Author/s:
Sung, V;Downie, L;Paxton, GA;Liddle, K;Birman, CS;Chan, WW;Cottier, C;Harris, A;Hunter, M;Peadon, E;Peacock, K;Roddick, L;Rose, E;Saunders, K;Amor, DJ

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Sung Valerie (Orcid ID: 0000-0003-2029-6331)

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Full names of authors:

1. Valerie Sung
   - Murdoch Children's Research Institute, 50 Flemington Road, Parkville, VIC, 3052
   - Royal Children's Hospital, 50 Flemington Road, Parkville, VIC, 3052
   - Department of Paediatrics, University of Melbourne, Parkville, VIC, 3052

2. Lilian Downie
   - Murdoch Children's Research Institute, 50 Flemington Road, Parkville, VIC, 3052
   - Royal Children's Hospital, 50 Flemington Road, Parkville, VIC, 3052
   - Victorian Clinical Genetics Service, 50 Flemington Road, Parkville, VIC, 3052
   - Department of Paediatrics, University of Melbourne, Parkville, VIC, 3052

3. Georgia A. Paxton
   - Murdoch Children's Research Institute, 50 Flemington Road, Parkville, VIC, 3052
   - Royal Children's Hospital, 50 Flemington Road, Parkville, VIC, 3052
   - Department of Paediatrics, University of Melbourne, Parkville, VIC, 3052

4. Karen Liddle
   - Queensland Children's Hospital, Stanley St, South Brisbane, QLD, 4101

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- University of Queensland, Herston Rd, Herston, QLD, 4006

5. Catherine S. Birman
   - The Children's Hospital at Westmead, Corner Hawkesbury Road and Hainsworth Street, Westmead, NSW, 2145
   - Sydney Cochlear Implant Centre, PO Box 188, Gladesville, NSW, 2111
   - Sydney Medical School, The University of Sydney, Camperdown, NSW, 2006
   - Macquarie University, NSW, 2109

6. Wei Wei Chan
   - Department of Paediatrics, Gold Coast University Hospital, 1 Hospital Boulevard, Southport, QLD, 4215
   - School of Medicine, Griffith University, Parklands Drive, Southport, QLD, 4215

7. Carolyn Cottier
   - Sydney Children's Hospital, High Street, Randwick, NSW, 2031
   - University of New South Wales, Sydney, NSW, 2052

8. Alison Harris
   - Queensland Children's Hospital, Stanley St, South Brisbane, QLD, 4101
   - University of Queensland, Herston Rd, Herston, QLD, 4006

9. Matthew Hunter
   - Monash Genetics, Monash Health, Clayton, VIC, 3168
   - Department of Paediatrics, Monash University, Clayton, VIC, 3168

10. Elizabeth Peadon

- Deafness Centre, The Children's Hospital at Westmead, Corner Hawkesbury Road and Hainsworth Street, Westmead, NSW, 2145

11. Kenneth Peacock
    - Deafness Centre, The Children's Hospital at Westmead, Corner Hawkesbury Road and Hainsworth Street, Westmead, NSW, 2145

12. Laurence Roddick
    - John Hunter Children's Hospital, Locked Bag 1, HRMC, NSW, 2310
    - University of Newcastle, University Drive, Callaghan, NSW, 2308

13. Elizabeth Rose
    - Royal Children's Hospital, 50 Flemington Road, Parkville, VIC, 3052
    - Department of Otolaryngology, University of Melbourne, Parkville, VIC, 3052
    - Murdoch Childrens Research Institute, 50 Flemington Road, Parkville, VIC, 3052
    - Royal Victorian Eye and Ear Hospital, 32 Gisborne Street, East Melbourne VIC, 3002

14. Kerryn Saunders
    - Paediatric Hearing Services, Monash Children's Hospital, Clayton, VIC, 3168
    - Department of Paediatrics, Monash University, Clayton, VIC, 3168

15. David J Amor
    - Murdoch Children's Research Institute, 50 Flemington Road, Parkville, VIC, 3052
    - Royal Children's Hospital, 50 Flemington Road, Parkville, VIC, 3052

- Victorian Clinical Genetics Service, 50 Flemington Road, Parkville, VIC, 3052
- Department of Paediatrics, University of Melbourne, Parkville, VIC, 3052

Corresponding author

Dr Valerie Sung

Valerie.sung@rch.og.au

Murdoch Children's Research Institute

Royal Children's Hospital

50 Flemington Road, Parkville, VIC, 3052, Australia

Ph: +613 9345 4363

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Hearing loss, child, guideline, aetiology, disease management

Introduction

Permanent hearing loss affects 1–3 per 1000 children in Australia;(1) this may be congenital or acquired, unilateral or bilateral, and ranges in severity from mild to profound. Hearing loss types include sensorineural (SNHL), including auditory neuropathy, conductive and mixed (Table 1, Figure 1).

