Australian Government

Department of Health

Consultation Survey on MSAC Application 1675

Whole Genome Sequencing for the diagnosis of mitochondrial disease

MSAC welcomes feedback on MSAC applications for public funding from individuals, organisations representing health professionals or consumers and/or carers, and from other stakeholders. Please use this template to prepare your feedback. You may also attach additional information if you consider it may be useful in informing MSAC and its sub-committees.

Sharing consultation feedback

Submitted consultation feedback will be shared with the Applicant and with MSAC and its sub-committees.

- The applicant will receive a summary of comments from individuals, with the individual's name and other identifying information removed.
- MSAC and its sub-committees will receive both the summary and copies of the comments, with the name of the individual and other identifying information removed.
- Consultation feedback from groups or organisations will be provided in a complete form to both the Applicant and to MSAC and its sub-committees.

Please do not include information in your feedback that you do not want shared as outlined above. In addition, to protect privacy, do not include identifying personal (e.g. name) or sensitive (e.g. medical history) information about third parties, such as medical professionals or friends/relatives.

How consultation feedback is used

MSAC and its sub-committees consider consultation feedback when appraising an application, including to better understand the potential impact of the proposed medical technology/service on consumers, carers, and health professionals. A summary of consultation feedback will be included in the Public Summary Document (PSD) published on the MSAC website once MSAC has completed its appraisal. The PSD may also cite feedback from groups/organisations, including the name of the organisation. As such, organisations should not include information or opinions in their feedback that they would not wish to see in the public domain.

Consultation deadlines. Please ensure that feedback is submitted by the pre-PASC or pre-MSAC consultation deadline for this application. Consultation deadlines for each PASC and MSAC meeting are listed in the PASC and MSAC and ESC calendars available on the MSAC website. They are also published in the MSAC Bulletin. Feedback received after the respective deadlines may not be considered.

For further information on the MSAC consultation process please refer to the MSAC Website or contact the Consumer Evidence and Engagement Unit on email: commentsMSAC@health.gov.au.
Thank you for taking the time to provide your feedback. Please return your completed survey to:

Email: commentsMSAC@health.gov.au

Mail: MSAC Secretariat,
MDP 960, GPO Box 9848,
ACT 2601

PART 1 – PERSONAL AND ORGANISATIONAL INFORMATION

1. Respondent details

Name: Matilda Haas

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2. Is the feedback being provided on an individual basis or by a collective group?

☐ Individual
☒ Collective Group

If an individual, specify the name of the organisation you work for

If a collective group, specify the name of the group

Australian Genomics

3. How would you best identify yourself?

☐ General Practitioner
☐ Specialist
☐ Researcher
☐ Consumer
☐ Care giver
☒ Other

If other, please specify

Research Projects and Partnership Manager submitting a response on behalf of Australian Genomics in consultation with our network of researchers, clinicians, and diagnosticians.

PART 2 – CLINICAL NEED AND PUBLIC HEALTH SIGNIFICANCE

4. Describe your experience with the medical condition (disease) and/or proposed intervention and/or service relating to the application form

Australian Genomics is an Australian Government initiative supporting genomic research and its translation into clinical practice. Through broad engagement and a national collaborative approach, it achieves two key objectives: to improve efficiency, reach and timeliness of genomic research projects, and to support Commonwealth State and Territory health departments in the implementation of genomics research outcomes by refining and communicating evidence to inform policy development.

Australian Genomics engages with current and emerging government policy and priorities to identify gaps and opportunities, to support policy and action for integrating genomic technologies into the health system. By interfacing with consumers, governments, industry and global genomics initiatives, Australian Genomics drives change and growth in the sector.

Under the Targeted Call for Research "Preparing Australia for genomic medicine" (2016-2020) the Australian Genomics Mitochondrial Flagship enrolled more than 140 participants with suspected mitochondrial disease (MD) for genomic sequencing and compared the diagnostic efficacy of whole genome sequencing (WGS) in comparison with whole exome sequencing and mitochondrial DNA sequencing combined (WES+mtDNA) in paediatric and adult cohorts. The study also looked at the cost-effectiveness of the different sequencing approaches (Wu et al., 2021 DOI: 10.1038/s41431-021-00916-8).

