Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1680 Genetic testing for childhood hearing impairment

Applicant: **Murdoch Children's Research Institute**

Date of MSAC consideration: **24-25 November 2022**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of virtual gene panel-based whole exome analysis (WEA) and copy number variant (CNV) analysis for the diagnosis of a genetic cause of hearing impairment (HI) in children (<18 years old) was received from the Murdoch Children's Research Institute by the Department of Health and Aged Care.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC supported the creation of new Medicare Benefits Schedule (MBS) items for genetic testing for childhood hearing impairment. MSAC supported this testing as it had non-inferior safety compared to the current standard of care and superior effectiveness in affected children. MSAC considered genetic testing for hearing loss was cost-effective, and the financial impact to the MBS was acceptable.

MSAC advised this genetic testing may allow further investigations such as MRI to be avoided in affected children and provide prognostic information, which families value, and would also support the identification of the aetiology of hearing loss detected through neonatal hearing screening. MSAC advised virtual gene panel testing should not be restricted to genes for non-syndromic hearing loss, because hearing loss may be due to a syndrome not clinically apparent at the time of testing.

MSAC supported MBS items for testing affected individuals using singleton and trio virtual gene panel-based analysis of whole exome or genome data, data re-analysis, cascade testing of biological relatives, and reproductive partner testing. MSAC did not support the item for *GJB2* and *GJB6* genetic testing, proposed as a prerequisite to virtual panel testing, and advised that virtual panel testing should be conducted upfront because it has similar cost-effectiveness.

Consumer summary
This was an application from the Murdoch Children's Research Institute requesting Medicare Benefits Schedule (MBS) listing of genetic testing in children aged under 18 years old with moderate to severe hearing loss. Childhood hearing loss can be genetic (can be inherited) or non-genetic, and variants in many genes are known to be involved. Where the cause is genetic, the *GJB2* and *GJB6* genes are the

Consumer summary

most common genes involved, with a variant in these genes found in 20% of people with genetic childhood hearing loss. Childhood hearing loss can be one part of a syndrome that also affects the child in other ways (called syndromic hearing loss), or the child can have no symptoms other than their hearing loss (called non-syndromic hearing loss). Genomic testing is already funded for children with multiple congenital anomalies, but not where the child's hearing loss is non-syndromic.

MSAC considered genetic testing for childhood hearing loss to be safe, as it only requires a blood sample, and effective because it would reduce the time to diagnosis and may allow children to avoid other investigations. MSAC also considered that families place considerable value on the prognostic information this testing can provide for their child's hearing loss, meaning information about how the child's hearing loss is likely to be over time, for example whether it will get worse. Genetic testing that can identify the cause of the hearing loss would also align with newborn hearing screening programs. There may also be non-health benefits to this testing, such as supporting the child to access the right schooling, including bilingual education, and other accommodations they require. Genetic testing may assist parents to better understand and reduce concerns about the cause of their child's hearing loss.

There are a wide range of views on hearing loss and deafness in society and in the Deaf community. Deaf people who belong to the Deaf community are fully engaged citizens who participate in the community with Auslan and other sign languages, including Indigenous Sign Languages, legally recognised and respected as their language of preference. MSAC considered that publicly funding this testing was ethically acceptable as it would increase equity of access for families who wanted to undergo testing. Families would not have to undergo genetic testing for hearing loss if they did not want to.

This application proposed different types of genetic testing for people with childhood hearing impairment: testing for variants in *GJB2* and *GJB6*, then if no genetic diagnosis is found moving next to virtual gene panel testing. Virtual gene panel testing is where all the person's genes are sequenced, then the analysis is restricted to a panel of genes known to be involved in hearing loss. MSAC considered that testing *GJB2* and *GJB6* before the virtual gene panel was not necessary, because using the panel test upfront was about the same value for money but faster.

The application proposed that the virtual panel of genes should only include genes that are associated with non-syndromic hearing loss, but MSAC advised that the panel should not be restricted to genes for non-syndromic hearing loss, because hearing loss may be part of a syndrome (such as Usher syndrome) that was not obvious at the time of testing. MSAC also considered that as long as the hearing loss symptoms appeared during childhood, the virtual panel testing would not have to be done before the child turns 18 years old.

If testing the affected individual finds a genetic variant causing their hearing loss, then the person's relatives may choose to have cascade testing to see if they also have the genetic variant. Depending on how the genetic variant can be inherited, it may also be useful to test reproductive partners for genetic variants that could result in a child being born with a hearing impairment, to support their ability to make informed reproductive decisions.

MSAC considered that genetic testing for childhood hearing loss is good value for money, and that the financial cost to the MBS was acceptable.

MSAC's advice to the Commonwealth Minister for Health and Aged Care

MSAC supported listing genetic testing for moderate to severe childhood hearing loss on the MBS. MSAC considered the testing to be safe, effective, good value for money, and to have an acceptable financial cost to the MBS.

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

MSAC noted that this application from the Murdoch Children's Research Institute requested Medicare Benefits Schedule (MBS) listing of singleton (population 1) or trio (population 2) virtual gene panel-based analysis of whole exome sequencing (WES) or whole genome sequencing (WGS) data, including copy number variant (CNV) analysis, for the diagnosis of a genetic cause of childhood hearing loss. MSAC noted that the application also requested items for re-analysis of WES/WGS data (population 3), cascade testing of the biological relatives of probands (population 4), reproductive partner testing where the proband has a recessive pathogenic or likely pathogenic (P/LP) variant (population 5), and GJB2/GJB6 genetic testing (population 6).

MSAC noted that it had not previously considered genetic testing for childhood hearing impairment, though recalled it had been involved in the evaluation prior to the introduction of universal newborn hearing screening.

MSAC noted that in Australia congenital hearing loss has a prevalence of around 1 per 1,000 live births, and each year in Australia approximately 331 children are born with bilateral moderate to profound permanent childhood hearing loss. MSAC noted most studies identified a genetic basis in at least a quarter of patients, and that 56% had a genetic diagnosis in an Australian study using WEA and microarray technologies (Downie 2020[1]).

MSAC noted that the proposed benefits of genetic testing include decreased time to diagnosis for some individuals, and that it may allow some patients to avoid ongoing clinical review and investigations with potential for adverse events (e.g., general anaesthetic for magnetic resonance imaging (MRI) in infants). This testing was also proposed to identify targeted investigations, surveillance or treatment of potential complications if a syndromic cause for hearing loss (such as Usher Syndrome) is confirmed. Genetic testing may reduce the diagnostic odyssey for patients, and could provide non-health benefits such as earlier intervention leading to better speech and language development outcomes, as well as value of knowing (empowerment, reassurance and support) for affected families. Reproductive partner testing was also proposed to provide an opportunity for informed reproductive decision making.

MSAC also noted that the National Framework for Neonatal Hearing Screening[2] supports the identification of the aetiology of hearing loss, and considered that publicly funding genetic testing for childhood hearing loss aligns with this.

MSAC noted potential ethical concerns around genetic testing for hearing loss, that deaf people often experience and view their deafness as part of who they are and not something to lament or change, and that the Department-contracted assessment report (DCAR) had comprehensively explored ethical issues around the proposed testing. MSAC acknowledged that for culturally Deaf people, to be Deaf is a natural state of being, and having a deaf baby is to be celebrated and does not require intervention. MSAC acknowledged these views are also shared by many in the wider community. MSAC noted consumer comments that parents would have a choice whether to undertake this testing for their child, and that some families would choose not to pursue testing. MSAC considered that publicly funding this testing would increase equity of access amongst families who wanted to undergo testing, and that this was appropriate given testing would be optional.

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[1] Downie, L, Halliday, J, Burt, R, et al. 2020, 'Exome sequencing in infants with congenital hearing impairment: a population-based cohort study', *European Journal of Human Genetics*, **28**(5).

[2] National Framework for Neonatal Hearing Screening (2013). Available at: https://www.health.gov.au/resources/publications/national-framework-for-neonatal-hearing-screening

MSAC noted that six MBS items were proposed:

- AAAA1 – singleton virtual gene panel testing (proposed fee = $2,100)
- AAAA2 – trio virtual gene panel testing (proposed fee = $2,900)
- BBBBB – re-analysis of data from AAAA1 or AAAA2 (proposed fee = $500)
- CCCC1 – cascade testing of biological relative (proposed fee = $400)
- CCCC2 – reproductive partner testing (proposed fee = $1,200)
- DDDDD – *GJB2* and *GJB6* genetic testing (proposed fee = $607.90).

MSAC noted the proposed population did not include children with mild hearing loss, but that consultation comments had suggested the justification for excluding people with mild hearing loss was insufficient. MSAC considered that as the population of patients with mild hearing loss had not been in scope for the HTA, evidence had not been presented that could inform consideration of virtual gene panel testing in patients with mild hearing loss. Extending testing to this population would need to be proposed in a future MSAC application. MSAC also considered it unnecessary to state bilateral hearing loss in the item descriptors, as children are frequently unable to successfully complete hearing tests on both ears to permit an accurate diagnosis of bilateral hearing loss.

MSAC noted the application proposed testing for non-syndromic deafness only, and that the applicant stated in the pre-MSAC response that the proposed testing was designed to be used for patients not eligible under childhood syndromes items 73358 and 73359. MSAC noted the applicant advised that the proportion of patients with a syndromic cause of hearing loss in Downie 2020 was 20% (21/106), and 18 of these cases would have been eligible for items 73358 and 73359. MSAC noted the pre-MSAC response also clarified that the proposed Deafness_Isolated virtual panel also includes genes associated with 'hidden' syndromes. MSAC agreed that it was unnecessary to limit virtual panel testing to genes associated with non-syndromic childhood hearing loss, as some syndromes only become clinically apparent later.

MSAC noted the applicant proposed using the "Deafness_Isolated" list on PanelApp Australia[3] to define the virtual panel of genes for analysis. MSAC considered that PanelApp Australia, PanelApp UK or another curated and recognised reference source for a comprehensive list of relevant genes would be appropriate, and advised a practice note referring generically to "a recognised test directory" should be used instead to allow the pathologist to choose an appropriate high-quality reference source to use in determining the genes to be assessed on the virtual panel.

MSAC noted the proposed age limit for virtual panel testing, and considered it more appropriate to support testing for people whose hearing loss first presented before 18 years of age, irrespective of the age at which genomic testing takes place – that is, they could be 18 years old or older at the time of genetic testing as long as their hearing loss emerged before they turned 18 years old.

MSAC noted the proposed item descriptor wording required CNVs to be tested in all genes on the virtual panel, and that the applicant in its pre-MSAC response commented that it was appropriate to restrict CNV analysis to genes where this is a proven and common mechanism. MSAC considered that a reasonable CNV analysis can be conducted based on WES data in line with routine clinical practice, and agreed that CNV analysis was only necessary in relevant genes.

MSAC noted that the fees proposed for virtual gene panel testing items AAAA1 and AAAA2 were significantly higher than the cost of similar tests in public sector laboratories. MSAC considered that the laboratory cost to conduct standard exome or genome testing is approximately $900,

[3] PanelApp Australia – available at: https://panelapp.agha.umccr.org/

and that because virtual gene panels are pre-curated lists of relevant genes only approximately $300 of curation and reporting time is required in addition, making $1,200 the appropriate fee for virtual gene panel testing. MSAC recalled it had previously supported a fee of $1,200 as being suitable for virtual panel-based testing for inheritable cardiac arrhythmia and cardiomyopathy. MSAC noted that unrestricted analysis of the entire exome/genome was not proposed in this application, but considered that it would warrant a higher fee because it requires a substantial increase in the number of variants requiring review and time required for curating the relevance of a gene and reporting. For trio testing, MSAC noted that the reagent cost along for library preparation and sequencing is approximately $1,800, and a small amount of time for curation given the analysis is restricted to the genes on a virtual panel, $2,100 would be appropriate. MSAC noted the DCAR's sensitivity analyses of fees of $1,200 for AAAA1 and $1,800 for AAAA2 showed these fees gave a 26% decrease in the ICER, and a substantial reduction in the financial cost, for example in year 1 from $6.8 million to $4.7 million. Thus, MSAC supported fees of $1,200 (singleton, AAAA1) and $2,100 (trio, AAAA2) as being appropriate for virtual gene panel-based testing for childhood hearing loss.

MSAC noted that BBBBB was proposed by the applicant to have a minimum timeframe for re-analysis of 18 months in line with similar previously supported re-analysis items, but that ESC had proposed the minimum interval be extended to 24 months based on newly published systematic review (k=29) of re-analysis in Australian populations[4]. MSAC agreed that the appropriate minimum timeframe for re-analysis was 24 months.

MSAC noted that ESC proposed further re-analysis (BBBBB) would not be required upon a genetic diagnosis, and that the applicant agreed with this in its pre-MSAC response. However, MSAC considered the restriction of re-analysis to patients who have not yet received a genetic diagnosis for their hearing loss to be unnecessary, as it is possible to have more than one genetic diagnosis, and an additional diagnosis may change clinical management.

MSAC noted that restricting cascade testing to variants that were pathogenic or likely pathogenic would not permit segregation testing of variants of uncertain significance (VUSs), but considered that segregation testing could be important in identifying the cause of hearing loss, and noted that the applicant in its pre-MSAC response also supported the expansion to include segregation testing for VUSs. MSAC advised that CCCC1 should describe cascade testing for variants "potentially causative" of hearing loss, as this would also include VUSs.

MSAC noted that frequency restrictions such as 'once per lifetime' can be enforced in an automated manner through Medicare payment systems prior to the payment of benefits, but that others such as 'once per gene per partner per lifetime' may not be automatically enforced, and are typically enforced through post-payment compliance activity. MSAC considered that stating the intended frequency may guide requestors, and on balance considered it more appropriate to include frequency restrictions that cannot be enforced in an automated manner prior to the payment of benefits as guidance in a practice note.

MSAC noted the list of requestors in the proposed MBS item descriptors, and considered listing specialities was unnecessarily specific as the key aspect is that the requestor has the relevant expertise (irrespective of their speciality) and can offer enough knowledge to ensure informed consent. MSAC advised the appropriate requestor for virtual panel testing, re-analysis and reproductive partner testing (AAAA1, AAAA2, BBBBB and CCCC2) should be described in item descriptors as simply "a specialist or consultant physician experienced with childhood hearing

[4] Dai P, Honda A, Ewans, L, et al. (2022). Recommendations for next generation sequencing data reanalysis of unsolved cases with suspected Mendelian disorders: a systematic review and meta-analysis. *Genetics in Medicine*, **24**(8): 1618–29.

loss". MSAC was confident that removing the list of specialties would not lead to inappropriate utilisation; rather, it would be a pragmatic approach to ensure the appropriate requestors can order these tests in practice. MSAC also advised that this pragmatic approach to requestors should be applied more broadly and in future draft MBS items.

MSAC noted that the National Pathology Accreditation Advisory Council (NPAAC) Requirements for Medical testing of Human Nucleic Acids[5] classify DNA testing according to the ethical implications into tier 1 (standard), and tier 2 (the test has the potential to lead to complex clinical issues). MSAC considered that the appropriate requestor for cascade testing differs depending on the disease in question: here in the context of hearing loss, cascade testing would be tier 1 – however for conditions such as neurological disease and cancer, cascade testing would be tier 2. MSAC considered that fetal testing would be tier 2, given the level of expertise required. MSAC advised that for cascade testing in relation to hearing loss (CCCC1), it would therefore be appropriate for any clinician to be able to request the test.