Australia has high quality universal infant hearing screening which facilitates early diagnosis, and enables early intervention, hearing device fitting and timely planning for cochlear implantation if indicated.(1, 2) Although the *National Framework for Neonatal Hearing Screening* provides guidance on infant screening and early intervention pathways are well established, aetiological investigation and medical management of newly diagnosed infants has varied. National guidelines are important to streamline management, ensure investigations are completed within relevant timeframes, and reduce unnecessary stressors for families.

Local and international evidence for the aetiological investigation of childhood hearing loss is heterogeneous and generally of low quality, with limited guidance on the structure or cost-effectiveness of investigations. A 2017 review recommended consensus guidelines to improve management of hearing-impaired children,(3) and both the British Association of Audiovestibular Physicians (BAAP)(4-6) and the International Pediatric Otolaryngology Group (IPOG)(7) have released guidelines. This position paper provides consensus recommendations for the aetiological investigation and medical management of

children with sensorineural hearing loss, including auditory neuropathy, intended for general practitioners, paediatricians, otolaryngologists and genetic services in the Australian context.

Materials and Methods

The Childhood Hearing Australasian Medical Professionals (CHAMP) network of paediatricians, otolaryngologists and geneticists was established in 2016 with the goal of improving care for hearing-impaired children in Australasia. A working group of fifteen members held round-table discussions at the 2016 *Healthy Hearing Symposium* in Brisbane, and the 2017 *Australasian Newborn Hearing Screening Conference* in Melbourne. We examined the IPOG and BAAP recommendations, and completed literature reviews. Working group members voted on the grade and strength recommendations as per the National Health and Medical Research Council (NHMRC) guidelines (Table 2).(8)

We developed recommendations based on:

- bilateral versus unilateral hearing loss,
- clinical presentation,
- availability, quality, consistency, generalisability and applicability of evidence,
- consideration of limited resource settings and family preferences.

Recommendations are presented in three tiers:

1) first line investigations for non-syndromic hearing loss,
2) investigations based on clinical presentation, and
3) investigations to consider if tier 1 and 2 investigations are negative.

Children with non-syndromic hearing loss who have a definitive diagnosis from tier 1 investigations will not require other diagnostic investigations. However, investigations to aid management decisions should be on a case by case basis.

Results/Discussion

All hearing-impaired children should have a comprehensive medical history (Table 3) and examination (Table 4). Recommended investigations and suggested referrals are summarised in Tables 5 and 6.

1. *Tier 1 (first-line) investigations*

1.1. Cytomegalovirus salivary testing within 21 days of birth

Congenital cytomegalovirus (cCMV) infection is the most common infectious cause of childhood SNHL.(9) Saliva polymerase chain reaction (PCR) has high sensitivity (100%, 95% CI 95.8-100.0) and specificity (99.9%, 95% CI 99.9-100.0) for detecting cCMV,(10) and should be completed within 21 days of birth for all infants with SNHL to facilitate accurate diagnosis.(11) Saliva swabs are collected more than one hour after breastfeeding to avoid potential contamination from maternal CMV in breast milk.(11) Urine CMV PCR is an alternative, but is more difficult to obtain.(11) After 21 days of age, testing for cCMV should be completed by checking CMV PCR on the newborn screening dried blood spot (Guthrie) card; however, the sensitivity (42.3%, 95% CI 23.4-63.1 at 4 years) and specificity (73.3%, 95% CI 67.6-78.5 at 4 years) are low.(12) Thus while a positive CMV result on the Guthrie card is useful to confirm the diagnosis of cCMV, a negative result does not exclude the diagnosis.