Australian Genomics also partners with the Mito Foundation, an organisation that supports both MD research and the mito community, and has a great depth of understanding of the lived experience of individuals and families affected by MD.

5. What do you see as the benefit(s) of the proposed medical service, in particular for the person involved and/or their family and carers?

Australian Genomics strongly supports the endeavour to have WGS funded by the MBS to facilitate the diagnosis of MD in both adult and paediatric cases.

Improving access to WGS is likely to reduce the time it takes for many people with a suspected MD to receive a diagnosis. A diagnosis can be of great benefit to an individual and their families, as it can alter the course of treatment or management of the condition. There are many other benefits to having a diagnosis, including avoiding more invasive tests such as muscle biopsy, which often necessitates a hospital stay and general anaesthesia, and is a procedure which may be further complicated by the presence of MD.

A diagnosis can lead to expansion of testing to relatives, which may identify pre-symptomatic disease and help to understand disease inheritance. It can also be of great value in reproductive decision-making and guide the use of assisted reproductive therapies, including mitochondrial donation when it becomes available. A genetic diagnosis of MD can also determine suitability for clinical trials and potentially gene therapy.

Having a diagnosis may provide access to NDIS and other financial and psychosocial support, and there is increasing acknowledgement of the 'value of knowing', which may help to alleviate feelings of uncertainty and guilt, amongst many others.

6. What do you see as the disadvantage(s) of the proposed medical service, in particular for the person involved and/or their family and carers?

Some modifications to the delivery of the medical services as described in this application should be considered, to ensure access to the testing has the most positive impact on people and their families/carers. Issues and considerations are discussed in response to subsequent questions (see Q's 9, 10 and 11).

7. What other benefits can you see from having this intervention publically funded?

Aside from the benefits to individuals and families described in response to Q5, publicly funded WGS for the diagnosis of MD will have broader health system impacts. It will increase the equity of access to such testing, which has previously only been available ad hoc through research programs or state / territory health funding, or on a user pay basis. Since the introduction of MBS item number 73358 (whole exome analysis for a suspected monogenic condition) some children <10 years of age with a suspected MD will have had access to testing, but this has not been possible for children over 10 years of age or adults, or those who do not fulfil all the criteria of that item number. All suspected MD cases should have equal opportunity to have WGS testing early in the development of clinical features, as a timely diagnosis has been shown to have significant impact on outcomes in some cases.

In addition, the Australian Genomics Mitochondrial Flagship showed significant cost savings of $2,000 - $9,000 per child tested, and with an 11 – 14% increased diagnostic rate, and that early implementation of genomic testing for mitochondrial disorders could translate to an annual cost saving of ~$700,000 annually for paediatric patients (Wu et al., 2021 DOI: 10.1038/s41431-021-00916-8).

8. What other services do you believe need to be delivered before or after this intervention, eg Dietician, Pathology etc?

It is our view that pre-test and post-test genetic counselling should be delivered in association with this intervention by a qualified genetic counsellor, rather than by a "caring physician with mitochondrial experience" as described in the application. Genetic counselling is a specialist field with formal qualifications. Counselling can be delivered in consultation with the clinical geneticist. Not all experts in MD, neurologists (adult and paediatric), metabolic physicians, ophthalmologists and clinical/metabolic geneticists would necessarily be appropriately qualified to engage in genetic counselling with a family. Engaging the services of genetic counsellors also maximises efficiency of specialist and multidisciplinary clinics.

PART 3 – INDICATION(S) FOR THE PROPOSED MEDICAL SERVICE AND CLINICAL CLAIM

9. Do you agree or disagree with the proposed population(s) for the proposed medical service as specified in Part 6a of the application form?

