Australian Government

Department of Health

Application 1680

Genetic testing for childhood hearing impairment

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 name: Murdoch Childrens Research Institute
ABN: **REDACTED**

Primary contact name: REDACTED

Primary contact numbers
Business: **REDACTED**
Mobile: **REDACTED**
Email: **REDACTED**

Alternative contact name: REDACTED

Alternative contact numbers
Business: **REDACTED**
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?

N/A

PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

3. Application title

Genetic testing for childhood hearing impairment.

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)

Childhood hearing impairment is the most common condition of all those included in newborn screening. It has a genetic bases in more than 50% of cases. The genetic causes are highly heterogenous with >100 genes currently implicated in childhood onset hearing impairment. Congenital or childhood onset deafness, although most frequently isolated, can be the first sign of more complex medical problems and syndromes making molecular diagnosis of these conditions well suited to next generation sequencing. Early understanding of the aetiology of a child's hearing impairment guides intervention and service use, streamlining care and maximising a child's communication and developmental potential.

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)

Singleton next generation sequencing of coding regions in clinically affected individuals, delivered by NATA accredited diagnostic laboratories with appropriate accreditation (Massively parallel sequencing – full exome sequencing studies or genome sequencing studies), including copy number variant analysis of relevant genes.

While next generation sequencing has the ability to investigate all genes in the one test, only genes known to cause hearing impairment should be analysed. Genes currently not known to be associated with hearing impairment should be excluded from the analysis. The gene list used for analysis should be regularly reviewed to ensure clinical validity, this may be through an open source platform such as PanelApp Australia **(**https://panelapp.agha.umccr.org/), or similar.

The suggested diagnostic test is agnostic of technology, and hence it is not prescriptive to the methodologies/equipment and reagents involved. For the purposes of this application the proposed test will be referred to as whole exome analysis (WEA) as investigation will be limited to the coding regions of the genome. For this indication, copy number variant analysis should also be included as these account for around 15% of pathogenic variants responsible for congenital or childhood hearing impairment. Cascade testing would also be required for relatives of affected individuals for whom a diagnosis was made via WEA. This would involve investigation of only the causative gene variant(s) found in the affected individual.

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

(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:

N/A

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. ☒ Is for genetic testing for heritable mutations in clinically affected individuals and, when also appropriate, in family members of those individuals who test positive for one or more relevant mutations (and thus for which the Clinical Utility Card proforma might apply)

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

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

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

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

N/A

(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?

☐ Yes
☐ No

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

N/A

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

N/A

PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

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:

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?

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*?

N/A

(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)?

N/A

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?

N/A

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?

N/A

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)**	**Short description of research**	**Website link to journal article or research (if available)**	**Date of publication**
1.	Intervention (WEA) in a population cohort, in parallel to standard care.	Exome sequencing in infants with congenital hearing impairment: a population-based cohort study.	Infants diagnosed with congenital hearing impairment over a 2 year period were offered WEA. Of 106 enrolled infants, 59 received a diagnosis (56%) compared with 22 (21%) who would have been identified on standard testing. Clinical management changed following exome diagnosis in 92% of the diagnosed cohort. Six relatives received a diagnosis following cascade testing and 51 couples were identified as being at high risk of recurrence in future pregnancies.	https://www.nature.com/articles/s41431-019-0553-8	November 2019
2.	Health economic analysis (cost-effectiveness)	Exome sequencing for isolated congenital hearing loss: a cost-effectiveness analysis	The costs and outcomes associated with WEA and standard care for infants presenting with isolated deafness were analysed. The incremental cost of WES was $1000 per child and added 30 diagnoses per 100 children tested. The ICER was $3333; compared to a mean societal willingness to pay this demonstrated cost-effectiveness.	https://pubmed.ncbi.nlm.nih.gov/33382469/	December 2020