Recent evidence suggests that when commenced within one month of life, six months of oral valganciclovir for symptomatic cCMV may benefit hearing and neurodevelopmental outcomes.(13) However, there is currently insufficient

evidence to recommend early antiviral treatment for isolated SNHL due to cCMV.(11) International guidelines recommend targeted screening for cCMV for infants at risk of SNHL to enable early diagnosis, audiology and developmental monitoring, and discussion of treatment options.(11)

Other Tier 1 investigations are still recommended for children diagnosed with cCMV, because cCMV may co-exist with other conditions that cause SNHL.

1.2. Magnetic resonance imaging (MRI)

MRI of the brain including parasagittal sections of the internal acoustic canal is recommended for all infants with SNHL where resources are available. MRI is essential before cochlear implantation, and is preferred over computerised tomography (CT) as the first-line radiological evaluation of inner ear anatomy, as it provides superior images of the brain and cochlear nerves, and avoids radiation exposure. CT provides more details about bony structures but risks associated with radiation (14, 15) means CT use and timing should be considered carefully, and limited to children who have permanent conductive loss (as a guide to possible surgical correction), or if a major abnormality of the cochlea is identified on MRI.

The diagnostic yield from cranial imaging for hearing loss is approximately 30%.(16, 17) In unilateral hearing loss or bilateral auditory neuropathy, MRI abnormalities are identified in more than 50% of cases, including cochlear nerve dysplasia in one third.(17, 18) MRI is also important for diagnosis of large endolymphatic ducts and sacs (LEDS), associated with enlarged vestibular aqueducts (EVA), also known as large vestibular aqueduct syndrome (LVAS). LEDS/EVA/LVAS is associated with progressive SNHL and deterioration can occur with mild head trauma.

The timing of MRI depends on local resources, but ideally should be offered within the first year of life, either as a 'feed-and-wrap' (infant fed and settled to sleep – usually achievable in those aged under 3–4 months), under sedation or under a general anaesthetic (GA). In most resource-limited settings, early MRI should be prioritised for infants with bilateral severe to profound SNHL to assess for cochlear implantation and also if unilateral, asymmetric or auditory neuropathy. MRI with GA should be completed in children with progressive SNHL, for cochlear implant work-up, or where there are other indications, such as developmental regression or neurological symptoms. In children with SNHL who did not have an early MRI, MRI without GA should be offered as a Tier 3 investigation around school entry.

1.3. Genetic testing

All families of children with *bilateral* SNHL should be offered the option of genetic testing with pre-test counseling, as more than half will have a genetic aetiology. Parents should understand the implications of both positive and negative results, and that a negative test does not exclude a genetic cause. Access to funded genetic testing will vary between health services. Testing for GJB2/GJB6 (connexin 26/30) is recommended for all non-syndromic children with bilateral SNHL. It is the most genetic cause and accounts for approximately 20% of congenital SNHL.(19)

For non-syndromic children with *unilateral* loss, a genetic diagnosis is less likely,(20) and connexin testing is not recommended. Although there is evidence of a higher rate of heterozygous mutations in *GJB2* in this population,(21) there is no clinical utility in detecting these cases.

1.4. Family audiograms

We recommend audiology testing of first-degree family members, especially siblings and parents,(4-6) to complete the family pedigree and detect hearing loss (which may be subclinical) in family members who may benefit from further management.

1.5. Ophthalmology assessment

Ophthalmic abnormalities are prevalent in hearing-impaired children, affecting 30–60%.(16, 22, 23) Multisensory deficits are likely to have compounding effects on language and cognitive development. All hearing-impaired children should have visual acuity assessed before school entry by an optometrist or ophthalmologist. Ophthalmology assessment is recommended for hearing-impaired children where there are features suggestive of congenital infection, syndromic features, concerns about vision (particularly night vision), delayed motor milestones, hypotonia, poor coordination or where hearing loss is profound or progressive. Ophthalmology assessment is also recommended as a tier 3 investigation.

2. Tier 2 investigations for specific indications

2.1. Genetic testing

Children with syndromic features should be offered chromosome microarray testing to look for relevant copy number variants (CNVs). If negative we recommend clinical genetics review to consider further testing. Hearing loss is genetically heterogeneous, with more than 100 associated genes now identified, therefore a genomic approach is preferable to testing individual genes.(24) Genomic approaches include:

i) targeted hearing loss panels,

ii) whole exome sequencing (WES, which analyses the 1% of the genome that encodes genes) and
iii) whole genome sequencing (WGS, which analyses the entire DNA sequence).(25) Genomic testing is expected to reveal a specific genetic diagnosis in more than half of children with bilateral SNHL, and may direct management (e.g. Pendred or Usher syndromes). Access to and costs of genetic testing will vary, depending on location and health service.