MSAC noted that currently, *GJB2/GJB6* genetic testing, which was proposed as a prerequisite to virtual panel testing, is publicly funded in some jurisdictions but not nationally. MSAC noted that the *GJB2/GJB6* genetic testing had a diagnostic yield of 20.8%. MSAC noted Downie 2020 had used upfront virtual panel testing for all patients, and that the DCAR's scenario analysis of the cost-effectiveness of upfront virtual panel testing showed the incremental cost-effectiveness ratio (ICER) to be $1,544 per additional proband and/or carrier identified, which MSAC considered represented similar cost-effectiveness to the base case ICER including prior *GJB2/GJB6* testing of $1,480 per additional proband and/or carrier identified. MSAC also noted the DCAR's scenario analysis of the financial cost of upfront virtual panel testing showed upfront testing would cost only an additional $22,652 to $24,191 per year to the MBS. MSAC also considered that upfront gene panel testing also saves time and conserves sample. MSAC therefore advised it supported upfront virtual panel testing for all patients, so did not support prior *GJB2/GJB6* genetic testing (DDDDD).

On practice notes, MSAC noted that ESC had considered both pre-test and post-test counselling would be appropriate in conjunction with this testing, and therefore both PN.0.23 and PN.0.27 to be relevant. MSAC agreed with the Department's subsequent proposal to move post-test counselling from PN.0.27 to PN.0.23, and apply the revised PN.0.23 to the items supported under this application.

MSAC's supported item descriptors are provided at the end of this section (Table 1).

MSAC noted the current and proposed clinical management algorithms.

MSAC noted that the DCAR reported no significant safety issues, and that suitable samples for genetic testing include peripheral blood or other easily obtained tissues such as buccal cells. MSAC noted that psychological outcomes improved or stayed the same for parents whose child received a definite diagnosis, and worsened for parents whose child received no diagnosis or inconclusive results. MSAC considered genetic testing to have non-inferior safety.

MSAC noted that most of the clinical effectiveness evidence was derived from a single Australian study (Downie 2020) that conducted genomic testing of 106 children with hearing loss. The study's results were that:

- 59/106 (55.7%) of children received a genetic diagnosis
- 21/106 (19.8%) had *GJB2/GJB6*-related deafness (one digenic)

[5] NPAAC Requirements for Medical testing of Human Nucleic Acids (Second edition, 2013). Available at: https://www.safetyandquality.gov.au/publications-and-resources/resource-library/requirements-medical-testing-human-nucleic-acids-second-edition-2013

- 12/106 (11.3%) had variants with autosomal dominant inheritance (including one *GJB2*)
- 47/106 (44.3%) had variants with autosomal recessive inheritance
- 8/59 (13.6%) of genetic causes were *de novo* variants, which do not require cascade testing
- 92% of participants with a genetic diagnosis had a change in management (50% overall, consistent with other studies)

MSAC noted that the literature review was restricted to WEA studies reporting diagnostic yield for hearing impairment that used between 120 and 190 genes in their virtual panel. MSAC noted the diagnostic yield increased from 24.8% to 47.5% for WEA compared to *GJB2/GJB6* testing alone. MSAC noted effectiveness was also evidenced through changes in management for approximately half of the affected individual population following WEA: 25.8% were discharged from further testing, and 15.1% entered a different management pathway. There was also 'value of knowing' associated with the proposed testing. Re-analysis and cascade testing were effective as they resulted in further genetic diagnoses, and MSAC considered reproductive partner testing is important to families as it supports informed reproductive decision-marking. Overall, MSAC advised genetic testing for hearing loss had superior effectiveness.

MSAC noted the comparators and considered them to be appropriate.

MSAC noted that the economic evaluation was a cost-effectiveness analysis, and the base case ICER was $1,629 per additional proband and/or carrier identified, which it considered to be acceptable and in line with previously supported ICERs that used similar measures of effectiveness. MSAC noted that key drivers of the cost-effectiveness were the diagnostic yield, the number of relatives undergoing cascade testing and the cost of WEA, and considered that at its supported fees genetic testing for hearing loss would likely be more cost-effective than had been estimated.

MSAC noted service volumes were estimated using an epidemiological approach, and that a market data approach would likely also include cascade testing resulting in higher estimates. MSAC considered that taking into account its advice to not require prior *GJB2/GJB6* testing, the uptake of WEA would increase slightly. MSAC noted that the model assumed a 15% singleton/85% trio split for WEA, and that uptake was estimated at 67%. MSAC considered that this uptake rate may have been underestimated as clinical geneticist experience suggests that nearly all parents choose genetic testing, and MSAC considered this resulted in some uncertainty in the financial estimates.

MSAC noted the DCAR had calculated the financial impact to the MBS at the proposed fees and with prior *GJB2/GJB6* testing to be $6.8 million in year 1 (2023), decreasing to $1.7 million in year 6 (2028) after the prevalent pool of patients had been exhausted. MSAC considered that the financial impact was acceptable, and that its advice would decrease the cost to the MBS. MSAC noted post-MSAC updates to the financial analyses to incorporate its advice (see updated analyses in Table 19) showed that the financial cost to the MBS would decrease to $5.0 million in Year 1 to $1.4 million in Year 6. MSAC noted the cost offsets of not requiring MRI under general anaesthesia for infants had not been included in the financial analysis. MSAC also noted that the financial analysis showed a cost offset of approximately $250,000 per year to the States and Territories for current *GJB2/GJB6* testing (of affected individuals and the biological parents) that would be replaced by MBS-funded genetic testing, resulting in an updated net financial cost across all government funding sources of $4.7 million in Year 1 to $1.2 million in Year 6.

Table 1 MSAC's supported MBS item descriptors

Category 6 – PATHOLOGY SERVICES Group P7 – GENETICS
MBS item AAAA1 Genomic testing and copy number variant analysis of genes known to be causative or likely causative of childhood hearing loss, if: (a) the characterisation is requested by a specialist or consultant physician experienced with childhood hearing loss; and (b) the patient has congenital or childhood onset hearing loss that presented prior to age 18 years and is permanent moderate, severe, or profound (>40 dB in the worst ear over three frequencies) and classified as sensorineural, auditory neuropathy or mixed; and (c) the patient is not eligible for a service to which items 73358 or 73359 apply; (d) the characterisation is not performed in conjunction with or following a service to which MBS item AAAA2 applies Applicable once per lifetime. Fee: $1,200.00 Benefit: 75% = $900.00 85% = $1,106.80
MBS item AAAA2 Genomic testing and copy number variant analysis of relevant genes known to be causative or likely causative of childhood hearing loss, if: (a) the characterisation is requested by a specialist or consultant physician experienced with childhood hearing loss; and (b) the patient has congenital or childhood onset hearing loss that presented prior to age 18 years and is permanent bilateral moderate, severe, or profound (>40 dB in the worst ear over three frequencies) and classified as sensorineural, auditory neuropathy or mixed; and (c) the characterisation is performed using a sample from the patient and a sample from each of the patient's biological parents; and (d) the patient is not eligible for a service to which items 73358 or 73359 apply; (e) the characterisation is not performed in conjunction with or following a service to which MBS item AAAA1 applies. Applicable once per lifetime. Fee: $2,100.00 Benefit: 75% = $1,575.00 85% = $2,006.80
MBS item BBBBB Re-analysis of whole exome or genome data obtained under a service to which item AAAA1 and AAAA2 apply, for characterisation of previously unreported germline gene variants for childhood hearing loss, if (a) the re-analysis is requested by a specialist or consultant physician experienced with childhood hearing loss; and (b) the re-analysis is performed at least 24 months after (i) a service to which items AAAA1 or AAAA2 applies; or (ii) a service to which this item applies. Applicable twice per lifetime MBS Fee: $500.00 Benefit: 75% = $375.00 85% = $425.00
MBS item CCCC1 Characterisation of one or more familial germline gene variants potentially causative of childhood hearing loss if: (a) the person tested is a biological relative of a patient with a germline gene variant(s) potentially causative of hearing loss confirmed by laboratory findings; and (b) the result of the previous proband testing is made available to the laboratory. Fee: $400.00 Benefit: 75% = $300.00 85% = $340.00

MBS item CCCC2

Characterisation of all germline variants in one or more genes known to cause hearing loss for the reproductive partner of an individual with a causative recessive pathogenic or likely pathogenic variant for hearing loss identified in the same gene(s), if:

(a) the characterisation is for a reproductive partner of a patient with a pathogenic or likely pathogenic recessive germline gene variant(s) known to cause hearing loss confirmed by laboratory finding, and

(b) the result of the previous individual's testing is made available to the laboratory.

Fee: $1,200.00 Benefit: 75% = $900.00 85% = $1,106.80

85% benefit reflects the 1 November 2022 Greatest Permissible Gap (GPG) of $93.20. All out-of-hospital Medicare services that have an MBS fee of $621.50 or more will attract a benefit that is greater than 85% of the MBS fee – being the schedule fee less the GPG amount. The GPG amount is indexed annually on 1 November in line with the Consumer Price Index (CPI) (June quarter).

Practice notes:

AAAA1, AAAA2:

The list of phenotypically driven genes should be based on a recognised test directory.

AAAA1, AAAA2, BBBBB, CCCC1, CCCC2: revised PN.0.23:

Informed consent and genetic counselling for genetic tests

Items 73297, 73300, 73305, 73334, 73339, 73340, 73393, 73394, 73417 and 73418

Prior to ordering these tests the ordering practitioner should ensure the patient (or approximate proxy) has given informed consent. Testing should only be performed after genetic counselling. Appropriate genetic counselling should be provided to the patient either by the specialist treating practitioner, a genetic counselling service or a clinical geneticist on referral. Further counselling may be necessary upon receipt of the test results.

Items 73295, 73296, 73304, 73333, 73392, 73395, 73416 and 73419

Patients who are found to have any form of affected allele should be referred for post-test genetic counselling as there may be implications for other family members. Appropriate genetic counselling should be provided to the patient either by the specialist treating practitioner, a genetic counselling service or a clinical geneticist on referral.

CCCC1, CCCC2: new practice note:

Genomic testing for childhood hearing loss

Prior to requesting or performing these tests, the requesting practitioner or pathologist should consider if the patient has previously received equivalent testing.

Item CCCC1: Testing should not be required more than once per variant per lifetime; additional testing should only be performed if it is clinically relevant.

Item CCCC2: Testing should not be required more than once per gene per lifetime; additional testing should only be performed if it is clinically relevant.

4. Background

MSAC has not previously considered virtual gene panel-based WEA and CNV analysis for the diagnosis of a genetic cause of HI in children.

The abbreviation WEA (whole exome analysis) used throughout this document refers to computer-based analysis of DNA sequence data using a virtual panel of HI-related genes. DNA sequence data can be obtained by either whole exome sequencing (WES) or whole genome sequencing (WGS), typically using massively parallel next generation sequencing (NGS) methodology. The process used by the laboratory should include a method of identifying copy number variants (CNVs) for HI genes. Although WGS is considered the gold standard for testing, it is not currently widely available in Australia. The request for funding therefore allows for use of either a WES or WGS approach and subsequent analysis of the sequence data using a virtual hearing loss gene panel, including CNV analysis.

5. Prerequisites to implementation of any funding advice

Children identified as having bilateral isolated HI identified by neonatal hearing screening or subsequent audiology testing later in childhood, with a suspected genetic cause receive a genetic test to determine if they have P/LP variants in the *GJB2/GJB6* genes that encode connexin 26 and connexin 30, respectively. P/LP variants in the *GJB2/GJB6* genes are the most common cause of non-syndromic isolated HI in Australia. To be eligible for virtual gene panel-based WEA, the child with bilateral isolated HI must have received a non-diagnostic *GJB2/GJB6* genetic test result.

GJB2/GJB6 genetic testing is not available on the MBS. Currently, *GJB2/GJB6* genetic testing is funded by individual Australian states and territories. It is unclear whether there is currently equity of access to this genetic test across Australia. The Department of Health and Aged Care has requested that the cost of funding *GJB2/GJB6* testing via the MBS is examined as part of the MSAC 1680 assessment report.

6. Proposal for public funding

There are six MBS items proposed for MBS funding (singleton testing; trio testing; re-analysis; cascade testing of biological relatives; reproductive partner testing; *GJB2/GJB6* testing). Five items were proposed by the applicant and the sixth by the Department.

The proposed MBS item fees for the first five items associated with MSAC 1680 are based on equivalent MBS items supported by MSAC for testing of childhood monogenic syndromes (MSAC Application 1476). PASC recommended that the minimum gene list used for virtual panel testing should include the HI genes that are clinically validated as having confirmed gene-disease associations (“green genes”) on PanelApp Australia or PanelApp UK. The MSAC Executive has advised that virtual panel testing fees should be aligned with comparable services previously supported by MSAC, and that the proposed fees should be justified in the assessment report. The proposed MBS item descriptions, as ratified by PASC, are detailed in Table 2. The fees associated with the items, as described in the ratified PICO, have been changed in this document to reflect the fees associated with other similar MBS items, and to account for the Greatest Permissible Gap (as at November 2021).

The sixth item was proposed by the Department to remove the need for patients to move between public (states/territories funded) and private (MBS funded) streams, as a non-diagnostic *GJB2/GJB6* genetic test is proposed as a prerequisite for WEA eligibility.