- ☐ Strongly Agree
- ☒ Agree
- ☐ Disagree
- ☐ Strongly Disagree

Specify why or why not:

Although in broad agreement with the proposed population outlined in the application, the list of clinical features/indicators (Q26) should be reviewed, through expanded expert consultation.

For example, for the <16 years old cohort, the Australian Genomics Mitochondrial Flagship showed that the increasing Nijmegen score tracks correlatively with achieving a diagnosis through genomic testing, and so could be used for this cohort or incorporated with current defined clinical features/indicators.

It would be important to determine what proportion of children <10 years old with suspected MD would qualify for testing under MBS item 73358 (whole exome analysis for a suspected monogenic condition) and how this impacts the proposed uptake of a MD specific WGS test, and following from that, how it would impact the cost-effectiveness / health economics of the proposed item number if 73358 increasingly becomes considered as standard of care for this sub cohort.

The application states that "should WGS fail to identify a causative nDNA or mtDNA variant, then further genetic testing such as long-range PCR in samples such as saliva, urinary epithelial cells, or muscle tissue, may still be required, but only in cases with high indexes of clinical suspicion of MD". We understand that for laboratories doing this as a follow up test, muscle tissue is the preferred choice of biological sample.

10. Have all the associated interventions been adequately captured in Part 6b of the application form?

☐ Yes
☒ No

Please explain:

This part of the application says that while blood is the preferred specimen for WGS, other samples such as saliva and epithelial cells can be used. However, laboratories are not yet accredited to use such samples for WGS due to concerns around contamination from non-human DNA (including food).

The application also states that data would be permanently recorded for later analysis - NPAAC guidelines say data for the purposes of generating the report the VCF must be retained but BAM/FASTQ can be deleted after 4 years. Though in practice, most public labs retain, for now.

In relation to training and qualifications for ordering the test, the applicants suggest *"risk of leakage will be managed by restricting ordering of WGS testing to neurologists (adult and paediatric), metabolic physicians, ophthalmologists, and clinical geneticists with experience in the assessment, management and treatment of MD. The Australian Mitochondrial Disease Medical Network would provide support and education to doctors seeking to gain this level of expertise"* and that *"neurologists, metabolic physicians, ophthalmologists and clinical/metabolic geneticists with clinical expertise and experience in MD care would be able to access the test results".* Does the newly formed Mitochondrial Disease Medical Network have plans to deliver formal education and credentialling to fulfil this in a standardised way?

Another suggestion could be that such specialists can order the test in consultation with a clinical geneticist, as is the case with MBS item number 73358 (whole exome analysis for a suspected monogenic condition), and specialist metabolic physicians. This is a good opportunity to review this in practice and whether there have been implementation issues, as this may introduce downstream issues whereby clinical geneticists cannot appropriately record or bill their time for such consultation activities.

In deciding who can order WGS for MD, it will be of great importance to the mito community that accessible specialists can order the test, rather than patients experiencing long wait times for appointments in specialised clinics to get access to tests.

11. Do you agree or disagree that the comparator(s) to the proposed medical service as specified in Part 6c of the application form?

☐ Strongly Agree
☐ Agree
☒ Disagree

☐ Strongly Disagree

Please explain:

The applicants suggest that the comparator is no genetic testing. We believe that there are potentially two other comparators not considered:

1) for the paediatric group (<10 years old), the MB item number 73358 (whole exome analysis for a suspected monogenic condition – although we recognise that few children with suspected MD will have had sequencing under this item number at this time).
2) Non-genetic approaches to diagnosing MD not covered in this section (which mainly refers to muscle biopsy).

12. Do you agree or disagree with the clinical claim made for the proposed medical service as specified in Part 6d of the application form?

☐ Strongly Agree
☒ Agree
☐ Disagree
☐ Strongly Disagree

Specify why or why not:

The applicant sets out key measures for the clinical claim, both major and minor, with respect to clinical effectiveness and safety outcomes. This is a comprehensive list, and we have no further comments to add.