Some mitochondrial DNA variants are associated with SNHL.(26) *MT-RNR1* variants 1555A>G and 1494C>T are associated with aminoglycoside-induced SNHL, which occurs in almost all affected individuals who are treated with aminoglycoside antibiotics.(27) Mitochondrial DNA variant 3243A>G is associated with the maternally inherited diabetes and deafness (MIDD) syndrome.(28) The clinical utility of testing for mitochondrial DNA variants for SNHL has not been established, but should be considered where there is family history of SNHL consistent with matrilineal inheritance, SNHL following aminoglycoside administration, and personal and/or family history suggestive of MIDD.

2.2. Thyroid function

SNHL may be associated with hypothyroidism in two different clinical conditions: Pendred syndrome and hypopituitarism. In Pendred syndrome, children develop SNHL early, with goitre and/or thyroid dysfunction occurring later (usually after 10 years old).(29) In hypopituitarism, central hypothyroidism may occur early, but SNHL typically develops later, and is usually not the first or only clinical manifestation of the condition.(30)

Currently, there is inadequate evidence to support routine thyroid function testing in hearing impaired infants beyond existing newborn screening for hypothyroidism. Thyroid function testing is indicated where there is clinical indication of thyroid dysfunction (developmental delay, abnormal growth), a history of early newborn bloodspot screen (before 48 hours of age), or presence of goitre.(5, 6)

2.3. Electrocardiogram ECG

Jervell and Lange-Nielsen syndrome is an uncommon but important cause of bilateral profound SNHL.(31) This autosomal recessive condition is characterised by a prolonged QT interval on ECG, and is associated with tachyarrhythmias and risk of sudden death. Children with bilateral severe to profound SNHL, a personal history of syncopal episodes, or a family history of unexplained sudden death, arrhythmias or syncope should have an ECG at diagnosis and cardiology review if abnormalities are identified. Availability of genomic testing will reduce the need for ordering ECGs in the future.

2.4. CT petrous bone/inner ear

CT scanning should only be performed under otolaryngology guidance for specific anatomical indications (see Section 1.2).

2.5. Perinatal infection screening

Perinatal infections in the TORCH group (**T**oxoplasmosis, **O**ther (syphilis, varicella, parvovirus B19), **R**ubella, **C**ytomegalovirus and **H**erpes simplex virus) are associated with SNHL.(32) Maternal antenatal serology results should be reviewed for all hearing-impaired infants, however routine infant screening for non-CMV perinatal infections is not recommended, due to low population

prevalence.(33) Screening for TORCH infections should be considered in infants with risk factors (known maternal infection, maternal risk factors, born to immigrant parents) or with a suggestive history or clinical signs (e.g. fundoscopy suggesting congenital infection).(34)

Syphilis and HIV infection, both congenital and acquired, are known causes of SNHL,(35, 36) but are uncommon in Australia.(33) Children with risk factors or clinical indications should be tested after adequate counseling and guidance by an infectious diseases physician.(5, 6, 37, 38)

2.6. Metabolic testing

Bilateral SNHL occurs in a range of metabolic disorders such as congenital disorders of glycosylation, lysosomal storage, mitochondrial and peroxisomal disorders, but is rarely the presenting feature. Routine metabolic testing is not recommended in children with isolated SNHL, but should be considered if there are other suggestive clinical features, such as MIDD syndrome, developmental regression, encephalopathy, intellectual disability, autism, features of storage disorders, hepatosplenomegaly, progressive SNHL, family history of progressive SNHL or auditory neuropathy with suspected Brown Vialetto-Van Laere syndrome.(39)

2.7. Renal ultrasound

Congenital hearing loss and ear anomalies may be associated with renal abnormalities as part of syndromes such as CHARGE syndrome, Townes-Brocks syndrome, branchio-oto-renal (BOR) syndrome, or diabetic embryopathy. Renal ultrasound is recommended in patients with multi-system abnormalities, family history of renal malformations associated with hearing loss,(40) and those with

isolated preauricular pits, cup ears or other ear anomaly accompanied by one or more of the following: cochlear/vestibular malformations, other branchial abnormalities, family history of hearing loss, or maternal history of gestational diabetes.(40)

2.8. Urinalysis

The kidney and ear share a number of ciliary proteins, structural proteins and transcription factors. Disease in both organ systems can be related to mutations in these pathways, including glomerulopathies, tubulopathies, ciliopathies and congenital anomalies of the kidney and urinary tract.(41) Examples are listed in Table 5.(41-43) Urinalysis is recommended where there is delayed onset of SNHL, progressive SNHL or if there is a family history of renal disease as listed above.