	Type of study design	Title of journal article or research project)	Short description of research	Website link to journal article or research (if available)	Date of publication
3.	Retrospective cohort study	Clinical application of whole-exome sequencing across clinical indications	A single diagnostic laboratory audited 3040 consecutive cases of WEA for clinical indication and diagnostic yield. The overall diagnostic yield for WEA across all indications was 28.8% with the highest being for hearing impairment (55%).	https://pubmed.ncbi.nlm.nih.gov/26633542/	July 2016
4.	Prospective cohort study	Utility and limitations of exome sequencing as a genetic diagnostic tool for children with hearing loss	WEA was performed on 43 probands with hearing loss, the diagnostic rate was 37.2% compared to a hearing loss panel test demonstrating improved diagnostic yield.	https://pubmed.ncbi.nlm.nih.gov/29907799/	December 2018
5.	Prospective cohort study	The diagnostic yield of whole-exome sequencing targeting a gene panel for hearing impairment in The Netherlands	This study investigated the diagnostic utility of WEA targeting a panel of hearing loss genes. Testing of 200 patients resulted in a diagnostic yield of 33.5%.	https://pubmed.ncbi.nlm.nih.gov/28000701/	February 2017
6.	Prospective cohort study	Comprehensive genetic testing in the clinical evaluation of 1119 patient with hearing loss	Comprehensive testing of 1119 patients with hearing loss identified a genetic cause in 440 (39%).	https://pubmed.ncbi.nlm.nih.gov/26969326/	April 2016

	Type of study design	Title of journal article or research project)	Short description of research	Website link to journal article or research (if available)	Date of publication
7.	Literature Review	Massively Parallel Sequencing for Genetic Diagnosis of Hearing Loss: The New Standard of Care	30 studies were identified which evaluate new genetic sequencing techniques for comprehensive genetic testing for hearing loss. The overall diagnostic rate was 41% (range. 10-83%). Based on these results, comprehensive genetic testing should form the cornerstone of a tiered approach to clinical evaluation of patients with hearing loss.	https://pubmed.ncbi.nlm.nih.gov/26084827/	August 2015
8.	Prospective cohort study	Comprehensive analysis via exome sequencing uncovers genetic aetiology in autosomal recessive non-syndromic deafness in a large multiethnic cohort	160 families received WEA after excluding mutations in the most common gene, GJB2. Variants in known hearing loss genes were detected in 56% of families.	https://pubmed.ncbi.nlm.nih.gov/26084827/	April 2016
9.	Prospective cohort study	Diagnostic outcomes of exome sequencing in patients with syndromic or non-syndromic hearing loss	49 probands underwent exome sequencing to investigate hearing loss. 30% had a genetic diagnosis made. WEA proved to be effective in detecting unrecognised hearing loss syndromes and deciphering complex phenotypes in which hearing loss is a separate feature and not part of a syndrome.	https://pubmed.ncbi.nlm.nih.gov/29293505/	January 2018

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.*

	Type of study design	Title of research	Short description of research	Website link to research (if available)	Date
1.	Qualitative analysis	Personal utility of genomic sequencing for infants with congenital deafness	Analysis of surveys (N=67) completed by parents who had WEA for their child diagnosed with congenital deafness. Parents placed high value on diagnostic WES for hearing loss. Diagnostic results provided certainty. WES also represented an opportunity to promote their child's best interests.	Under review at American Journal of Medical Genetics	July 2021

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)

    Royal Australasian College of Physicians (RACP)

    The Australian Society of Otolaryngology Head and Neck Surgery (ASOHNS)

    Human Genetics Society of Australasia (HGSA)

    Childhood Hearing Australasian Medical Professionals (CHAMP) Network

    Australasian Newborn Hearing Screening (ANHS) Committee

    Acadamy of Child and Adolescent Health (ACAH)

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

    As above

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

    Deafness Foundation

    Deaf Children Australia

    Aussie Deaf Kids

    UsherKids

    NextSense

    Aurora Early intervention services

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):**

    REDACTED

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:

Childhood hearing loss affects 1-3/1000 children. In the majority of cases this is isolated, affecting only a child's hearing, however, it is essential this is detected early in order for the child to develop communication and subsequently achieve normal neurodevelopment. A more complex genetic syndrome is identifiable in 20% of children detected through newborn hearing screening. This may present with isolated hearing impairment but other health problems emerge over time. Currently, the only effective way to detect these conditions is through regular screening for these complications in all children which is costly and burdensome for families. 60% of childhood hearing loss has a genetic aetiology with around 160 genes currently identified. While treatment with hearing aids and cochlear implants is not currently determined by an aetiological diagnosis, precision therapies are in development that will be guided by genetic diagnosis. In addition, establishing a diagnosis allows avoidance of expensive and time consuming investigation as well as the potential of restoring reproductive confidence for families.

