The number of services required for the determination of resistance in new TB patients can be easily quantified, at approximately 1,300 new cases per year. However, the number of services for other microbial infections can only be estimated at approximately 10,000 bacterial genomes sequenced, which would account for all infections associated with prosthetic devices, central lines and recurrent disease that require hospital admission in children and adults.

50. **Estimate the anticipated uptake of the proposed medical service over the next three years factoring in any constraints in the health system in meeting the needs of the proposed population (such as supply and demand factors) as well as provide commentary on risk of 'leakage' to populations not targeted by the service:**

    Uptake and usage of this service should remain relatively stable over the first 3-years, and may even decrease with a reduced burden of persistent bacterial infections associated with recurrent disease due to appropriate treatment guided by WGS results.

PART 8 – COST INFORMATION

51. **Indicate the likely cost of providing the proposed medical service. Where possible, please provide overall cost and breakdown:**

    Costs of conducting WGS are dependent on the size of batch runs. Larger laboratories are capable of economies of scale by conducting up to three WGS runs per week, whereas smaller centres may only conduct one run per week. SA Pathology (small centre, one run per week) currently quotes approximately $214 for WGS of one *M tuberculosis* isolate, with approximate costs of consumables and overheads to be $116 and $98, respectively. These costs align with those quoted in the peer reviewed literature of US$70–250 per isolate (Outhred et al 2015) and €150-180 (Olaru et al 2018) per isolate.

52. **Specify how long the proposed medical service typically takes to perform:**

    A realistic turn-around time for whole-genome sequencing is 1–2 weeks from nucleic acid extraction (Outhred et al 2015).

53. **If public funding is sought through the MBS, please draft a proposed MBS item descriptor to define the population and medical service usage characteristics that would define eligibility for MBS funding.**

Category 6 (Pathology Services) – Group P7 Genetics
Proposed item descriptor: Sequencing and analysis of the whole microbial genome (bacterial, mycobacterial, fungal, viral or parasitic) of an isolate or to characterise an organism from a patient for the purpose of determining the antibiotic resistance markers (resistome) of the isolate to guide the patient's treatment and/or chemoprophylaxis of close contacts in cases of recurrent/persistent disease.   Fee: $120

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