Table 2 Proposed MBS items, as ratified by PASC

Proposed MBS items
MBS item number: AAAA1 Characterisation, via whole exome or genome sequencing and copy number variant analysis, of germline variants known to cause childhood hearing loss, if: (a) the characterisation is (i) requested by a consultant physician practising as a clinical geneticist; or (ii) requested by a consultant physician practising as a specialist paediatrician with expertise in genetics; or (iii) requested by a consultant physician practising as a specialist paediatrician, following consultation with a clinical geneticist; and (b) the patient is aged 17 years or younger with congenital or childhood onset hearing loss that is permanent bilateral moderate, severe, or profound (>40 dB in the worst ear over three frequencies) and classified as non-syndromic sensorineural, auditory neuropathy or mixed; and (c) the characterisation is performed following completion of a service described in item DDDDD, for which the results were non-informative; and (d) the patient is not eligible for a service to which items 73358 or 73359 apply; (e) the characterisation is not performed in conjunction with or following a service to which MBS item AAAA2 applies Applicable once per lifetime. MBS Fee: $2,195 *(Note – fee for singleton testing in Item 73358 from Application 1476 is $2100)* Benefit: 75% = $1,646.25 85% = $2,107.10 MBS Fee: $2,100.00[a] Benefit: 75% = $1,575.00 85% =$2,012.10 Practice Notes Appropriate genetic counselling should be provided to the patient either by the specialist treating practitioner, a genetic counselling service or a clinical geneticist (PN.0.23)
MBS item number: AAAA2 Characterisation, via whole exome or genome sequencing and copy number variant analysis, of germline variants known to cause childhood hearing loss, if: (a) the characterisation is (i) requested by a consultant physician practising as a clinical geneticist; or (ii) requested by a consultant physician practising as a specialist paediatrician with expertise in genetics; or (iii) requested by a consultant physician practising as a specialist paediatrician, following consultation with a clinical geneticist; and a specialist paediatrician; and (b) the patient is aged younger than 17 years or younger with congenital or childhood onset non-syndromic hearing loss that is permanent bilateral moderate, severe, or profound (>40 dB in the worst ear over three frequencies) and classified as sensorineural, auditory neuropathy or mixed; and (c) the characterisation is performed following completion of a service described in item DDDDD, for which the results were non-informative; and (d) the characterisation is performed using a sample from the patient and a sample from each of the patient's biological parents; and (e) the patient is not eligible for a service to which items 73358 or 73359 apply; (f) the characterisation is not performed in conjunction with or following a service to which MBS item AAAA1 applies. Applicable once per lifetime. MBS Fee: $2,900.00[b] Benefit: 75% = $2,175.00 85% = $2,812.10

Proposed MBS items

Practice Notes

Appropriate genetic counselling should be provided to the biological parents and child either by the specialist treating practitioner, a genetic counselling service or a clinical geneticist (PN.0.23)

MBS item number: BBBBB

Re-analysis of whole exome or genome data obtained under a service to which item AAAA1 and AAAA2 apply, for characterisation of previously unreported germline gene variants for childhood hearing loss, if

(a) the re-analysis is

(i) requested by a consultant physician practising as a clinical geneticist; or

(ii) requested by a consultant physician practising as a specialist paediatrician with expertise in genetics; or

(iii) requested by a consultant physician practising as a specialist paediatrician, following consultation with a clinical geneticist; and

(b) The re-analysis is performed at least 18 months after

(i) a service to which items AAAA1 or AAAA2 applies; or

(ii) a service to which this item applies

Applicable twice per lifetime

MBS Fee: $500.00[c]

Benefit: 75% = $375.00 85% = $425.00

Practice Notes

Appropriate genetic counselling should be provided to the patient either by the specialist treating practitioner, a genetic counselling service or a clinical geneticist (PN.0.23)

MBS item number: CCCC1

Characterisation of one or more familial pathogenic or likely pathogenic germline gene variants known to cause childhood hearing loss, if:

(a)The characterisation is

(i) requested by a consultant physician practising as a clinical geneticist; or

(ii)requested by a consultant physician practising as a specialist paediatrician with expertise in genetics; or

(iii)requested by a consultant physician practising as a specialist paediatrician, following consultation with a clinical geneticist; and

(b) the person tested is a biological relative of a patient with a pathogenic or likely pathogenic germline gene variant(s) known to cause hearing loss confirmed by laboratory findings; and

(c) the result of the previous proband testing is made available to the laboratory.

Applicable only once per variant per lifetime.

MBS Fee: $400.00[d]

Benefit: 75% = $300.00 85% = $340.00

Practice Notes

Appropriate genetic counselling should be provided to the patient either by the specialist treating practitioner, a genetic counselling service or a clinical geneticist (PN.0.23)

MBS item number: CCCC2

Characterisation of all germline variants in one or more genes known to cause hearing loss for the reproductive partner of an individual with a causative pathogenic or likely pathogenic variant for hearing loss identified in the same recessive gene(s), if

(a)The characterisation is

(i) requested by a consultant physician practising as a clinical geneticist; or

(ii); requested by a consultant physician practising as a specialist paediatrician, following consultation with a clinical geneticist; and

((b) the characterisation is for a reproductive partner of a patient with a pathogenic or likely pathogenic germline recessive gene variant(s) known to cause hearing loss confirmed by laboratory finding, and

Proposed MBS items
(c) the result of the previous proband testing is made available to the laboratory. Applicable only once per gene per lifetime. MBS Fee: $1,200.00[e] (Note – based on MBS item number 73394) Benefit: 75% = $900.00 85% = $1,112.10 Practice Notes Appropriate genetic counselling should be provided to the patient either by the specialist treating practitioner, a genetic counselling service or a clinical geneticist (PN.0.23)
MBS item: DDDDD Characterisation of germline gene variants in the *GJB2* and *GJB6* genes, if: (a) The characterisation is (i) requested by a consultant physician practising as a clinical geneticist; or (ii) requested by a consultant physician practising as a specialist paediatrician with expertise in genetics; or (iii) requested by a consultant physician practising as a specialist paediatrician, following consultation with a clinical geneticist; or (iv) requested by a consultant physician practising as an otolaryngologist; (b) the patient is aged 17 years or younger with congenital or childhood onset bilateral hearing loss. Applicable only once per lifetime. MBS Fee: $607,90[f] Benefit: 75% = $455,95 85% = $520.00 Practice Notes Appropriate genetic counselling should be provided to the patient either by the specialist treating practitioner, a genetic counselling service or a clinical geneticist (PN.0.23)

dB = decibels; MBS = Medical Benefits Scheme; MSAC = Medical Services Advisory Committee

[a] This is aligned with the fee for similar MBS Item 73358 from Application 1476. The applicant had considered the fee for singleton testing $2,100.00 would be appropriate, as proposed by the Department, rather than the proposed fee of $2,195.00 (see Ratified PICO, p36).

[b] The fee for trio testing in item 73359 from Application 1476.

[C] The fee proposed by the applicant ($425) was aligned with the similar fee for item 73360 from Application 1476 ($500).

[d] The fee proposed was comparable to item 73362 from Application 1476.

[e] The fee proposed was comparable to item 73362 from Application 1599.

[f] This fee is based on the *GJB2/GJB6* diagnostic testing fee ($520) charged by Victorian Clinical Genetic Services for non-Victorian residents.

7. Population

The intended population for the proposed items is based around children <18 years with congenital or childhood-onset hearing impairment, their parents, and reproductive partners of individuals with a P/LP variant. The first three populations use the WEA test, Population 4 uses variant specific testing, and Population 5 uses Sanger sequencing of one or more relevant genes, whilst Population 6 is for *GJB2/GJB6* testing only. In populations 1 through 5, WEA is an additional test. The test for Population 6 represents a cost shift away from the States and Territories to the MBS. The populations, as described in the ratified PICO document, are detailed in Table 3

Population 1 includes the affected child only, with bilateral HI who has tested negative on *GJB2/GJB6* testing (singleton population), whilst Population 2 includes the affected child and their biological parents simultaneously (trio testing population). Population 3 comprises affected children from population 1 who did not receive a positive genetic diagnosis, and for whom further testing may reveal variants newly associated with HI (re-analysis population). Population 4 includes biological relatives of an individual with a P/LP HI variant (cascade population) and Population 5 is the reproductive partner of an individual with a recessive P/LP HI variant

(identified in previous testing). Population 6 is the population for *GJB2/GJB6* testing, and comprises people with congenital or childhood-onset permanent bilateral hearing impairment confirmed by audiology testing.

Table 3: Description of populations included in the assessment, as detailed in the ratified PICO document

Population	Description
Population 1	Children (<18 years) with permanent bilateral moderate, severe or, profound (>40 dB in the worst ear over three frequencies) sensorineural, auditory neuropathy or mixed isolated hearing loss and a non-diagnostic *GJB2/GJB6* gene test result. Child should not meet the criteria for testing under MBS item 73358 or 73359.
Population 2	A child (<18 years) and biological parents of a child with permanent bilateral moderate, severe or, profound (>40dB in the worst ear over three frequencies) sensorineural, auditory neuropathy or mixed isolated HI and a non-diagnostic *GJB2/GJB6* gene test result. The child should not meet the criteria for testing under MBS item 73358 or 73359.
Population 3	A child (<18 years) and biological parents of a child with permanent bilateral moderate, severe or, profound (>40 dB in the worst ear over three frequencies) sensorineural, auditory neuropathy or mixed isolated HI and a non-diagnostic *GJB2/GJB6* gene test result. The result of the initial germline gene variant analysis should be at least 18 months prior and should be non-diagnostic for a pathogenic or likely pathogenic gene variant of hearing loss for the individual. Child should not meet the criteria for testing under MBS item 73358 or 73359.
Population 4	Biological relative[a] of an individual with a confirmed pathogenic or likely pathogenic variant for hearing loss.
Population 5	Reproductive partner of an individual with a confirmed recessive pathogenic or likely pathogenic variant for hearing loss.
Population 6	Child (<18 years) with congenital or childhood-onset permanent bilateral hearing loss confirmed by audiology testing

dB = decibels; *GJB2/GJB6* = connexin 26 and connexin 30 genes

[a] The intention is that it will predominantly be first-degree relatives tested, but has not been restricted, so that if a first-degree relative is not available or refuses testing, another biological relative may be tested at the clinician's discretion.

8. Comparator

The comparator for Populations 1 through 5 is no virtual gene panel-based analysis. A description of the comparators from the ratified PICO documents can be found in Table 4. Testing in Population 6 represents a cost-shift from the States and Territories to the MBS; thus the comparator is testing without using an MBS item.

Table 4 Description of comparators for each population included in the assessment, as detailed in the ratified PICO document

Population	Description of the comparator
Population 1	No virtual gene panel-based analysis of whole exome/genome data including CNV analysis (prior tests alone, i.e. Clinical assessment and family history including audiology testing)
Population 2	No virtual gene panel-based analysis of whole exome/genome data including CNV analysis (prior tests alone, i.e. Clinical assessment and family history including audiology testing; *GJB2/GJB6* (connexin 26/30) gene testing for affected child only)
Population 3	No re-analysis of WES or WGS data
Population 4	No cascade genetic testing
Population 5	No reproductive partner genetic testing
Population 6	Testing for common *GJB2/GJB6* gene variants (connexin 26/30) without using an MBS item (state/territory funding only)

CNV = copy number variants; *GJB2/GJB6* = Connexin 26 and connexion 30 genes; MBS = Medical Benefits Scheme; WES = whole exome sequencing; WGS = whole genome sequencing

9. Summary of public consultation input

Consultation input was received from twelve (12) organisations, all of whom were supportive of the application: Australian Genomics, Australasian Newborn Hearing Screening Committee (ANHSC), Australian Pathology (AP), Aurora School, Centre for Genetics Education NSW Health, Deafness Foundation (DF), Genetic Undiagnosed and Rare Disease (GUARD) Collaborative Australia, the Human Genetics Society of Australasia (HGSA) including its Ethics and Social Issues Committee, Neurodevelopmental and Behavioural Paediatric Society of Australasia (NBPSA), Public Pathology Australia (PPA), the Royal College of Pathologists of Australasia (RCPA), and UsherKids Australia.

Advantages of the test stated in the feedback received were:

- Genomic testing has better diagnostic yield than current standard of care (*GJB2/GJB6* only), allowing for an understanding of the genetic cause of hearing loss, and more tailored care.
- Earlier detection and targeted treatment would mainly lead to avoiding other tests and surveillance strategies, including MRIs, which may reduce costs to the public purse.
- The main value of a genetic diagnosis is release from investigations. A genetic diagnosis may end or avoid the diagnostic odyssey, streamline ongoing care and interventions, predict the severity of hearing loss and future health problems (prognosis), and with interventions provide better quality of life. It may in future provide appropriate access to precision therapies currently in development. Whether it could result in earlier cochlear implants is unclear.
- Value of knowing or personal utility: genomic testing can empower families and provide sovereignty in one's life, and give relief to parents even if no genetic cause is identified. It may reduce the anxiety felt by parents told to 'watchfully wait' to see if their child develops signs of an evolving syndrome.
- Early diagnosis and intervention may also have non-health benefits such as improving educational attainment, maximising language development and developmental potential, improving education, employment, and social connection.
- It would support reproductive decision-making, and whether the condition is likely to recur within families, which may be cost saving to the parents and health system. It enables families to be fully informed.
- Public funding would increase equity of access to testing, including geographically, and in doing so align with Australia's National Health Genomics Policy Framework 2018-2021.

Disadvantages of the test stated in the feedback received were:

- The clinical effectiveness outcomes do not include any change in management or access to precision therapies.
- A positive result through genetic testing may not be found even where there is a genetic cause, due to the many possible genetic causes, not all of which are known.
- VUSs can sometimes be clarified by segregation testing of the parents. This could be included in CCCC1 by replacing P/LP with 'potentially causative'.
- Consideration should be made of First Nations peoples, including underrepresentation in genomic databases, and provisions for material and data sovereignty.
- A parent may receive unwanted information, though this risk could be part of consent. Biological parental lineage and custodial parent roles may be re-defined, causing stress.
- The cost of WEA will be high unless larger volumes of testing occur.
- Restricting requestors may not lead to nil leakage, and may depend on appropriate training.
- Testing >100 genes inevitably raises genetic counselling issues.

- Access to counsellors can be limited and is not always feasible. Low uptake (60% in a research cohort) could indicate need for improved counselling.
- Restricting counselling to specialists with expertise in deafness and genetic counselling training is unworkable and would limit access and increase the cost to patients. Requestors should be a paediatrician or clinical geneticist, and genetic counselling funded separately.
- The test outcome may have implications for risk-rated insurance.

Other information provided in the consultation feedback was:

- It is important to take into consideration the Deaf community and their views on this testing.
- Parents would have a choice, and some families would choose not to pursue testing.
- The role of the *GJB6* coding sequence in deafness has been refuted: rather, it is deletions in the upstream regulatory region that are critical (see ClinGen[6]).
- If it is integrated as standard of care following newborn hearing screening, it could further improve outcomes of the hearing test in an equitable way.
- Genetic counselling should be provided pre-test and following the test result.
- NGS testing has been the standard of care overseas for many years.
- CNV analysis should only be mandatory for genes where it is a proven mechanism. Whether CNV analysis is feasible to do from accredited WES should be determined.
- This testing is complex and would require supervision by a genetic pathologist.
- Some of the children with a more complex genetic syndrome, including those detected through newborn hearing screening, may be eligible for items 73358/9.
- Deafness could be added as a criterion to 73358/9 rather than making new items.
- A separate Mendeliome item could be created to analyse 4000-6000 genes.
- It is not clear why the age limit for this testing is different to the 10 years in 73358/9.
- *GJB2/GJB6* testing is not MBS funded but is assumed to be freely available – 'no genetic testing' may be a more appropriate comparator.
- If WES requires a negative *GJB2/GJB6* sequencing result, then there should be a separate MBS item for this, to avoid out of pocket costs to patients and impeding access to WES.
- The fees should be aligned with equivalent items already on the MBS, however genetic testing is becoming cheaper.
- The setting for the proposed service should be a laboratory.

10. Characteristics of the evidence base

Included studies were retrospective or prospective cohorts, cross-sectional studies or case series (case reports of one or two cases were excluded) (Table 5). There were no comparative studies comparing WEA with *GJB2/GJB6* testing alone in the populations of interest, and the evidence was therefore level III-3 or IV according to NHMRC levels of evidence. Populations ranged in size from four families who underwent trio WEA, to 53,711 children with sensorineural hearing loss (SNHL) in a United States database.

The majority of evidence was identified for Population 1, for which articles were identified for three steps of linked evidence.