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:

Infant hearing screening covers 98% of all births in Australia and diagnoses between 250-300 infants per year with hearing loss. In addition, children can be diagnosed at some stage in childhood due to delayed acquisition of developmental milestones or a change in behaviour that indicates a reduction in hearing.

If detected on newborn hearing screening, children are referred directly to audiology. For older children, they are referred from a general practitioner or paediatrician to an audiology service for investigation of type and severity of hearing loss. If the child is confirmed to have a hearing loss they will then see a paediatrician or otolaryngologist in the outpatient setting where investigation to determine the underlying aetiology is performed.

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):

There are recently published Australian guidelines on what investigations are recommended (Appendix 1). This includes comprehensive genetic testing, but recognises the funding limitations to healthcare services and families.

These guidelines detail what investigations should be performed for the different subtypes of hearing impairment, these may include blood tests for biochemical studies, imaging of the brain and ear and referrals to other specialists such as ophthalmologist or cardiologist to assess for associated health problems that can accompany hearing impairment. While some of these tests would continue to be required for management decisions (such as brain imaging in preparation for cochlear implant), many would no longer be required if WEA was available. If the criteria for the test is met (see MBS item descriptor) a non-diagnostic GJB2/6 test would remain a requirement before proceeding to WEA.

For any child with bilateral hearing loss, single gene sequencing is recommended of GJB2/6. If this is negative WEA would be offered to the family as a diagnostic test. The flowchart (attached) shows the standard of care pathway versus the exome sequencing pathway. Further investigation is characterised in the guidelines (Appendix 1).

PART 6b – INFORMATION ABOUT THE INTERVENTION

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

Children (<18years) with onset of hearing impairment of any degree that is classified as permanent and sensorineural, auditory neuropathy or mixed. Children do not qualify for item 73358 or 73359 and have had non diagnostic sequencing of genes *GJB2/6*.

A paediatrician with expertise in managing children with hearing loss, or clinical geneticist will request WEA. The patient would be required to provide a sample or consent to access of a stored sample to use for the test.

Multiple diagnostic laboratories are accredited to deliver equivalent services of whole exome analysis for diagnostic purposes in Australia. It is expected that other diagnostic laboratories will become accredited to deliver equivalent services in the future.

The whole exome data would undergo bioinformatics analysis, filtered based on a list of genes for which there is evidence of association with childhood hearing impairment. As new disease genes are identified this list is expanded, allowing subsequent re-analysis of the initial whole exome data. Ideally, provision should be available to permit re-analysis of the initial data at a future date.

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

No.

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):

Whole exome analysis for childhood deafness would be delivered as a one off diagnostic test accessed through paediatricians or a clinical genetics service. Provision should be made for future re-analysis of the initial whole exome data in patients, for whom a genetic diagnosis is not established with initial testing, as new disease genes are identified. The frequency is suggested at a minimum of 2 yearly intervals and only as clinically indicated if new genes linked to the phenotype are known to have been identified or new symptoms arise in the child that are suspicious for a genetic condition not analysed in the initial round of testing. It is possible that the child develops symptoms and signs that would then make other testing more appropriate than re-analysis.

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:

Consultation with a paediatrician, with expertise in managing children with hearing loss, or clinical geneticist would be required at the time WEA is initially offered to eligible patients. For the delivery of results, a formal consultation with a specialist in genetics would be appropriate (Clinical geneticist or Genetic counsellor).