PART 4 – COST INFORMATION FOR THE PROPOSED MEDICAL SERVICE

13. **Do you agree with the proposed service descriptor?** MSAC is transitioning to new application forms so the relevant question in the application form will vary depending on the version used. For medical services on the MBS, see question 51 or 53. For medical services seeking funding from a source other than the MBS, see question 52 (new application forms only—labelled v. 2.5).

☐ Strongly Agree
☒ Agree
☐ Disagree
☐ Strongly Disagree

Specify why or why not:

Again, the service descriptor refers to "experience in the diagnosis and treatment of mitochondrial disease". This statement should be clarified so that there is no ambiguity in the service descriptor about who qualifies as having appropriate experience.

Other service descriptor considerations include:
- A specific item number for mtDNA mutant load testing should be included in this application or included as part of a redefinition of item H
- If initial analysis of nuclear encoded mitochondrial genes and the mitochondrial genome is negative, analysis of the nuclear genomic data should be expanded to Mendeliome analysis.
- item H should not just be restricted to mtDNA deletion testing and should be rephrased to whole mitochondrial genomic testing.

14. **Do you agree with the proposed service fee?** MSAC is transitioning to new application forms, so the relevant question in the application form will vary depending on the version used. For medical services on the MBS, see question 51 or 53. For medical services seeking funding from a source other than the MBS, see question 52 (new application forms only—labelled v. 2.5).

☐ Strongly Agree
☐ Agree
☒ Disagree
☐ Strongly Disagree

Specify why or why not:

The costing for SEALS-NSW PATHOLOGY whole exome sequencing does not include the cost of mtDNA analysis (in which case, if WES is to be offered without mtDNA analysis the diagnostic yield and test benefits should be revisited).

The cost of genetic counselling performed by MD expert under MBS 116 or 110 ($100-200) for 30-60min duration is a similar cost for a genetic counsellor to provide the service under IHPA's ABF 40.53 code ($232), noting the latter is described as a service event with no time limit.

PART 5 – ADDITIONAL COMMENTS

15. Do you have any additional comments on the proposed intervention and/or medical condition (disease) relating to the proposed medical service?

The applicant describes in answer to Q5 of the application form that a similar result to WGS can be achieved by WES. We do not agree that this is the case, as evidenced by data from the Australian Genomics Mitochondrial Flagship. In fact, a similar result can be achieved using WES+mtDNA analysis. Thus, this application should focus on WGS and should not suggest the proposed intervention is WGS or WES (agnostic of technology), as we believe that WGS is preferred option. This will be important for molecular diagnosis of MD that is caused by disease causing variants in mitochondrial DNA genes, thus informing suitability for mitochondrial donation when it becomes available. One disadvantage is that currently only VCGS is accredited for WGS. To ensure equitable access, a competitive market and good turnaround times, other laboratories should complete their accreditation requirements.

In Part 2, question 5 the applicants refer to a list of known mitochondrial disease *genetic variants*, of which there are more than 350. Did the applicants instead mean more than 350 *genes*, as supported by PanelApp Australia and the publication by Ng et al, 2021 referred to in Part 4, the summary of evidence?

In Part 3, question 14 and other associated questions, the medical device or service is incorrectly classified – the applicants answered N/A but all human genetic tests are classed as TGA Class 3 IVDs https://www.tga.gov.au/sme-assist/medical-devices-regulation-introduction

In part 6, question 25 applicants could also refer to the more recent paper "Parental health spillover effects of paediatric rare genetic conditions" DOI: 10.1007/s11136-020-02497-3

The application says that there are no data documenting the incidence of MD in Australia and expand estimates of MD and test uptake from NSW data. Whether more accurate data could be sought to inform expected uptake should be revisited.

16. Do you have any comments on this feedback survey? Please provide comments or suggestions on how this process could be improved.

Again, thank you for taking the time to provide valuable feedback.