2.9. Vestibular testing

Vestibular testing may help in assessing conditions associated with vestibular dysfunction, but may not be readily available or practical for younger children. Vestibular testing can be considered where there is progressive SNHL, delayed motor milestones, suspicion of Usher or Pendred syndromes, poor balance/ dizziness or known temporal bone malformations.(44, 45)

Tier 3 investigations (where Tier 1 and 2 investigations are negative)

3.1. Genetic testing

If connexin testing does not yield informative results in children with non-syndromic bilateral SNHL, chromosome microarray should be offered as it may allow detection of a number of other genetic causes, including copy number variants of known deafness genes, such as *OTOA*, which are implicated in 15% of

cases.(46) We also recommend a clinical genetics review to consider testing for other hearing loss genes. In the future, increasing availability of genomic testing is likely to reduce the need for other investigations.

3.2. MRI at school entry

In children who did not have an early MRI, an MRI without GA should be offered around age 5–6 (when GA is no longer required) to define the inner ear anatomy and assess for LEDS/EVA/LVAS to allow for appropriate management and counseling regarding participation in contact sports.

3.3. Ophthalmology assessment

All children for whom the cause of hearing loss is not known should have repeat ophthalmology assessment at 7–9 years, even if previous ophthalmology assessments are normal, to assess for retinitis pigmentosa that can occur in late childhood as a sign of Usher syndrome.(5, 6) Electroretinography (ERG) should be considered to assess for retinal dystrophy as reduced responses on ERG can be detected even if ophthalmoscopy is normal.(5, 6, 47)

3.4. Urinalysis

Older children should be offered urinalysis at 8–10 years to examine for haematuria/proteinuria to exclude Alport syndrome.(42)

Conclusions

In addition to detailed history taking and examination, all children with congenital hearing loss should have CMV testing, MRI, ophthalmology assessment and family audiograms. Children with bilateral SNHL should be offered genetic testing after adequate genetic counseling, with connexin testing as first-line and microarray as second-line. Genomic testing may become a possibility for all children with bilateral SNHL in the future, and reduce the need for other investigations. The role of genetic testing in unilateral loss is limited and should be guided by clinical presentation. Older children with unknown aetiology for SNHL should be offered MRI, urinalysis and repeat ophthalmology assessment in the primary school years. All other investigations should be based on clinical presentation.

References

1. Ching T, Oong R, Wanrooy v E. The Ages of Intervention in Regions With and Without Universal Newborn Hearing Screening and Prevalence of Childhood Hearing Impairment in Australia. Australian and New Zealand Journal of Audiology. 2006;28(2):137-50.
2. Ching TYC, Dillon H, Button L, Seeto M, Van Buynder P, Marnane V, et al. Age at Intervention for Permanent Hearing Loss and 5-Year Language Outcomes. Pediatrics. 2017.
3. Gurtler N, Gysin C, Schmid N, Pieren C, Vischer M, Schumacher S, et al. Bilateral congenital deafness: What investigations should be performed? Swiss medical weekly. 2017;147:w14416.
4. Guidelines for aetiological investigation into unilateral permanent childhood hearing impairment. Hearing, Balance and Communication. 2016;14(3):146-55.
5. Guidelines for aetiological investigation into severe to profound bilateral permanent childhood hearing impairment. Hearing, Balance and Communication. 2016;14(3):135-45.
6. Guidelines for aetiological investigation into mild to moderate bilateral permanent childhood hearing impairment. Hearing, Balance and Communication. 2016;14(3):125-34.
7. Liming BJ, Carter J, Cheng A, Choo D, Curotta J, Carvalho D, et al. International Pediatric Otolaryngology Group (IPOG) consensus recommendations: Hearing loss in the pediatric patient. International journal of pediatric otorhinolaryngology. 2016;90:251-8.
8. National Health and Medical Research Council. NHMRC additional levels of evidence and grades for recommendations for developers of guidelines 2009 [26th April 2018]. Available from: https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf.
9. Rawlinson WD, Palasanthiran P, Hall B, Al Yazidi L, Cannon MJ, Cottier C, et al. Neonates with congenital Cytomegalovirus and hearing loss identified via the universal newborn hearing screening program. Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology. 2018;102:110-5.
10. Boppana SB, Ross SA, Shimamura M, Palmer AL, Ahmed A, Michaels MG, et al. Saliva polymerase-chain-reaction assay for cytomegalovirus screening in newborns. New England Journal of Medicine. 2011;364(22):2111-8.
11. Rawlinson WD, Boppana SB, Fowler KB, Kimberlin DW, Lazzarotto T, Alain S, et al. Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy. The Lancet Infectious diseases. 2017;17(6):e177-e88.