[6] ClinGen: https://search.clinicalgenome.org/kb/gene-validity/CGGV:assertion_f281869c-25e5-44ad-94e7-c7d6374755fd-2018-09-10T180132.444Z

Case series and cohort studies reporting on test accuracy (yield) were assessed using a modified version of the QUADAS 2 checklist for diagnostic accuracy studies, and the majority of studies were rated low or moderate for risk of bias. Change in management studies were assessed using an interventional NHLBI checklist and studies were rated low or moderate for risk of bias for Population 1. One study included for change in management evidence for Population 5 was rated high for risk of bias. Applicability to the population of interest was the most common domain of shortfall in both groups of studies. A negative *GJB2/GJB6* result was not always an inclusion criterion for studies, but if data could be separated for this result, they were considered for inclusion. The intervention across the studies varied by the number of genes assessed by WEA, the method used for gene curation, and whether or not CNV analysis was performed. Studies were considered for inclusion if these factors were consistent enough with the PICO criteria that the outcomes would not be impacted greatly by the differences.

A case series and several cross-sectional studies reporting non-health related outcomes were also assessed using the interventional NHLBI checklist and were rated low and moderate for risk of bias. The studies used questionnaires to determine the value of knowing (personal utility) of genetic testing to parents of children with HI.

Table 5 Key features of the included evidence

Population	Test results (diagnostic yield)	Change in management decisions	Non-health related outcomes[a]	Safety (psychological impact)
1. Children <18 years of age with congenital or child-hood onset isolated hearing loss (individual WEA)	n=609 k=14 retrospective cohorts ROB moderate-high	n=54931 k=5 retrospective cohorts ROB low-moderate	n=236 k=2 cross-sectional ROB low-moderate	n=395 k=3 1 cohort, 2 case series ROB low
2. Children <18 years of age with congenital or child-hood onset isolated hearing loss or their parents (trio WEA)	n=166 k=2 case series ROB moderate	0	0	
3. Children with isolated hearing loss with a non-diagnostic WEA result (whole exome virtual panel re-analysis)	n=210 k=1 retrospective cohort ROB high	0	0	
4. Biological relatives of an individual with a P/LP HI variant (cascade testing)	n=10 families (22 relatives tested) k=2 case series ROB moderate-high	0	0	
5. Reproductive partner of an individual with a recessive P/LP HI variant (individual gene sequencing)	0	n=29 couples k=1 cross-sectional ROB high	0	

GJB2/GJB6 = Connexin 26 and connexion 30 genes; NA = not applicable; ROB = risk of bias; WEA = whole exome analysis

a. No evidence for health-related outcomes was identified

11. Comparative safety

POPULATIONS 1 to 5

There was no evidence for safety comparisons between children with HI who undergo WEA and those who receive *GJB2/GJB6* testing alone. Both the proposed and prior tests are performed on peripheral blood or other easily obtained DNA source such as buccal cells and sampling does not provide any serious risk to the individual. DNA prepared from either source would be expected to provide the same diagnostic yield when tested. However some evidence suggests that it is harder to get a sufficiently large DNA sample from a buccal cell swab, than from a blood sample[7]. All studies included from the literature that provided diagnostic yield data, used peripheral blood as the DNA source.

Psychological impact of genetic testing was the only safety outcome identified in the literature. One study measured the psychological impact in parents of children offered WEA for HI (Population 1). The parents who chose WEA for their child were asked to decide between receiving different levels of analysis on the results. Parents who chose to receive diagnostic analysis only (without additional analysis of childhood-onset illness with or without medical actionability) were more likely to be anxious and have decisional conflict than those who chose to receive additional analysis. There was a similar trend for intolerance of certainty and decisional regret, but these outcomes did not reach statistical significance.

There was some evidence on the psychological impact of genetic testing in parents of children with HI who underwent *GJB2/GJB6* testing. Data on anxiety levels were inconsistent across two studies. Parents of children testing positive for a P/LP variant showed a decrease in anxiety at 6 months after testing, but an increase in anxiety at 6 weeks post-test in different studies. Parents of children testing negative or inconclusive had the opposite changes in anxiety. The inconsistencies make it difficult to draw any conclusion for this outcome.

Another outcome showing changes from baseline at post-test follow-ups was perceived personal control (PPC) or self-efficacy. Parents of children testing negative had a strong reduction of PPC at 6 weeks post-test, while parents of those testing positive experienced little change from baseline. The direction of results were similar in the two studies. In the second study the differences in self-efficacy between negative and positive groups at 6 weeks post-test were statistically significant, but changes from baseline in both groups were not significant.

The same two studies found that post-test changes in depression from baseline were not statistically significant in either positive or negative groups.

There are some limitations on the application of these outcomes to the population of interest in this DCAR, however many aspects of genetic testing for children are similar regardless of the reason for testing. In the case of genetic testing for HI, when parents are offered genetic testing for their child, psychological impact tends to be more negative for those receiving a non-diagnostic than for those receiving a diagnostic result. The decision about testing is a source of conflict for some parents. Results are summarised in Table 6.

[7] Trost, B, Walker, S, Haider, SA, et al. 2019, 'Impact of DNA source on genetic variant detection from human whole-genome sequencing data', *Journal of Medical Genetics*, **56**(12): 809.

Table 6 Summary of psychological impact of *GJB2/GJB6* or WEA testing for HI

Outcome K studies	Results	Reliability/Applicability
Change in psychological factors on receiving *GJB2* test results		
Anxiety N=289 K=2	Inconsistent direction in changes in anxiety from baseline to 6 weeks or 6 months post-test for groups testing negative and positive for *GJB2* variants in two studies. It is possible that increased anxiety at 6 weeks declines by 6 months after testing for those testing positive, and the reverse happens for those testing negative.	Low level evidence and insufficient power in the studies to make strong conclusions Results are likely to be transferrable to WEA
Depression N=289 K=2	The changes in depression from baseline to post-test were not statistically significant for either negative or positive groups who tested for *GJB2* in two studies.	Low level evidence and Insufficient power in the studies to make strong conclusions Results are likely to be transferrable to WEA
PPC, self-efficacy N=289 K=2	The negative testing group in one study showed a decrease in PPC compared to the positive group at 6 months post-test compared to baseline. In a second study changes from baseline were not significant but at 6 weeks post-test there were statistically significant differences between the two groups, with those testing positive having higher self-efficacy.	Low level evidence and insufficient power in the studies to make strong conclusions Results are likely to be transferrable to WEA
Psychological impact of choosing either diagnostic only (A) or extended analyses (B and C) of WEA results		
Anxiety N=106 K=1	There was statistically significant greater level of anxiety in those choosing diagnostic analysis only compared to those who chose extended analyses.	Low level evidence and insufficient power in the studies to make strong conclusions Results applicable to WEA
Decisional conflict N=106 K=1	Decisional conflict was greater in group A when compared to groups B and C combined	Low level evidence and insufficient power in the study to make strong conclusions Results applicable to WEA
Decision regret N=106 K=1	No significant differences between groups	Low level evidence and insufficient power in the study to make strong conclusions Results applicable to WEA
Intolerance of uncertainty N=106 K=1	No significant differences between groups	Low level evidence and insufficient power in the study to make strong conclusions Results applicable to WEA

GJB2/GJB6 = Connexin 26 and connexin 30 genes; HI = hearing impairment; PPC = perceived personal control; WEA = whole exome analysis

12. Effectiveness

A linked evidence approach was taken to show the effectiveness of WEA for children with HI, as no direct evidence was identified.

POPULATION 1: Children <18 years of age with congenital or child-hood onset isolated hearing impairment (individual WEA)

Results for Population 1 are summarised in Table 7. There was no comparative evidence for *GJB2/GJB6* plus WEA versus *GJB2/GJB6* testing alone. Studies that reported on the yield of WEA for HI either conducted WEA in a population that tested negative for *GJB2/GJB6,* or reported on the *GJB2/GJB6* variant frequency. An incremental increase in diagnostic yield for WEA of 24.8% to 47.5% was reported (when between 120 and 190 genes were analysed). The yield varied partly according to the gene panel size analysed, and also by the level of selection for HI of the tested population (for example the extent of exclusion of syndromic cases), its ethnicity, and test methodology (for example if CNV analysis was performed).

One Australian study found that WEA resulted in management changes in approximately 50% of those tested when *GJB2/GJB6* was included in the WEA gene panel. Of 59 genetic diagnoses, there were 16 due to a non-syndromic HI variant (16/59 diagnoses, 27.1%). Children diagnosed with syndromic HI went on to other diagnostic or treatment pathways (16/59 diagnoses, 27.1%). The most common management change in the children with a genetic diagnosis was discharge from further testing. There was no change in management for 49.1% of 106 cases (5 syndromic diagnoses, and 47 cases testing negative).

There were no health outcomes identified or assessed for WEA for HI. The literature suggests that in the near future, genetic testing may indicate which children will not benefit from a cochlear implant (CI), however there is not sufficient evidence for this outcome as yet. Assessment of the non-health related outcome value of knowing showed that parents valued maximising their child's health and planning for their future. About a third of parents chose to receive diagnostic results only from WEA when given the option, rather than extended analysis of either actionable or non-actionable health outcome results from WEA.

When all linked evidence for Population 1 is considered, there is insufficient evidence for health benefits despite incremental diagnostic yield from WEA. Benefits to families identified are the chance of being discharged from further diagnostic testing, and the value of knowing, which may give certainty and the opportunity to plan for their child's future.

Table 7 Summary of linked evidence for effectiveness of singleton WEA in Population 1

Linked evidence step	Outcome	Results	Interpretation	Reliability/ Applicability
Test accuracy	Incremental diagnostic yield	24.8% to 47.5% with a diagnostic result	An additional 24.8% to 47.5% received a genetic diagnosis using WEA compared to *GJB2/6* testing alone	Moderate reliability High applicability
Change in management	Management changes following WEA	35.8% discharged from further testing 15.1% entered a different management pathway 49.1% no change in management	There were changes in management pathways for approximately 50% of those tested, mostly for those who received a genetic diagnosis	Moderate reliability High applicability
	Factors associated with receiving genetic testing for HI	Patient factors: younger age, more recent diagnosis Clinical factors: geneticist or otolaryngologist consultation Socioeconomic factors: insurance; higher income; White, Asian or Hispanic ethnicity	There were varied patient, clinical and socioeconomic factors associated with receiving or not receiving testing	Moderate reliability Moderate applicability
Non-health related outcomes	Value of knowing (pre and post-test personal utility)	*Pre-test values* Parents hope: to find a cause, enable future planning, learn what to expect for child's future Parents value: medical advances, maximising child's health, contributing to research Reasons for testing: find cause for child's HI, learn recurrence chance *Post-test values* Understanding of their child's HI was greater in positive versus negative groups	*Pre-test* Parents had valid hopes and reasons for undergoing testing *Post-test* Value of knowing for parents of children testing positive was greater than that for those of negative testing children	Low reliability Moderate applicability

GJB2/6 = connexin 26 and connexin 30 genes; HI = hearing impairment; WEA = whole exome analysis

POPULATION 2: Children <18 years of age with congenital or child-hood onset isolated hearing impairment and their biological parents (trio WEA)

Linked evidence results for Population 2 are summarised in Table 8. There was no comparative evidence for *GJB2/GJB6* plus trio WEA versus *GJB2/GJB6* testing alone. Studies that reported on the yield of trio WEA for HI were not well aligned with the PICO criteria and did not provide sufficient evidence of incremental increase in diagnostic yield. There was no evidence from other steps of linked evidence identified in the literature for Population 2.

Table 8 Summary of linked evidence for effectiveness of trio WEA in Population 2

Linked evidence step	Outcome	Results	Interpretation	Reliability/ Applicability
Test accuracy	Diagnostic yield	Diagnostic yield from two studies reported as 29% and 47.9%	Insufficient data to support incremental increase in diagnostic yield for trio WEA compared to individual WEA or *GJB2/6* testing alone	Moderate reliability Low applicability

GJB2/6 = connexin 26 and connexin 30 genes; WEA = whole exome analysis

POPULATION 3: Children with isolated hearing loss with a non-diagnostic WEA result (whole exome virtual panel re-analysis)

Linked evidence results for Population 3 are summarised in Table 9. No studies from the literature search met the inclusion criteria. One study performed re-analysis by targeted panel sequencing with NGS, rather than WEA. The number of genes analysed on each panel was 81 or 127. The diagnostic yield for children with congenital and prelingual HI increased from 39% to 43% by re-analysis. CNV analysis was included at the time of the original genetic testing and during re-analysis for individuals without a causative single nucleotide variant (SNV) identified. The time interval to re-analysis was not provided. There was no evidence for other steps of the linked evidence. Although in this case the study design enabled retesting of individuals who had already received a genetic diagnosis, this is not expected to occur in current clinical practice. MSAC may like to consider revising item descriptor for Population 3 (Item BBBBB), as it is not explicit about excluding individuals from testing who have already received a genetic diagnosis.

Table 9 Summary of linked evidence for effectiveness of WEA (re-analysis) in Population 3

Linked evidence step	Outcome	Results	Interpretation	Reliability/ Applicability
Test accuracy	Diagnostic yield	Diagnostic yields of 39% and 43% for gene panels of 81 and 127 genes respectively, targeted panel with NGS	An additional 9 individuals (4%) received a genetic diagnosis by re-analysis, and 1 individual had a diagnosis revoked by re-analysis (0.5%)	Moderate reliability Low applicability

NGS = next generation sequencing; WEA = whole exome analysis

POPULATION 4: Biological relatives of an individual with a P/LP HI variant (cascade testing)

Linked evidence results for Population 4 are summarised in Table 10.

Two studies provided data on 10 families in whom 12 probands tested positive for a HI variant. Twenty-two relatives of the probands underwent cascade testing by variant-specific testing and 19 (86.4%) were confirmed to have the variant. It was not possible to make strong conclusions from this small amount of data.

Table 10 Summary of linked evidence for effectiveness of cascade testing following WEA in Population 4

Linked evidence step	Outcome	Results	Interpretation	Reliability/ Applicability
Test accuracy	Diagnostic yield	In 10 families, 12 probands tested positive for a HI variant, 22 relatives underwent cascade testing by Sanger sequencing and 19 (86.4%) were confirmed to have the variant.	2.2 relatives per family HI variant positive proband underwent cascade testing, and 86.4% of relatives tested positive for the variant.	Moderate reliability Moderate applicability

HI = hearing impairment; WEA = whole exome analysis

POPULATION 5: Reproductive partner of an individual with a recessive P/LP HI variant (individual gene sequencing)

There was no evidence for diagnostic yield identified in Population 5.

Pregnant couples with and without family history of HI offered genetic testing for HI make different choices about follow-up testing. In a study of 29 couples pregnant or planning pregnancy, further testing was avoided in 18 couples (and their fetuses) for whom one or both partners tested negative. Of five couples testing positive, four proceeded to have their fetus tested, three of whom were found to be carriers and one tested negative. The pregnancy of the fifth couple was too advanced to proceed with prenatal testing[8]. Results are summarised in Table 11.