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

An appropriately qualified laboratory geneticist would be responsible for overseeing the WEA in the laboratory and providing the clinical report that would include interpretation of the results. Genetic counselling should be provided by qualified genetic counsellors to all patients at the time of results delivery. A clinical geneticist would be required for some cases dependant on the complexity of results.

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:

Clinical geneticists or paediatricians with expertise in managing children with hearing loss can confirm eligibility and suitability.

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:

Paediatricians would be required to complete basic training in genetic counselling, testing and consent. Clinical geneticists will have the appropriate formal qualifications as genetic specialists to provide consultation to paediatricians and patients.

36. (a) Indicate the proposed setting(s) in which the proposed medical service will be delivered (select ALL 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

PART 6c – INFORMATION ABOUT THE COMPARATOR(S)

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):

The comparator is the current standard of care which is single gene sequencing for *GJB2/6* variants. This has a much lower diagnostic rate of 20% versus 60% with WEA therefore the use of health services in the undiagnosed population should also be considered as an element of the comparator.

In the absence of an aetiological diagnosis, children with deafness undergoing regular investigation and review by a specialist. In the absence of a known cause of the child's hearing loss investigations are performed to look for associated medical conditions that can arise, for example a child may see an ophthalmologist intermittently to assess vision and look for one of the syndromes that can affect vision and hearing such as Usher or Stickler syndrome. Parents are unable to have accurate information or options regarding recurrence risk and there are missed opportunities with regards to specific therapies or disease surveillance.

A minority of parents or individual health services may choose to fund genetic panel testing for this indication, therefore, this may be considered a comparator. The diagnostic rate of panel testing is similar or slightly higher than for WEA depending on the technology utilised. This is currently not offered by any laboratory in Australia. The mostly common utilised deafness panel tests are OtoSCOPE which is currently priced at $1950 USD ($2665 AUD) and OtoGenome $3950 USD ($5397.72 AUD).

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

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):

The comparator is single gene sequencing with *GJB2/6.* If this test is diagnostic, children do not require further investigation looking for the cause. If it is negative the following investigations are recommended according to the severity of hearing loss and other clinical features.

Diagnostic pathway of further investigation

Further investigation	Mild/Moderate (60%)	Severe/Profound (40%)
MRI brain	✓	
MRI brain with general anesthetic		✓
CMV PCR testing on saliva/urine of newborns less than 21 days old	✓	✓
CMV PCR Guthrie card testing	✓	✓
Family audiograms	✓	✓
Ophthalmology assessment	✓	✓
ECG with cardiologist interpretation		✓
Renal ultrasound	*If indicated*	
Vestibular testing	*If indicated*	

MRI magnetic resonance imaging, ECG electrocardiogram

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:

If a child receives a genetic diagnosis through WEA they will either avoid the investigations listed above completely, or have a tailored investigation pathway suitable to their specific diagnosis.

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):

The number of children receiving an aetiological diagnosis will increase from approximately 20% to 60%, reducing the number of children receiving investigation looking for a cause. In our study of infants with congenital hearing impairment, 36% received a non-syndromic diagnosis and were discharged from further screening or surveillance and 9% received a syndromic diagnosis that required a tailored management and screening approach. Importantly, recurrence risk was determined in all who families who received a diagnosis. The use of WEA in this cohort reduced the burden of the diagnostic odyssey for the 56% of families who received a diagnosis and decreased the utilisation of health care resources overall that would have been used for ongoing investigation in these families.

PART 6d – INFORMATION ABOUT THE CLINICAL OUTCOME

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):

The clinical claims of provision of WEA for this patient population include provision of a molecular diagnosis, decreased time to diagnosis avoiding ongoing review and testing, potential for targeted surveillance when required; in only those individuals who remain undiagnosed or who receive a syndromic diagnosis and restoration of reproductive confidence and accurate recurrence risk advice.

Compared to standard of care, provision of WEA, regardless of it resulting in a diagnosis or not, is unlikely to cause harm. Targeted analysis for hearing loss genes would minimise the risk of unintended findings in WEA data.