12. Ross SA, Ahmed A, Palmer AL, Michaels MG, Sánchez PJ, Stewart A, et al. Newborn dried blood spot polymerase chain reaction to identify infants with congenital cytomegalovirus-associated sensorineural hearing loss. Journal of Pediatrics. 2017;184:57-61. e1.
13. Kimberlin DW, Jester PM, Sánchez PJ, Ahmed A, Arav-Boger R, Michaels MG, et al. Valganciclovir for symptomatic congenital cytomegalovirus disease. New England Journal of Medicine. 2015;372(10):933-43.
14. Mathews JD, Forsythe AV, Brady Z, Butler MW, Goergen SK, Byrnes GB, et al. Cancer risk in 680,000 people exposed to computed tomography scans in childhood or adolescence: data linkage study of 11 million Australians. Bmj. 2013;346:f2360.
15. Pearce MS, Salotti JA, Little MP, McHugh K, Lee C, Kim KP, et al. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. Lancet. 2012;380(9840):499-505.
16. Wiley S, Arjmand E, Jareenmeinzen D, Dixon M. Findings from multidisciplinary evaluation of children with permanent hearing loss. International journal of pediatric otorhinolaryngology. 2011;75(8):1040-4.
17. Licameli G, Kenna MA. Is computed tomography (CT) or magnetic resonance imaging (MRI) more useful in the evaluation of pediatric sensorineural hearing loss? The Laryngoscope. 2010;120(12):2358-9.
18. Clemmens CS, Guidi J, Caroff A, Cohn SJ, Brant JA, Laury AM, et al. Unilateral cochlear nerve deficiency in children. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2013;149(2):318-25.
19. Chan DK, Chang KW. GJB2-associated hearing loss: systematic review of worldwide prevalence, genotype, and auditory phenotype. The Laryngoscope. 2014;124(2):E34-53.
20. Paul A, Marlin S, Parodi M, Rouillon I, Guerlain J, Pingault V, et al. Unilateral Sensorineural Hearing Loss: Medical Context and Etiology. Audiology & neuro-otology. 2017;22(2):83-8.
21. Gruber M, Brown C, Mahadevan M, van der Meer G, Neeff M. The Yield of Multigene Testing in the Management of Pediatric Unilateral Sensorineural Hearing Loss. Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology. 2016;37(8):1066-70.
22. Nikolopoulos TP, Lioumi D, Stamataki S, O'Donoghue GM. Evidence-based overview of ophthalmic disorders in deaf children: a literature update. Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology. 2006;27(2 Suppl 1):S1-24, discussion S0.
23. Johnston DR, Curry JM, Newborough B, Morlet T, Bartoshesky L, Lehman S, et al. Ophthalmologic disorders in children with syndromic and nonsyndromic