Table 11 Summary of linked evidence for effectiveness of reproductive partner testing following WEA in Population 5

Linked evidence step	Outcome	Results	Interpretation	Reliability/ Applicability
Change in management	Management changes following WEA	18 couples for whom 1 or more partner or fetus tested negative: no further testing 5 couples for whom one or more partner tested positive: 4 had fetus tested, none were homozygous for HI variants 1 couple with advanced pregnancy: did not undergo testing	The choice to have testing and follow-up testing for their fetus depends on test results of pregnant couples, history of HI, and degree of advancement in pregnancy.	Moderate reliability High applicability

HI = hearing impairment; WEA = whole exome analysis

POPULATION 6: Children < 18 years of age with congenital or childhood-onset permanent bilateral hearing loss confirmed by audiology testing

PASC noted that diagnostic yield was required for this population, but not other effectiveness data, as *GJB2/GJB6* testing is already an established practice in Australia. Evidence from the literature review was not considered for the outcome of diagnostic yield, as Downie 2020[9] was thought to give the best estimate of prevalence of P/LP *GJB2* and *GJB6* variants in Australia amongst those with moderate to profound syndromic or non-syndromic HI. The study reported a

[8] Antoniadi, T, Pampanos, A & Petersen, MB 2001, 'Prenatal diagnosis of prelingual deafness: carrier testing and prenatal diagnosis of the common GJB2 35delG mutation', *Prenat Diagn*, **21**(1).

[9] Downie, L, Halliday, J, Burt, R, et al. 2020, 'Exome sequencing in infants with congenital hearing impairment: a population-based cohort study', *European Journal of Human Genetics*, **28**(5).

yield of 20.8% (22/106 tested) *GJB2* variants in infants with moderate to profound hearing loss in Australia. Genetic testing was conducted by WES and chromosome microarray analysis. The study population was a 2-year cohort of infants who failed newborn hearing screening, excluding those with mild, unilateral, or conductive HI. One (0.9%) of the 22 infants testing positive for a *GJB2* variant was diagnosed with syndromic HI due to the presence of other symptoms, and the remaining 21 patients (19.8%) were diagnosed with non-syndromic HI, with one patient heterozygous for both *GJB2* and *GJB6* variants (0.9%).

Clinical claim

Population 1

The use of whole exome analysis results in **superior diagnostic yield** compared with *GJB2/GJB6* testing alone for children <18 years of age with congenital or child-hood onset isolated hearing impairment or their parents.

There was insufficient evidence for change in health outcomes resulting from WEA to support this superiority claim. Changes in management (predictive yield) were observed for children who received a positive genetic diagnosis, mostly for children who avoided further investigation. Potentially important changes in management for children diagnosed with syndromic HI were also observed, however the numbers of children reported were small. Whilst no evidence on health outcomes was available for participants receiving a change in management, it is expected that there will be more children who receive management changes from WEA compared to *GJB2/GJB6* testing, and that there will be likely non-health benefits for example, the value of knowing.

The use of whole exome analysis results in **non-inferior safety** compared with *GJB2/GJB6* testing alone in children <18 years of age with congenital or child-hood onset isolated hearing loss or their parents.

Populations 2 to 5

There was insufficient evidence to make effectiveness or safety conclusions about Populations 2 to 5. It should be noted that genetic information about HI may be important to some families for reproductive decision making.

Population 6

Population 6 was not considered in the literature review as testing of these individuals (*GJB2/GJB6* testing) is already an established practice in Australia, therefore no clinical claim was made.

13. Economic evaluation

Based on the clinical evidence that suggest a superior diagnostic yield for the use of WEA in comparison to *GJB2/GJB6* testing alone in the proposed population, a cost-effectiveness analysis (CEA) is presented to assess the cost per additional proband identified of the proposed WEA technology. The economic model performed in the assessment is a decision tree analysis to evaluate the listing of WEA in comparison to standard of care (SoC). As the eligibility criteria for the proposed WEA listing requires a non-diagnostic *GJB2/GJB6* test result, the model is structured to capture the cost impacts of *GJB2/GJB6* testing, which was proposed by the Department to analyse the impact of cost-shifting from states/territories funding to MBS funding. Therefore, the base case has two components: (i) the proposed WEA technology, and (ii)

GJB2/GJB6 genetic testing to determine the eligibility for WEA. A stepped analysis approach is chosen for the generation of the base case for both components.

In the base case for WEA, the first step includes the impact of WEA testing for the children (<18 years) with undiagnosed suspected hearing loss that previously had a non-diagnostic *GJB2/GJB6* test result, assuming a 15%:85% ratio of singleton and trio testing, respectively. Then the economic analysis is extended to include cascade testing for the first-degree relatives of the proband and then cascade testing of second-degree relatives. Finally, the impact of reproductive partner testing is included in the last step.

Similarly, the evaluation of *GJB2/GJB6* genetic testing is presented as a stepped analysis, starting with the children <18 years with hearing loss confirmed by audiology testing, The analysis includes a change from parent cascade testing (current SoC) to biological relative cascade testing, and the availability of reproductive partner testing in the following steps.

The economic base-case does not include the periodical re-analysis of whole exome or genome sequencing data for inconclusive WEA results or repeating WEA after 5 years, but the first re-analysis is included in the exploratory sensitivity analysis.

In addition to the base case, a scenario analysis explores the impact of no prior *GJB2/GJB6* genetic testing in the WEA arm, but analysing the *GJB2/GJB6* variants using proposed WEA technology.

Other scenario analyses include the use of only WEA singleton testing (with no trio testing) or only trio testing.

A summary of the economic evaluation is provided in Table 12.

Table 12 Summary of the economic evaluation

Component	Description
Perspective	Australian health care system perspective
Population	A. A child (<18 years) and biological parents of a child with permanent bilateral (moderate, severe or, profound) sensorineural, auditory neuropathy or mixed isolated HI and a non-diagnostic *GJB2/GJB6* gene test result (affected individuals with non-diagnostic *GJB2/GJB6* results) B. Biological relatives (might include second degree relatives) of proband with molecular diagnosis of HI C. Eligible reproductive partner of a proband identified with recessive P/LP variant for HI D. Child (<18 years) with congenital or childhood-onset permanent bilateral HI confirmed by audiology testing
Prior testing	Clinical assessment and family history including audiology testing, *GJB2/GJB6* (connexin 26/30) gene testing (for affected child only).
Intervention	A. Virtual gene panel-based exome/genome analysis for germline HI variants, including analysis of CNVs B. Cascade testing for a single P/LP variant C. Testing for all P/LP variants in a recessive gene(s) D. *GJB2/GJB6* testing using an MBS item
Comparator	A. Standard of care B-C. No genetic testing and SoC D. *GJB2/GJB6* testing without using an MBS item
Outcomes	Identification of P/LP variant to provide a definitive diagnosis in affected individuals, or the identification of a P/LP variant in cascade testing / reproductive partner testing for the purpose of informing reproductive planning.
Type(s) of analysis	Cost-effectiveness analysis
Time horizon	Time to diagnosis/treatment decision
Computational method	Decision tree analysis
Generation of the base case	Modelled for eligible children with HI who are determined by *GJB2/GJB6* genetic testing Step 1: Singleton or trio WEA testing for a child with HI without a *GJB2/GJB6* genetic cause Step 2a: Step 1 + Cascade testing of biological relatives (first-degree relatives) Step 2a: Step 2 + Cascade testing of second-degree relatives Step 3: Reproductive partner testing
Transition probabilities	Proportion of WEA singleton vs trio testing Diagnostic yield in affected cases Number of biological relatives/reproductive partners tested per proband Diagnostic yield in cascade testing of relatives/partners
Software	TreeAge Pro 2022

CNV = copy number variants, *GJB2/GJB6* = connexin 26 and connexin 30 genes, HI = hearing impairment, P/LP = pathogenic or likely pathogenic, SoC = standard of care, WEA = whole exome analysis

Key variables used in the model

Key variables used in the model are the diagnostic yields of the genetic tests: *GJB2/GJB6* and WEA, which determine the patient flow in the model. According to the definitive or inconclusive test results, the biological relatives of the proband enter the model for cascade testing or segregation analysis, whose reproductive partners might receive genetic testing for known variants in recessive genes, including *GJB2/GJB6*. Therefore, in addition to the diagnostic yield in affected individuals, the number of relatives tested and the probability of a pathogenic or likely pathogenic familial variant in cascade testing of biological relatives are the key variables. The

number of cascade tested biological relatives differs for singleton and trio testing, however is assumed to be equivalent once the parents that are captured by trio testing are accounted for. The costs of singleton and trio testing differ as the parents of the affected child are tested simultaneously with a trio test, and therefore the proportion of individuals receiving WEA singleton versus trio is important.

Assumptions used in the model

- The same diagnostic yield (of the affected individual population) input for WEA is used for both singleton and trio testing, and the yield assumed to be the same for both WES and WGS.
- The diagnostic yield for *GJB2/GJB6* is sourced from a clinical trial where the analysis was performed using the proposed WES (and microarray) rather than gene sequencing (standard practice in the absence of WEA).
- The consent for genetic test is assumed to represent the uptake rate of the proposed technology. In addition, if the individuals or the parents of the affected individuals have given consent for the initial *GJB2/GJB6* test, then they are all assumed to consent for the following WEA, if eligible.
- The costs of further investigations, including diagnostic odyssey, following a negative or inconclusive test results are assumed to be zero.

Results

The results for the two components of the base-case and the combined base-case is presented in Table 13.

Table 13 Results of the stepped analysis for the base case for singleton or trio WEA[a] and other proposed test items

Base case for WEA (100% uptake)	**WEA pathway**	**No WEA pathway**	**Increment**
Step 1 WEA testing for a child with HI without a *GJB2/GJB6* genetic cause			
Weighted average cost of singleton and trio WEA	$3,388	$520	$2,868
Definitive diagnosis	0.4405	0.0000	0.4405
Incremental cost per additional proband identified			**$6,511**
Step 2.a Step 1 + Cascade testing of first-degree relatives			
Cost	$3,617	$520	$3,097
Definitive diagnosis	1.6518	0.0000	1.6518
Incremental cost per additional proband and/or carrier identified			**$1,875**
Step 2.b Step 2a + Cascade testing of second-degree relatives			
Cost	$3,969	$520	$3,449
Definitive diagnosis	2.0923	0.0000	2.0923
Incremental cost per additional proband and/or carrier identified			**$1,649**
Step 3 Step 2b + Reproductive partner testing			
Cost	$4,181	$520	$3,661
Definitive diagnosis	2.0924	0.0000	2.0924
Incremental cost per additional proband and/or carrier identified			**$1,750**

Base case for *GJB2/GJB6* (100% uptake)	***GJB2/GJB6* using an MBS item**	***GJB2/GJB6* without using an MBS item**	**Increment**
Step 1 *GJB2/GJB6* genetic testing for a child with HI confirmed by audiology testing			
Cost	$608	$520	$88
Definitive diagnosis	0.2075	0.2075	0.0000
Incremental cost per additional proband identified			**Dominated**
Step 2.a Step 1 + Cascade testing of first-degree relatives			
Cost	$857	$661	$196
Definitive diagnosis	0.7783	0.6226	0.1557
Incremental cost per additional proband and/or carrier identified			**$1,258**
Step 2.b Step 2a + Cascade testing of second-degree relatives			
Cost	$1,023	$661	$362
Definitive diagnosis	0.9858	0.6226	0.3632
Incremental cost per additional proband and/or carrier identified			**$996**
Step 3 Step 2b + Reproductive partner testing			
Cost	$1,123	$661	$461
Definitive diagnosis	0.9859	0.6226	0.3633
Incremental cost per additional proband and/or carrier identified			**$1,270**
***TOTAL BASE CASE* (WEA and *GJB2/GJB2* combined) (68% consent to *GJB2/GJB6* testing)**			
Total costs	$2,687	$449	$2,237
Total definitive diagnosis	1.7966	0.4231	1.3735
Incremental cost per additional proband and/or carrier identified			**$1,629**

GJB2/GJB6 = connexin 26 and connexin 30 genes, HI = hearing impairment, SoC = standard of care, WEA = whole exome analysis
[a] WEA refers to virtual panel analysis of whole exome or whole genome data, including copy number variant analysis.

In the WEA base case, 100% of affected individuals enter the model having accepted WEA testing (the cost and implications of *GJB2/GJB6* testing are not included). In the *GJB2/GJB6* base case, 100% of affected individuals enter the model having accepted *GJB2/GJB6* testing (and the downstream effects of WEA testing are not included). In the Total Base Case, the costs and outcomes relate to the use of both *GJB2/GJB6* testing and WEA testing (if required), and also incorporates the consent rate for genetic testing.

Disaggregated and aggregated base-case results

Table 14 Disaggregated costs and outcomes for WEA[a] and other proposed test items for children with HI and cascade testing

	WEA[a] pathway	SoC[b] pathway	Increment
Cost of *GJB2/GJB6* testing	$413	$353	$60
Cost of WEA	$1,497	$0	$1,497
Cost of WEA re-analysis	$0	$0	$0
Cost of cascade testing of biological relatives	$595	$96	$499
Cost of testing reproductive partners	$182	$0	$182
Total costs	**$2,687**	**$449**	**$2,237**
Yield associated with testing of affected individuals	0.3782	0.1410	0.2372
Yield associated with testing of biological relatives	1.4183	0.2821	1.1362
Yield associated with testing of reproductive partners	0.0002	0.0000	0.0002
Total Yield	**1.7966**	**0.4231**	**1.3735**

HI = hearing impairment, SoC = standard of care, WEA = whole exome analysis
[a] WEA refers to virtual panel analysis of whole exome or whole genome data, including copy number variant analysis, and includes *GJB2/GJB6* genetic testing using an MBS item.
[b] Standard of care pathway refers to clinical investigations without WEA, including state/territory funded *GJB2/GJB6* for affected individuals and biological parents of the affected child.

Table 15 Results of the economic evaluation

	WEA[a] pathway	SoC[b] pathway	Increment
Total cost of WEA for affected individuals, biological relatives and reproductive partners	$2,687	$449	$2,237
Definitive diagnoses	1.7966	0.4231	1.3735
Incremental cost per additional proband and/or carrier identified			**$1,629**

HI = hearing impairment, SoC = standard of care, WEA = whole exome analysis
[a] WEA refers to virtual panel analysis of whole exome or whole genome data, including copy number variant analysis, and includes *GJB2/GJB6* genetic testing using an MBS item.
[b] Standard of care pathway refers to clinical investigations without WEA, including state/territory funded *GJB2/GJB6* for affected individuals and biological parents of the affected child.

Scenario analyses

Scenarios assuming 100% singleton testing, 100% trio testing, the use of WEA to identify *GJB2/GJB6* variants and testing of reproductive partners of probands or carriers with *GJB2/GJB6* using *GJB2/GJB6* MBS item rather than MBS item proposed for reproductive partner cascade testing have been presented below in Table 16.