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

☒ Superiority
☐ Non-inferiority

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:

Safety Outcomes: Avoidance of adverse events related to investigation such as general anaesthetic for brain imaging in young infants.

Clinical Effectiveness Outcomes:

Improved surveillance of known complications of a disorder or discharge from surveillance and investigation when appropriate.

Restoration of reproductive confidence

Personal utility for families

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

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

Based on numbers provided by each newborn hearing screening service we would expect approximately 250 infants to be eligible for testing Australia wide each year. An additional 50 children who develop childhood onset hearing impairment outside of the newborn period would also be eligible for testing. Based on our cohort study in which approximately 60% of families sought genetic investigation we estimate an overall number of 180-200 patients per year.

In addition, a backlog of patients will be eligible for testing. The maximum proposed population is approximately 3000.

On a population basis the incidence of congenital and childhood deafness that would meet criteria for eligibility for testing is 1 in 1000 live births.

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

WEA would be a one off test delivered per patient.

The applicants suggest a second service related to this diagnostic test, which would include the periodic reanalysis of the patients sequencing data, where clinically indicated. The advantage of this use of technology able to cover the whole exome in comparison to panel based testing for genes is the ability to reanalyse the data, without having to repeat the sequencing, when further clinical information about either the patient or new disease genes becomes available.

The re-analysis of the sequencing data would only be considered if clinicians become aware of new genes, or if changes in the child's condition suggest other possible candidate genes. Re-analysis would be considered in conjunction with clinical review, which would be every 1-2years, however it would not be an automatically triggered time-based re-analysis.

Cascade testing would also be a one-off single gene investigation for first degree relatives of the affected patient and where clinically indicated.

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

N/A

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

It is suggested that 1/4 of the backlog of currently eligible patients using clinical genetic services could be seen and offered WEA in the first year, along with the newly presenting population for that year. Hence the projected number of patients utilising the service in the first year would be approximately 930.

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:

In the first three years of WEA being available for this population all new patients and the majority of those eligible as backlog would be seen by a clinician eligible to order testing. This would a total proposed number of approximately 3500 patients nationally.

Risk of leakage would be considered nil due to targeted testing of a well-defined population, restricted ordering to paediatricians with appropriate training or clinical geneticists.

PART 8 – COST INFORMATION

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

Victorian Clinical Genetics Services

Overall cost of WEA from receipt of patient sample to clinical report produced is $2195 (+cascade sequencing if required for variant interpretation) for primary WEA analysis for deafness including common copy number variants.

Cascade testing of single variant: $400 per variant

Reanalysis of whole exome data: $425

Currently no other Australian laboratories offer **specific** analysis for this indication. Several laboratories (Queensland Health, Canberra Clinical Genomics, SEALS NSW) offer assessment of clinician provided gene list with or without copy number analysis. It is likely other laboratories will set up this service and/or improve capability for accredited copy number variant detection, if there is demand for it.

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

The turnaround times for WEA are approximately 8 weeks. Delivery of the results is recommended to be by a genetic counsellor or clinical geneticist and appointments could require 30 minutes to 1 hour.

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 2 _ Diagnostic Procedures and Investigations
Proposed item descriptor: *Affected individuals:* Characterisation, via whole exome or genome sequencing and analysis, of germline variants known to cause childhood deafness, if: The characterisation is: Requested by a consultant physician and The patient is aged <18years and Has congenital or childhood onset hearing loss that is bilateral with >40dB in the worst ear over three frequencies, classified as permanent and sensorineural, auditory neuropathy or mixed and Has non-diagnostic GJB2/6 sequencing and The patient does not meet criteria for item 73358 or 73359. *Re-analysis* Re-analysis of the data for characterisation of new germline gene variants in a patient with onset of hearing loss <18years. *Family members:* Request by a clinical geneticist for the detection of previously identified single gene variant, in a first degree relative of a patient with hearing impairment where previous genetic testing has detected the causative variant. Fee: Affected individual: $2195 Re-analysis: $425 Cascade testing of family members (single gene variant): $400