hearing loss. Archives of otolaryngology--head & neck surgery. 2010;136(3):277-80.
24. Shearer A, Hildebrand M, Smith R. Hereditary Hearing Loss and Deafness Overview. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1434 1999 Feb 14 [Updated 2017 Jul 27].
25. Downie L, Halliday JL, Burt RA, Lunke S, Lynch E, Martyn M, et al. A protocol for whole-exome sequencing in newborns with congenital deafness: a prospective population-based cohort. BMJ paediatrics open. 2017;1(1):e000119.
26. Usami S, Nishio S. Nonsyndromic Hearing Loss and Deafness, Mitochondrial. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, et al., editors. GeneReviews((R)). Seattle (WA)1993.
27. Dean L. Gentamicin Therapy and MT-RNR1 Genotype. In: Pratt V, McLeod H, Rubinstein W, Dean L, Kattman B, Malheiro A, editors. Medical Genetics Summaries. Bethesda (MD): National Center for Biotechnology Information (US); 2012.
28. Nesbitt V, Pitceathly RD, Turnbull DM, Taylor RW, Sweeney MG, Mudanohwo EE, et al. The UK MRC Mitochondrial Disease Patient Cohort Study: clinical phenotypes associated with the m.3243A>G mutation--implications for diagnosis and management. Journal of neurology, neurosurgery, and psychiatry. 2013;84(8):936-8.
29. Reardon W, Coffey R, Chowdhury T, Grossman A, Jan H, Britton K, et al. Prevalence, age of onset, and natural history of thyroid disease in Pendred syndrome. Journal of medical genetics. 1999;36(8):595-8.
30. Wasniewska M, De Luca F, Siclari S, Salzano G, Messina MF, Lombardo F, et al. Hearing loss in congenital hypothalamic hypothyroidism: a wide therapeutic window. Hearing research. 2002;172(1-2):87-91.
31. Niaz A, Rizvi SF, Khurram D. Prevalence of long QT syndrome and other cardiac defects in deaf-mute children. Journal of Ayub Medical College, Abbottabad : JAMC. 2011;23(1):5-8.
32. Cohen BE, Durstenfeld A, Roehm PC. Viral causes of hearing loss: a review for hearing health professionals. Trends in hearing. 2014;18:2331216514541361.
33. Australian Government Department of Health. Australian Paediatric Surveillance Unit annual report. Accessed 10th December 2018 from: http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-cdi4102f.htm 2015.
34. Palasanthiran P, Starr M, Jones C, Giles M. Australasian Society for Infectious Diseases: Mangement of perinatal infections. Accessed 10th December 2018 from: https://www.asid.net.au/documents/item/368. 2014.
35. Arnold SR, Ford-Jones EL. Congenital syphilis: A guide to diagnosis and management. Paediatrics & child health. 2000;5(8):463-9.

36. Torre P, 3rd, Zeldow B, Hoffman HJ, Buchanan A, Siberry GK, Rice M, et al. Hearing loss in perinatally HIV-infected and HIV-exposed but uninfected children and adolescents. The Pediatric infectious disease journal. 2012;31(8):835-41.
37. Communicable Diseases Network Australia (CDNA). National Guidelines for Public Health Units on Syphilis. 2015.
38. Communicable Diseases Network Australia (CDNA). National Guidelines for Public Health Units on Human Immunodeficiency Virus (HIV). 2014.
39. Bosch AM, Stroek K, Abeling NG, Waterham HR, Ijlst L, Wanders RJ. The Brown-Vialetto-Van Laere and Fazio Londe syndrome revisited: natural history, genetics, treatment and future perspectives. Orphanet journal of rare diseases. 2012;7:83.
40. Wang RY, Earl DL, Ruder RO, Graham JM, Jr. Syndromic ear anomalies and renal ultrasounds. Pediatrics. 2001;108(2):E32.
41. Phelan PJ, Rheault MN. Hearing loss and renal syndromes. Pediatric nephrology. 2018;33(10):1671-83.
42. Alves FR, de A Quintanilha Ribeiro F. Revision about hearing loss in the Alport's syndrome, analyzing the clinical, genetic and bio-molecular aspects. Brazilian journal of otorhinolaryngology. 2005;71(6):813-9.
43. Kimberling WJ, Borsa N, Smith RJ. Hearing loss disorders associated with renal disease. Advances in oto-rhino-laryngology. 2011;70:75-83.
44. Maes L, De Kegel A, Van Waelvelde H, Dhooge I. Association between vestibular function and motor performance in hearing-impaired children. Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology. 2014;35(10):e343-7.
45. Verbecque E, Marijnissen T, De Belder N, Van Rompaey V, Boudewyns A, Van de Heyning P, et al. Vestibular (dys)function in children with sensorineural hearing loss: a systematic review. Int J Audiol. 2017;56(6):361-81.
46. Shearer AE, Kolbe DL, Azaiez H, Sloan CM, Frees KL, Weaver AE, et al. Copy number variants are a common cause of non-syndromic hearing loss. Genome medicine. 2014;6(5):37.
47. Smith RJ, Berlin CI, Hejtmancik JF, Keats BJ, Kimberling WJ, Lewis RA, et al. Clinical diagnosis of the Usher syndromes. Usher Syndrome Consortium. American journal of medical genetics. 1994;50(1):32-8.
48. Rance G. Auditory neuropathy/dys-synchrony and its perceptual consequences. Trends in amplification. 2005;9(1):1-43