Table 16 Scenario analyses of the proposed WEA[a] and other proposed testing for children with HI and cascade testing

	Scenario analysis	WEA[a] pathway	SoC[b] pathway	Increment
1	Base case assuming all affected individuals tested via WEA singleton testing			
	Total cost of singleton WEA for affected individuals, biological relatives and reproductive partners	$2,482	$449	$2,033
	Definitive diagnoses	1.7966	0.4231	1.3735
	Incremental cost per additional proband and/or carrier identified			**$1,480**
2	Base case assuming all affected individuals tested via WEA trio testing			
	Total cost of trio WEA for affected individuals, biological relatives and reproductive partners	$2,723	$449	$2,274
	Definitive diagnoses	1.7966	0.4231	1.3735
	Incremental cost per additional proband and/or carrier identified			**$1,655**
3	Base case assuming no prior *GJB2/GJB6* testing in WEA arm (i.e., *GJB2/GJB6* is analysed using WEA, assuming a 15%:85% ratio of singleton and trio testing, respectively)			
	Total cost of WEA for affected individuals, biological relatives and reproductive partners	$2,570	$449	$2,121
	Definitive diagnoses	1.7966	0.4231	1.3735
	Incremental cost per additional proband and/or carrier identified			**$1,544**
4	Reproductive partners of *GJB2/ GJB26* carriers use proposed *GJB2/ GJB6* MBS item			
	Total cost of WEA for affected individuals, biological relatives and partners	$2,653	$449	$2,204
	Definitive diagnoses	1.7966	0.4231	1.3735
	Incremental cost per additional proband and/or carrier identified			**$1,605**

GJB2/GJB6 = connexin 26 and connexin 30 genes, SoC = standard of care, WEA = whole exome analysis
[a] WEA refers to virtual panel analysis of whole exome or whole genome data, including copy number variant analysis, and includes *GJB2/GJB6* genetic testing using an MBS item.
[b] Standard of care pathway refers to clinical investigations without WEA, including state/territory funded *GJB2/GJB6* for affected individuals and biological parents of the affected child.

Compared with the base case (ICER = $1,629 per additional proband and or carrier identified), the use of 100% singleton testing is dominant, and the use of trio testing is dominated. This result occurs because the model applies no additional yield to trio testing, yet trio testing is more costly as it entails the testing of a proportion of parents when no P/LP variant has been detected in the affected individual. Trio testing may result in a higher yield in practice.

The use of WEA in place of *GJB2/GJB6* followed by WEA is reasonably equivalent in cost, and is expected to be similar in terms of yield. If there are time savings associated with using a single test (i.e. WEA) rather than sequential testing, using WEA may be preferable to *GJB2/GJB6*.

Table 17 Key drivers of the model

Description	Method/Value	Impact Base case: $1,629 per additional proband and/or carrier identified for HI
Cascade testing	The number of biological relatives captured by cascade testing in the base case (n=5 in the singleton WEA, and n=3 in trio WEA) is tested in sensitivity analyses. Reductions in the size of the cascade population increase the ICER.	*High, higher number of biological relatives tested favours the proposed technology.* *Cascade testing of two family members, rather than five in the base-case, increased the ICER to $2,506 per proband and/or carrier identified (an increase of 54%).*
Diagnostic yield of WEA	The lower and upper limit of diagnostic yield of WEA (25% to 50%) from clinical section is tested.	*High, lower limit of the diagnostic yield (25%) for WEA increased ICER by 42%, and a yield of 50% decreased the ICER by 8%.*

HI = hearing impairment; ICER = incremental cost-effectiveness ratio; *GJB2/GJB6* = connexin 26 and connexin 30 genes, WEA = whole exome analysis.

Sensitivity analyses

The key drivers of the model are diagnostic yield and the size of the cascade testing population. If the diagnostic yield decreases to 30% (the mean of the diagnostic yield range presented in clinical evidence), the ICER increases by 27%. If cascade testing of biological relatives is restricted to parents, the ICER increases by 54%.

The results of key univariate sensitivity analyses are summarised in Table 18.

Table 18 Sensitivity analyses of the proposed WEA[a] testing for children with HI and cascade testing

	Incremental cost	Incremental effect	ICER	% change
Base-case	**$2,237**	**1.3735**	**$1,629**	
Diagnostic yield for WEA assumptions based on range of 24.8% to 47.5% *(Base-case: 44% translated from Downie 2020)*				
25%	$2,053	0.8863	$2,316	42%
30%	$2,101	1.0142	$2,072	27%
50%	$2,295	1.5258	$1,504	−8%
Different diagnostic yield for WEA singleton and trio tests (assumption based on 9 VUS in cohort of 106 in Downie 2020) *(Base-case: 44% for both, translated from Downie 2020)*				
DY WEA singleton = 33% DY WEA trio = 44% (base-case)	$2,216	1.3324	$1,663	2%
Diagnostic yield of GJB2/GJB6 (Base-case: 20.8%, Source: Downie 2020)				
15%	$2,307	1.3869	$1,663	2%
22% (Kenneson 2002)[10]	$2,222	1.3707	$1,621	0%
25% (assumption)	$2,186	1.3637	$1,603	−2%
Increase in GJB2/GJB6 testing due to listing on MBS OR due to listing of WEA, assumption *(Base-case: 68%, uptake rate assumed to be same as consent rate for genetic testing) Source: Downie 2020*				
80%	$2,714	1.6922	$1,604	−2%
90%	$3,109	1.9566	$1,589	−2%
100%	$3,505	2.2210	$1,578	−3%

[10] Kenneson, A, Van Naarden Braun, K & Boyle, C 2002, *'GJB2* (connexin 26) variants and nonsyndromic sensorineural hearing loss: A HuGE review', *Genetics in Medicine*, **4**(4): 258-274.

	Incremental cost	Incremental effect	ICER	% change
Cost of proposed WEA singleton and trio tests (Base-case: WEA singleton test (AAAAA1): $2,100.00, WEA trio test (AAAAA2): $2,900.00)				
AAAAA1: $1,200.00, AAAAA2: $1,800.00	$1,661	1.3735	$1,209	-26%
Cost of proposed GJB2/GJB6 testing (Base-case: $607.90, Source VCGS, and the applicant)				
$300	$2,028	1.3735	$1,477	−9%
$400	$2,096	1.3735	$1,526	−6%
First re-analysis included in analysis (Base-case: No re-analysis included)				
Cost of re-analysis: $500	$2,365	1.3735	$1,722	6%
Cost of re-analysis: $425	$2,388	1.3735	$1,739	7%
Family Size (Base-case: four biological relatives, which includes two second degree relatives in addition to three first-degree relatives tested per proband in previous MSAC Applications 1476, 1598)				
Parent cascade testing only and no reproductive partner testing	$1,784	0.7117	$2,506	54%

DY = diagnostic yield, GJB2/GJB6 = connexin 26 and connexin 30 genes, ICER = incremental cost effectiveness ratio, MBS = Medicare Benefits Schedule, SoC = standard of care, VCGS = Victoria Clinical Genetics Services, VUS = variant of uncertain significance; WEA = whole exome analysis

a WEA refers to virtual panel analysis of whole exome or whole genome data, including copy number variant analysis, and includes GJB2/GJB6 genetic testing using an MBS item.

b Standard of care pathway refers to clinical investigations without WEA, including state/territory funded GJB2/GJB6 for affected individuals and biological parents of the affected child.

The ICER is comprised of both costs and yield associated with testing affected individuals, biological relatives and reproductive partners. It is important to interpret the ICER in the context that the identification of a P/LP variant may not have the same relevance across the populations. Improvements in the ICER based on broader eligibility for cascade testing are related to the higher yields from cascade testing and lower costs of cascade testing than for the affected individual.

14. Financial/budgetary impacts

The number of affected individuals who would be eligible for the proposed WEA testing are estimated using an epidemiological approach. Similar to the economic evaluation, the base case assumes a ratio of 15%:85% WEA singleton and trio testing, respectively. In addition to the new incident patients, utilisation estimates assume the prevalent pool of patients will access testing over the first three years. Re-analyses test utilisations included in the financial estimates as of Year 3, based on a minimum of 24 weeks of turnaround time for a sequential *GJB2/GJB6* (8-12 weeks) and WEA (about 16 weeks). The utilisation of cascade testing in biological relatives and reproductive partner testing depends on the number of probands identified.

The financial implications to the MBS resulting from the proposed listing of a virtual gene panel-based WEA (including CNVs) for the diagnosis of a genetic cause of HI in children (< 18 years) and a proposed listing of *GJB2/GJB6* testing are summarised in Table 19. Post-MSAC updates to utilisation and financial analyses to incorporate MSAC's support for upfront WEA (including the prevalent population), and advice on appropriate fees for AAAA1 and AAAA2, and to use the November 2022 Greatest Permissible Gap are shown in green italics.

Table 19 Service volumes and net financial implications of genetic testing for hearing loss to the MBS

Parameter	Year 1 2023	Year 2 2024	Year 3 2025	Year 4 2026	Year 5 2027	Year 6 2028
Incident population who receive WEA (from DCAR Tables 67 and 77)	*369*	*375*	*380*	*385*	*390*	*394*
Prevalent population who receive WEA (from DCAR financial spreadsheet)	*1,683*	*1,683*	*1,683*	*0*	*0*	*0*
Total number of people who receive WEA	*2,052*	*2,058*	*2,063*	*385*	*390*	*394*
~~No. AAAAA1 tests~~	~~296~~	~~297~~	~~298~~	~~46~~	~~46~~	~~47~~
No. AAAAA1 tests	*308*	*309*	*309*	*58*	*58*	*59*
~~Cost of AAAAA1 tests ($2,012.10[a])~~	~~$596,349~~	~~$597,656~~	~~$598,903~~	~~$91,970~~	~~$93,233~~	~~$94,295~~
Cost of AAAA1 tests ($1,106.80)	*$340,755*	*$341,662*	*$342,528*	*$63,840*	*$64,717*	*$65,454*
~~No. AAAAA2 tests~~	~~1,679~~	~~1,683~~	~~1,687~~	~~259~~	~~263~~	~~266~~
No. AAAAA2 tests	*1,745*	*1,749*	*1,754*	*327*	*331*	*335*
~~Cost of AAAAA2 tests ($2,812.0[a])~~	~~$4,722,905~~	~~$4,733,259~~	~~$4,743,131~~	~~$728,375~~	~~$738,381~~	~~$746,788~~
Cost of AAAA2 tests ($2,006.80)	*$3,501,102*	*$3,510,426*	*$3,519,316*	*$655,926*	*$664,936*	*$672,508*
~~No. BBBBB tests~~	~~0~~	~~0~~	~~553~~	~~554~~	~~1090~~	~~621~~
No. BBBBB tests	0	0	*662*	*663*	*1,281*	*725*
~~Cost of BBBB tests ($425)~~	~~$0~~	~~$0~~	~~$235,025~~	~~$235,450~~	~~$463,250~~	~~$263,925~~
Cost of BBBB tests ($425)	$0	$0	*$281,138*	*$281,775*	*$544,213*	*$308,125*
No. CCCC1 tests[b]	2,681	2,691	2,702	753	764	772
Cost of CCCC1 tests ($340)	$911,455	$915,097	$918,568	$256,153	$259,672	$262,628
~~No. CCCC2 tests~~	~~105~~	~~105~~	~~105~~	~~17~~	~~17~~	~~17~~
No. CCCC2 tests[c]	*182*	*183*	*184*	*97*	*98*	*99*
~~Cost of CCCC2 tests ($1,112.10[a])~~	~~$116,771~~	~~$116,771~~	~~$116,771~~	~~$18,906~~	~~$18,906~~	~~$18,906~~
Cost of CCCC2 tests ($1,106.80)	*$201,438*	*$202,544*	*$203,651*	*$107,360*	*$108,466*	*$109,573*
~~No. of DDDDD tests[c]~~	~~446~~	~~452~~	~~459~~	~~464~~	~~471~~	~~476~~
~~Cost of DDDDD tests ($520)~~	~~$310,053~~	~~$310,498~~	~~$311,388~~	~~$48,043~~	~~$48,488~~	~~$49,377~~
~~**Total services for proposed items**~~	~~**5,381**~~	~~**5,403**~~	~~**5,978**~~	~~**2,120**~~	~~**2,677**~~	~~**2,226**~~
Total services for proposed items	***4,915***	***4,932***	***5,610***	***1,898***	***2,532***	***1,991***
~~**Total cost to MBS**~~	~~**$6,772,567**~~	~~**$6,791,747**~~	~~**$7,045,524**~~	~~**$1,601,447**~~	~~**$1,847,797**~~	~~**$1,664,574**~~
Total cost to MBS	***$4,954,750***	***$4,969,730***	***$5,265,200***	***$1,365,053***	***$1,642,004***	***$1,418,288***
Change in number of State/Territory funded services	523	531	538	545	552	558
Net cost offset to State/Territory Health Budgets	$244,323	$247,846	$251,236	$254,356	$257,783	$260,771
~~**Net financial impact to the Government (MBS + State/Territory Health Budgets)**~~	~~**$6,528,244**~~	~~**$6,543,902**~~	~~**$6,794,288**~~	~~**$1,347,091**~~	~~**$1,590,014**~~	~~**$1,403,803**~~
Net financial impact to the Government (MBS + State/Territory Health Budgets)	***$4,710,427***	***$4,721,884***	***$5,013,964***	***$1,110,697***	***$1,384,221***	***$1,157,517***

Green italicised text shows updates to reflect MSAC's advice that WEA should be conducted upfront (i.e., without prior DDDDD), the MSAC-supported fees for WEA, and to use the 1 November 2022 Greatest Permissible Gap.
Note: with upfront panel testing and removal of DDDDD, *GJB2/GJB6*-related reproductive partner testing was assumed to use CCCC2.
Note: service volumes for re-analysis are influenced by the DY of testing, which differs between the incident and prevalent populations because the prevalent population is assumed to have already had *GJB2/GJB6* testing and to not proceed to WEA where positive. The DY for WEA in the prevalent pool of patients was therefore estimated to be 33.7% (26.7% / 79.2% = 33.7%), calculated as the DY for non-*GJB2/GJB6* genes (47.5% - 20.8% = 26.7%) amongst only the proportion of patients who remain undiagnosed after *GJB2/6* testing (100% - 20.8% = 79.2%).
DCAR = Department-contracted assessment report; DY = diagnostic yield; *GJB2/GJB6* = connexin 26 and connexin 30 genes; MBS = Medicare Benefits Schedule; WEA = whole exome analysis
[a] The 85% benefits reflect the greatest permissible gap of $87.90 as of 1 November 2021.
[b] includes *GJB2/GJB6* associated cascade testing
[c] includes *GJB2/GJB6* associated reproductive partner testing

The financial impact of the proposed listing of WEA for persons with moderate to profound hearing impairment is based on an epidemiological approach. The prevalence of HI is estimated at 1.57 per 1000 persons by the age of 10. Prevalence estimates vary considerably, and the financial impact to the MBS is proportionally related to an increase in prevalence.

The key sources of uncertainty in the financial analysis relate to the incidence of hearing impairment in the target population, the derivation of the prevalent population, and the estimates of the extent to which cascade testing and reproductive partner testing will occur.

15. Other relevant information

Ethics review

People hold a range of positions on the matter of whether deafness should be considered a disability or a medical problem. The practice of genetic testing for deafness can cast deafness as a disability, but it need not do so. It is imperative to understand that deaf people often experience and view their deafness as part of who they are and not something to lament or change, with society sometimes contributing to reduced opportunity for deaf people. The perspectives of deaf people suggest that deafness does not simply constitute a disability but also, or instead, a difference that informs a distinctive culture and way of being that should be celebrated and preserved. How someone orients to that culture does not appear to be informed by their genetic test result.

There is a wide range of sentiment regarding genetic testing for deafness, including among people with hearing loss, who evidence greater caution than hearing people. The public generally has a low level of understanding when it comes to genetics and its relation to hearing loss, even after using genetic testing.

Parents of children with hearing loss opt for genetic testing of their child or themselves for many reasons, mainly to gain understanding (especially about the cause of hearing loss and the recurrence risk), to aid discussion, and to inform future choices relating to the child's clinical management, the child's future generally, and the parent's own future, including in terms of reproductive planning. Parents opt against genetic testing for equally many reasons, especially because they believe it will be of little value and because they are already overwhelmed by their child's diagnosis of hearing loss. People are worried about privacy and discrimination in insurance and other domains after testing.

The importance of skilled, responsible and language-appropriate genetic counselling cannot be overstated. This is needed before and after testing to ensure that consent to testing is informed and voluntary, and to adequately support the person and family. Counselling should generally be non-directive, allowing the person's own priorities to drive decision making. It should include information on the likelihood of incidental findings, whether they will be returned, and the role of individual preferences in this. It should include information on, and opportunity to engage with, the perspectives of deaf people and their families to avoid bias. This is especially important given concerns that genetic technologies pose a threat to the Deaf community and given a history of eugenics in which deaf people have been persecuted. Evidence is mixed on the success of genetic counselling in improving understanding and meeting expectations.

Multiple studies have proposed that genetic testing can empower people, such as helping with self-understanding or parental grieving. But this seems to depend on numerous factors, including whether the test result is positive, negative or inconclusive, and whether syndromic hearing loss is identified. Inconclusive test results have led to parental frustration and disappointment, though some parents still appreciate the possibility of future re-analysis and the test not

identifying syndromic deafness. Parents and clinicians have highlighted the importance offering genetic testing for children at the right time, having regard for families often being overwhelmed by the diagnosis of hearing loss.

People tend to share genetic testing news with some first-degree relatives to gain support and keep family updated, though they find it difficult to explain negative and inconclusive results. Family members tend to react to news as expected, for good or ill. Some families expect to be impacted by the genetic test result, but do not appear to be.

Most parents support, and would opt for, genetic testing for their child or partner. Hearing people tend to report a preference for having a hearing child, whereas deaf people tend to report having no preference. Some deaf people report a preference for having a hearing child, and some (often being culturally Deaf) report a preference for having a deaf child. For most deaf people, genetic test results would not inform their choice of reproductive partner.

People have used or would use prenatal genetic testing for numerous reasons, including to inform reproductive plans, to prepare for the child's needs, and to prepare for the child personally or emotionally, in particular. There are consistent patterns of parental interest in prenatal genetic testing across empirical studies. Parents tend to be supportive of prenatal genetic testing for deafness and think it should be available. Most hearing parents would utilise such testing, but fewer deaf parents would. Since the 1990s, scholars have debated questions concerning whether it is ethically permissible for doctors or parents to select for or against deafness, especially via genetic testing of the embryo or fetus.

16. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues:

- The patient population for the comparator management algorithm differed from that for the intervention management algorithm, which has had flow on effects for the assessment of incremental health benefits. Both comparator and intervention population should be patients ineligible for childhood monogenic syndromes MBS items 73358 (singleton WEA) and 73359 (trio WEA) – currently this is only present for the intervention population.
- It was unclear what proportion of patients with an underlying syndromic cause for hearing loss are eligible for testing under MBS items 73358/9 based on their clinical phenotype – the applicant may be able to provide further data from the Downie 2020 study on this. If a large enough proportion of children with syndromic hearing loss would not be eligible for 73358/9, then consideration may be given for expansion of the virtual panel analysis to include genes for syndromic hearing loss in addition to those for non-syndromic hearing loss.
- The overall incremental diagnostic yield (DY) and incremental clinical utility were uncertain and may have been overestimated. The estimate in the key study (Downie 2020) included genes for syndromic hearing loss as well as non-syndromic hearing loss, but some of the syndromic hearing loss genes are likely to have been detected through MBS items 73358 (singleton WEA) and 73359 (trio WEA).
- The incremental DY for non-syndromic hearing loss genes in the Downie 2020 study was 15% (16/106). This was above and beyond the DY of 21% (22/106) with *GJB2/GJB6* variants in the comparator. The small numbers used for these estimates mean that they were associated with considerable uncertainty.

- Evidence for clinical utility was limited, with only Downie 2020 providing direct evidence for change in management, and no evidence supporting improvements in health outcomes. The evidence suggests modest incremental utility for non-syndromic HI gene diagnosis enabling children to avoid further investigations. The assessment proposed that all children who receive a genetic diagnosis for their non-syndromic hearing loss (15%) would be discharged from further tests and surveillance, however clinical investigations can continue. A more detailed description of the usual care pathway for these children (e.g., frequency of surveillance for each type of test and clinical review) would allow a better understanding of how many tests and clinic visits might be offset.
- The incremental utility for syndromic HI gene diagnosis was uncertain due to lack of data on how many of the reported cases would have been eligible for MBS items 73358 and 73359. Changes in management reported included: screening protocol tailored to their genetic diagnosis, specific treatment offered, and complex neurodevelopmental syndrome diagnosed that informed medical care. Evidence on whether this would translate into health benefits was not provided.
- The value of knowing could be used in support of a claim of health benefit, though is not likely to be sufficient on its own.

Economic issues:

- There were very limited data to support even a testing-only cost-effectiveness analysis in terms of cost per proband/carrier. There was no evidence for improvement to health outcomes, and no downstream consequences were included.
- There was high uncertainty in most model inputs. Cost-offsets of investigations averted were uncertain as clinical investigations may continue after a genetic diagnosis.
- Upfront WEA was only a little less cost-effective than *GJB2/GJB6* testing prior to WEA.

Financial issues:

- The appropriate fees for AAAA1 and AAAA2 are unclear. The proposed fees align with some previously supported fees, however there are two sets of precedents for virtual panel WES/WGS and work to align the two sets of precedents is underway. The proposed fees for AAAA1/2 appear insufficiently justified as no disaggregated costing was provided.
- Uptake rate was a major driver of utilisation and financial estimates. The incident population was highly uncertain and differed widely depending on whether an epidemiological or market approach was used.
- There was significant uncertainty in the budget impact, as factors such as costs of downstream investigations and services, genetic counselling, incidence of childhood hearing loss and utilisation were not considered or were uncertain.

Other relevant information:

- There are ethical and moral issues around genetic testing for hearing loss. There is a wide range of sentiment on deafness and genetic testing for deafness, with some people not considering deafness to be a life-limiting condition, illness, nor a disability. Clear language and transparent involvement of stakeholders affected may help reduce negative feelings and worries about discrimination. Differing perspectives on deafness may influence decision-making and lead to no change in management of the affected individual.
- The impact of genetic testing on informing reproductive decision-making may vary.
- Genomic databases are dominated by people of European ancestry, creating uncertainty in the clinical validity of variants for people under-represented in genomic databases, including Aboriginal and Torres Strait Islanders.

ESC discussion

ESC noted that this application from the Murdoch Children's Research Institute was for Medicare Benefits Schedule (MBS) listing of virtual gene panel-based whole exome analysis (WEA) and copy number variant (CNV) analysis for the diagnosis of a genetic cause of non-syndromic hearing impairment (HI) in children (<18 years old).

ESC noted the proposed technology was analysis of a virtual panel of hearing loss-related genes in whole exome DNA sequence data. Whole exome DNA sequence data can be obtained by either whole exome sequencing (WES) or whole genome sequencing (WGS), typically using massively parallel next-generation sequencing (NGS) methodology. The test should include a method of identifying CNVs for hearing loss genes.

ESC noted the supportive consultation feedback received prior to PASC consideration. Feedback included the importance of using appropriate language when discussing the Deaf community, as this community considers deafness as a natural state of being, and not a medical problem to be fixed. ESC noted the ethical and moral issues around genetic testing for hearing loss, which the pre-ESC response addressed. ESC considered that clear language and transparent involvement of stakeholders affected by hearing impairment and/or deafness may help reduce negative feelings and worries about discrimination. ESC noted that differing perspectives on deafness may influence decision-making and lead to no change in management of the affected individual. ESC noted that 32% of the parents of newborns with HI who were offered WEA testing opted against receiving additional findings (Tutty 2021[11]). ESC commented that testing prospective parents for hearing loss genes presents further ethical complexities, and transparent ethical oversight may be relevant to processes in a broader sense. ESC noted there may be data storage considerations and also insurance implications, as with other WEA testing.

Consumer feedback included the diagnostic odyssey around non-syndromic hearing loss in children. Parents stressed that timely diagnosis of deafness through audiology assessment, with or without subsequent genetic testing, is key to ensure that children receive the support they need and that they enter the correct education pathway. ESC noted that genetic testing may help avoid subsequent investigations. ESC noted consumer concerns about parents finding out unanticipated information through WEA testing, but considered this could be managed with an appropriate consent process and counselling.

ESC noted that the applicant proposed five MBS items for five populations, and a sixth item was proposed by the Department to remove the need for patients to move between public (state/territory funded) and private (MBS funded) streams, because a non-diagnostic GJB2/GJB6 genetic test result is proposed to be a prerequisite for WEA. The populations were:

- population 1 – singleton WEA testing (item AAAA1; $2,100)
- population 2 – trio WEA testing (item AAAA2; $2,900)
- population 3 – re-analysis (item BBBBB; $500)
- population 4 – cascade testing of biological relatives (item CCCC1; $400)
- population 5 – reproductive partner testing (item CCCC2; $1,200)
- population 6 – *GJB2/GJB6* testing (item DDDDD; $607.90); currently funded by states and territories, covers the most common variants causing hearing loss

[11] Tutty, E, Amor, DJ, Jarmolowicz, A, Paton, K & Downie, L 2021, 'Personal utility of genomic sequencing for infants with congenital deafness', *American Journal of Medical Genetics, Part A*, **185**(12).

ESC noted the proposed fees, and considered that they were not yet adequately justified. ESC noted the MSAC Executive advice from December 2021 regarding the need for fee alignment across virtual panel testing items. The MSAC Executive had noted that the MBS fee of $2,100 for a singleton virtual panel performed under WES/WGS (MBS item 73358, and Application 1600 AAAA1/2) is higher than the MBS fee of $1,200 for method-agnostic gene panel tests (i.e., permitting virtual panel or amplicon-specific panel methods), and considered that aligning virtual panel testing under these two previously separate categories creates a fee inconsistency. The MSAC Executive had advised that the fees for virtual panel testing should be aligned, and that the fee for a singleton virtual panel test should be lower than $2,100 as the cost to perform genomic tests is reducing over time. ESC noted the fees proposed were in line with previous items, but that the Department is currently working to align the fees for virtual panel testing and other genomic tests. ESC considered it may be inappropriate to benchmark against existing fees without a clear component breakdown and justification (e.g., sequencing, quality control, bioinformatics, consumables). ESC suggested that future assessments for genomic testing should ideally include more disaggregated real-world data on cost offsets, especially when health outcomes are not being considered.

ESC noted that WES and WGS incur different resources so considered it would be appropriate for the fees to reflect this. ESC noted that a fee of $2,100 is low compared to the cost of privately provided WGS, though is more in line with the cost of privately provided WES. ESC noted that MSAC had previously supported a fee of $1200 as being appropriate for germline virtual panel testing of at least 20 genes (MBS item 73416) and at least 22 genes (MBS item 73392). ESC queried whether virtual panel testing is less costly to perform than amplicon-specific panels. ESC noted the fee of $607.90 for DDDDD was based on aligning the 85% benefit with the cost charged by Victorian Clinical Genetic Services for non-Victorian residents.

ESC noted that the proposed virtual panel for the testing is the Deafness_Isolated panel, which included 131 genes (107 “green” genes) on PanelApp Australia (at the time the DCAR was prepared, though as at 24 October 2022 (version 1.37) there were 105 green genes), but that the Downie 2020[12] study had examined genes known to cause syndromic HI in addition to genes for non-syndromic HI. ESC queried whether the gene panel should also include genes associated with syndromic hearing loss. ESC considered that the intent of this application was to capture children with hearing loss who do not have a clinical phenotype suggestive of syndromic hearing loss. However, ESC considered that it is possible that some children with a syndromic cause for their hearing loss may not present with the classical phenotype that would make them eligible for the existing childhood syndromes items (73358/9). ESC considered it was unclear what proportion of patients with syndromic hearing loss in the Downie 2020 study would have been diagnosed using the existing 73358/9 items, and commented that the applicant may be able to provide further data from the Downie 2020 study on this. ESC considered that if a large enough proportion of children with syndromic hearing loss would not be eligible for 73358/9, then virtual panel analysis could be expanded to include genes for syndromic hearing loss. ESC also commented that the item descriptor could state the minimum number of genes to be included in the virtual panel.

ESC noted that some of the item descriptors referred to pathogenic and likely pathogenic variants, and considered that given hearing loss is not a disease, it would be appropriate to interpret pathogenic variants in this case as referring to variants that cause hearing loss rather than disease.

[12] Downie, L, Halliday, J, Burt, R, et al. 2020, 'Exome sequencing in infants with congenital hearing impairment: a population-based cohort study', *European Journal of Human Genetics*, **28**(5).

Regarding item descriptors AAAA1/2, ESC noted that existing monogenic syndromes testing items 73358/9 are for children aged 10 years or younger, and children already covered by these item numbers are excluded from items AAAA1 and AAAA2. ESC noted AAAA1/2 are proposed to be for patients 17 years or younger (i.e., patients aged 17 years and 364 days or younger) and considered that the different age thresholds may be justified by differences in the ages that developmental syndromes present. ESC queried whether descriptors AAAA1/2 should omit the reference to "non-syndromic", as 73358/9 already cover WEA for "syndromic conditions strongly suspected on clinical grounds". ESC noted advice that for legislative reasons PanelApp "green genes" cannot be explicitly referred to within the item descriptor, so proposed that the item descriptor state "all" germline variants to convey this intent.

ESC noted that the minimum interval for re-analysis in BBBBB was proposed to be 18 months, in line with other previously supported re-analysis items, though any evidentiary basis behind the initial proposal of 18 months was unclear. ESC noted a 2022 systematic review[13] (k=29) of re-analysis had found the average DY of re-analysis was 10%, and had conducted a subgroup analysis dichotomising re-analysis timeframe to <24 months versus ≥24 months, and found the latter was better (though not statistically significantly) and therefore the authors recommended "that reanalysis be delayed to ≥24 months unless there was urgent clinical need to reanalyze earlier". ESC therefore considered that a minimum re-analysis interval of at least 24 months may be more appropriate.

ESC noted that the restriction proposed for re-analysis (BBBB) was twice per lifetime, though considered that it may be appropriate to exclude patients who have received a genetic diagnosis from further re-analysis, because the included genes do not lead to specific treatments. However, ESC considered that advice from a clinical geneticist could inform MSAC's consideration on this point.

Regarding item CCCC1, ESC considered that the proposed wording "biological relative of patient" would permit relatives of a wide range of relatedness to access cascade testing, and noted precedents vary on this point depending on clinical appropriateness. ESC noted the DCAR had interpreted biological relatives to mean "first or second degree relative".

ESC noted the applicant's pre-ESC response comments on the importance of appropriate counselling and consent for this testing, and agreed it is important that pre- and post-test genetic counselling be available. ESC considered practice note PN.0.23 to be appropriate to support this, and queried adding PN.0.27 to further support post-test counselling, however noting policy advice that these practice notes are mutually exclusive in current usage, opted to retain PN.0.23.

ESC's proposed amendments to the item descriptors are in green italics below (Table 20). ESC did not revise CCCC1, CCCC2 nor DDDDD, except for the addition of PN.0.27 to all proposed items.

[13] Dai P, Honda A, Ewans, L, et al. (2022). Recommendations for next generation sequencing data reanalysis of unsolved cases with suspected Mendelian disorders: a systematic review and meta-analysis. *Genetics in Medicine*, **24**(8):1618–29.

Table 20 ESC's revised item descriptors for AAAA1, AAAA2 and BBBBB

Proposed MBS items
MBS item number: AAAA1 Characterisation, via whole exome or genome sequencing and copy number variant analysis, of *all* germline variants known to cause childhood hearing loss, if: (a) the characterisation is (i) requested by a consultant physician practising as a clinical geneticist; or (ii) requested by a consultant physician practising as a specialist paediatrician with expertise in genetics; or (iii) requested by a consultant physician practising as a specialist paediatrician, following consultation with a clinical geneticist; and (b) the patient is aged 17 years or younger with congenital or childhood onset hearing loss that is permanent bilateral moderate, severe, or profound (>40 dB in the worst ear over three frequencies) and classified as ~~*non-syndromic*~~ sensorineural, auditory neuropathy or mixed; and (c) the characterisation is performed following completion of a service described in item DDDDD, for which the results were non-informative; and (d) the patient is not eligible for a service to which items 73358 or 73359 apply; (e) the characterisation is not performed in conjunction with or following a service to which MBS item AAAA2 applies Applicable once per lifetime. MBS Fee: $2,100.00 Benefit: 75% = $1,575.00 85% =$2,012.10
MBS item number: AAAA2 Characterisation, via whole exome or genome sequencing and copy number variant analysis, of *all* germline variants known to cause childhood hearing loss, if: (a) the characterisation is (i) requested by a consultant physician practising as a clinical geneticist; or (ii) requested by a consultant physician practising as a specialist paediatrician with expertise in genetics; or (iii) requested by a consultant physician practising as a specialist paediatrician, following consultation with a clinical geneticist; and a specialist paediatrician; and (b) the patient is aged younger than 17 years or younger with congenital or childhood onset ~~*non-syndromic*~~ hearing loss that is permanent bilateral moderate, severe, or profound (>40 dB in the worst ear over three frequencies) and classified as sensorineural, auditory neuropathy or mixed; and (c) the characterisation is performed following completion of a service described in item DDDDD, for which the results were non-informative; and (d) the characterisation is performed using a sample from the patient and a sample from each of the patient's biological parents; and (e) the patient is not eligible for a service to which items 73358 or 73359 apply; (f) the characterisation is not performed in conjunction with or following a service to which MBS item AAAA1 applies. Applicable once per lifetime. MBS Fee: $2,900.00 Benefit: 75% = $2,175.00 85% = $2,812.10
MBS item number: BBBBB Re-analysis of whole exome or genome data obtained under a service to which item AAAA1 and AAAA2 apply, for characterisation of previously unreported germline gene variants for childhood hearing loss, *for a patient who has not yet received a genetic diagnosis for their hearing loss,* if (a) the re-analysis is (i) requested by a consultant physician practising as a clinical geneticist; or (ii) requested by a consultant physician practising as a specialist paediatrician with expertise in genetics; or (iii) requested by a consultant physician practising as a specialist paediatrician, following consultation with a clinical geneticist; and (b) The re-analysis is performed at least ~~*18*~~ *24* months after (i) a service to which items AAAA1 or AAAA2 applies; or (ii) a service to which this item applies. Applicable twice per lifetime MBS Fee: $500.00 Benefit: 75% = $375.00 85% = $425.00

dB = decibels; MBS = Medical Benefits Scheme; MSAC = Medical Services Advisory Committee

Practice Notes (AAAA1, AAAA2, BBBBB, CCCC1, CCCC2, DDDDD): Appropriate genetic counselling should be provided to the patient either by the specialist treating practitioner, a genetic counselling service or a clinical geneticist (PN.0.23).

ESC noted the comparators and considered them to be largely appropriate, although considered the clinical management algorithm for the comparator had omitted the requirement that the child be ineligible for MBS items 73358/9. ESC considered that using different populations for the intervention versus the comparator is problematic for estimating incremental clinical value. ESC also noted that details of "further clinical investigations" were not provided; this would be helpful to determine incremental clinical utility.

ESC noted the clinical evidence used a linked approach to examine diagnostic yield, change in management, non-health related outcomes and safety. ESC noted that there was little data, and most of it came from retrospective cohorts and case series. ESC considered that while there were several studies evidencing the diagnostic yield (DY), only one study (Downie 2020, from the applicant group) provided direct evidence for clinical utility. ESC noted the DCAR's economic model predominantly used estimates of DY and change in management from Downie 2020, but that this study had included testing for syndromic HI genes as well as non-syndromic genes. The sample size in Downie 2020 was relatively small (n = 106) which leads to considerable uncertainty in estimates of incremental value. However, ESC agreed with the pre-ESC response that childhood hearing loss is a rare condition, which would explain the small sample size. ESC also agreed with the pre-ESC response that not having to undergo unnecessary tests after a genetic diagnosis is an important health outcome, however noted the pre-ESC response did not elaborate on the investigations that could be avoided (and these were not provided in the comparator clinical management algorithm). ESC also considered that not all children who receive a diagnosis will be discharged from further tests and surveillance, and that clinical investigations may continue.

Regarding comparative safety, ESC considered there was little evidence and it was of low quality, although there were likely to be no safety issues. ESC considered the claim of non-inferior safety for population 1 to be reasonable.

Regarding comparative effectiveness for population 1, ESC noted that an additional 24.8% to 47.5% of patients received a genetic diagnosis using WEA compared to *GJB2/GJB6* testing alone, and that there were changes in management pathways for approximately 50% of those tested, mostly for those who received a genetic diagnosis. ESC also noted there were varied patient, clinical and socioeconomic factors associated with receiving or not receiving testing for HI. In terms of non-health outcomes, value of knowing was more positive for parents of children that tested positive than parents of children who tested negative, given the identification of an aetiology and on informing future reproductive decision-making.

ESC noted that the overall diagnostic yield for variants related to hearing loss in population 1 was 56% of patients (59/106), although this was comprised of 36% (38/106) with a variant in a gene associated with non-syndromic hearing loss (21% (22/106) had causative *GJB2/GJB6* variants, and 15% (16/106) had another non-syndromic hearing loss gene), and 20% (21/106) had a variant in a gene associated with syndromic hearing loss. The incremental diagnostic yield of WEA compared to *GJB2/GJB6* testing, for non-syndromic hearing loss, was therefore 15%. ESC considered this DY to be comparable to previous germline genetic testing applications considered by MSAC and can be expected to vary with clinical acumen. ESC considered the incremental increase in diagnostic yield for non-syndromic hearing loss genes compared with *GJB2/GJB6* testing was modest. The incremental DY for syndromic hearing loss genes is uncertain as it is unknown how many would have been eligible for MBS items 73358/9. For this reason, ESC considered that the DY for population 1 was likely overestimated.

ESC noted that the DCAR assumed all patients who received a genetic diagnosis of non-syndromic hearing loss (i.e., 36% of patients) were discharged from further testing or surveillance (brain MRI, electrocardiogram, ophthalmology tests). ESC considered that it is possible that not all children who receive a genetic diagnosis will be discharged from further tests and surveillance. Nonetheless, ESC considered that there was modest incremental DY and clinical utility for non-syndromic hearing loss gene diagnosis enabling children to avoid further investigation. Further details on the extent of tests and surveillance expected under usual care that may be avoided may help define the size of this potential benefit. Issues included that the estimates were uncertain and based on small numbers in one Australian study, and there was no direct comparative evidence presented.

In the 15% of children with a genetic diagnosis of syndromic hearing loss, changes in management were reported for all (9% were moved to a screening protocol tailored to their genetic diagnosis, 2% had a specific treatment offered, and 4% had a complex neurodevelopmental syndrome diagnosed that informed medical care). Because data were not provided on how many of these children would have been eligible for MBS items 73358/9, ESC considered the incremental DY and clinical utility for syndromic hearing loss gene diagnosis to be uncertain. Further, no evidence was provided on the extent to which the changes in management might translate into benefits in health.

ESC noted that there was no evidence on health outcomes available for probands who receive a change in management following the identification of a heritable aetiology of hearing impairment. ESC considered that although there was evidence for non-health benefit such as value of knowing, there was insufficient evidence for change in health outcomes resulting from WEA to support the claim of superior effectiveness.

For population 2 (trio WEA), ESC noted that there was insufficient data to support an incremental increase in DY for trio WEA, compared to singleton WEA or *GJB2/GJB6* testing alone. For populations 3 and 4 (re-analysis and cascade testing) ESC considered there to be modest increases in incremental diagnostic yield, and for population 5 (reproductive partner testing) ESC considered there to be modest incremental clinical utility as whilst there is no fetal test item included in this application, parents identified as carriers can avail themselves of MBS-reimbursed PGD (which is not limited by the severity of condition) to inform reproductive decision-making. For population 6 (*GJB2/GJB6* testing). ESC noted that a DY of 19.8% *GJB2/GJB6* variants for non-syndromic HI was reported in Downie 2020 (noting one infant with a *GJB2* variant was diagnosed with syndromic HI), and that evidence beyond DY was not required because this testing is already established in clinical practice.

ESC considered that there was insufficient evidence to make effectiveness or safety conclusions about populations 2–5. ESC noted no clinical claim was made for population 6.

For population 5, ESC considered that genetic information about hearing loss may be important to some families for reproductive decision-making. ESC noted that one study[14] reported 6% of deaf, 11% of hard of hearing or deafened, and 16% of hearing people (who had either a deaf parent or child) would consider a termination if the fetus was deaf – but also that 2% of deaf people would consider a termination if the fetus was found to be hearing. ESC considered that the impact of genetic testing on informing reproductive decision-making may vary between parents with hearing loss compared to those without. ESC considered that some parents who are deaf may make different reproductive choices, though would still be making informed (rather than uninformed) reproductive decisions. ESC considered that transparent ethical decision-

[14] Middleton, A., Hewison, J. & Mueller, R, 2001. 'Prenatal Diagnosis for Inherited Deafness—What is the Potential Demand?'. *Journal of Genetic Counseling* **10**, 121–131.

making should align with what is considered acceptable to the public and communities defined by a shared interest.

ESC noted that the economic evaluation was a cost-effectiveness analysis, with the health outcomes being identification of P/LP variant to provide a definitive diagnosis in affected individuals, or the identification of a P/LP variant in cascade testing/reproductive partner testing for the purpose of informing reproductive planning. ESC considered the main issues with the economic model were the limited evidence to demonstrate cost-effectiveness and the high uncertainty of most of the model inputs.

ESC noted the estimated incremental cost-effectiveness ratio (ICER) of the proposed testing (including WEA, testing biological relatives and reproductive partners) was $1,629 per additional proband and/or carrier identified. ESC considered the model made some omissions and assumptions that may have affected the ICER:

- The appropriate fees for AAAA1 and AAAA2 are uncertain. Reducing the fees for AAAA1/2 to $1200 and $1800 respectively reduced the ICER by 26%.
- The model assumed the same DY for singleton vs trio WEA, and using WES vs WGS as the background, which may have decreased the ICER.
- The source data were from children under 2 years old, but the application included children up to 18 years old, with unknown effect on the ICER.
- The uptake rate was assumed to be 68% (from Downie 2020), which had little effect on the ICER.
- The costs of further investigations after a negative test were not considered, which decreased the ICER because these were cost offsets for the intervention.
- The costs of genetic counselling ($332) were omitted, which increased the ICER as counselling costs would be higher for the intervention.
- The model was based on a single re-analysis, and sensitivity analyses did not vary the diagnostic yield of re-analysis (e.g., Dai 2022 found 10% DY of re-analysis).
- The model did not consider the outcomes for biological relatives, which decreased the ICER with additional yield.
- DY was likely overestimated, which increased the ICER.

ESC noted that conducting *GJB2/GJB6* testing during WEA analysis instead (i.e., rather than first and separately with an uninformative result then permitting access to WEA) was only a little less costly, with an ICER of $1,544 per proband/carrier. ESC considered that upfront WEA would take longer (16-24 weeks, compared to 10-12 weeks for standalone *GJB2/GJB6* testing as per standard of care), but that this longer turnaround time would not have a consequence for health outcomes. ESC considered that shorter turnaround time may have non-health benefits such as earlier educational interventions, though assessing the effect of turnaround time would require a different type of economic model. ESC noted that the main drivers of the ICER were the DY of WEA, and family size (smaller family size increased the ICER).

ESC noted that the financial impact was estimated at $6.8–7.0 million per year in 2023-2025 (years 1–3) as the prevalent pool of affected individuals accessed testing, then $1.6–1.8 million per year in 2026-2028 (years 4-6), using an epidemiological approach to estimate utilisation. ESC considered the financial impact to be uncertain, as the costs of continuing investigations after a positive genetic diagnosis and the costs of further investigations in patients who do not receive a genetic diagnosis were uncertain. ESC noted that the DCAR assumed 34.9% of patients avoided clinical investigations if there was no diagnosis, but considered that costs for care are still incurred after a genetic diagnosis (such as brain MRIs, family audiograms and ophthalmology

assessments, at a weighted average cost of $3,300 according to Downie 2021[15]). ESC considered the DCAR's omission of the cost of future investigations avoided may be reasonable given they were highly uncertain in both arms.

ESC noted the DCAR conducted sensitivity analyses on the financial impact to the MBS. Replacing the *GJB2/GJB6* testing plus WEA with WEA only had a largely neutral effect on the cost, because the cost offset of *GJB2/GJB6* testing is replaced by higher cost WEA tests. Doubling the prevalence of childhood hearing loss to 3/1,000 persons results in the cost increasing to $12.2 million in 2023 (year 1). The budget impact is also sensitive to the number of reproductive partners and to consent rates for genetic testing. Using a market data approach increased the cost to $8.9 million in 2023.

ESC noted genomic databases are dominated by European ancestry, creating uncertainty in the clinical validity of variants for people under-represented in genomic databases, which includes Aboriginal and Torres Strait Islanders. ESC noted that the source data did include diverse populations, but that some groups were underrepresented. ESC noted the key Downie 2020 study did not conduct subgroup analyses by ethnicity, though considered this may not have been possible given its small sample size (n=106).

ESC noted advice from the National Pathology Accreditation Advisory Council (NPAAC), that this testing is in use in a small number of centres at present, and that an external quality assurance (EQA) program is in development.

17. Applicant comments on MSAC's Public Summary Document

There is a lot of research on the genetic basis of mild childhood hearing loss, and I agree with consultation comments that the justification for excluding patients with mild hearing loss is insufficient. There is some recent evidence that the rate of genetic diagnosis may be reasonably high (PMID: 32203226, PMID: 18270175). *STRC* gene deletion often causes mild hearing impairment. In addition, the group of children with mild hearing loss are already known to be at a disadvantage (PMID: 34346279) regarding how they are managed.

18. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website

[15] Downie, L, Amor, DJ, Halliday, J, Lewis, S, Martyn, M & Goranitis, I 2021, 'Exome Sequencing for Isolated Congenital Hearing Loss: A Cost-Effectiveness Analysis', *Laryngoscope*, **131**(7).