Table 1 : Types of hearing loss

Type of Hearing Loss	Description
Sensorineural hearing loss (SNHL)	Hearing loss that is caused by abnormalities of the cochlea and/or auditory nerve, which subsequently interferes with conversion of sound into electrical signals, or signal transmission along the auditory nerve to the brain. SNHL can be congenital or acquired (see figure 1).
Conductive hearing loss (CHL)	Hearing loss that occurs when there is injury, obstruction or disease of the outer or middle ear, which interferes with sound transmission to the inner ear. Permanent conductive loss may be caused by microtia, other outer ear malformations, tumours (cholesteatoma) or otosclerosis; temporary conductive loss may be caused by otitis media with or without effusion, impacted earwax, foreign bodies, or tympanic membrane perforation.

Mixed hearing loss	Hearing loss due to the presence of both SNHL and CHL.
Auditory Neuropathy / Auditory Neuropathy Spectrum Disorder	Hearing loss that is due to either a dys-synchronous signal along the auditory nerve (either due to inner hair cell or transmitter abnormalities) or a true neuropathy with a poor abnormal transmission of the auditory signal along the auditory nerve. Audiology testing in auditory neuropathy may have a number of different characteristics: classically there is normal cochlea outer hair cell function (seen by the presence of otoacoustic emissions) and absent or abnormal auditory nerve function (with abnormal Auditory Brainstem Response accompanied by presence of cochlear microphonics). Auditory neuropathy may be an indication of a) inner hair cell deficits (e.g. perinatal hypoxia, prematurity), b) disorder in the synapse between the inner hair cells and auditory nerve terminals (e.g. neurotransmitter release deficits with disruption of the otoferlin OTOF protein), c) auditory nerve dysfunction (e.g. jaundice, hypoplastic auditory nerve(s), neuropathies), d) myelin disorders (e.g. Charcot-Marie-Tooth disease type 1) or e) axonal neuropathies (e.g.

Friedreich ataxia).(48)

Table 2: Details of consensus voting process for Tier 1 investigations

For each Tier 1 investigation, each working group member voted for one NHMRC grade of recommendation: A: Body of evidence can be trusted to guide practice B: Body of evidence can be trusted to guide practice in most situations C: Body of evidence provides some support for recommendation(s) but care should be taken in its application D: Body of evidence is weak and recommendation must be applied with caution
The strength of recommendation was then recorded depending on the proportion of votes received: + : 26 – 49% of votes ++: 50 – 69% of votes +++: 70 – 99% of votes

++++: 100% of votes

Table 3. History to assess aetiology and guide management of hearing loss

Antenatal history	o Spontaneous/recurrent miscarriages o Infections, febrile/flu-like illnesses o Drug/alcohol use o Medication use (e.g. ototoxic medications) o Known in-utero infections: cytomegalovirus (CMV), toxoplasmosis, herpes simplex virus (HSV), varicella, rubella, syphilis, human immunodeficiency virus (HIV) o Maternal immunisation status and serological results: rubella immunity (rubella IgG>10IU/ml), syphilis, HIV and varicella testing

	○ Other investigations: ultrasound, amniocentesis, chorionic villus sampling, first trimester combined screen, non-invasive prenatal testing

Birth history	○ Gestation ○ Delivery type ○ Condition at birth (e.g. Apgar scores) ○ Birth weight, length and head circumference (chart percentiles) ○ Complications/interventions at delivery (e.g. resuscitation, respiratory/cardiovascular support, admissions to special care nursery/intensive care, duration of admission, sepsis, hypoglycaemia, seizures, use of ototoxic medications e.g. aminoglycosides/loop diuretics) ○ Jaundice requiring phototherapy/exchange transfusion, peak serum bilirubin ○ Abnormalities noted/suspected/diagnosed at birth
Post-natal history	○ Bacterial meningitis ○ Head injuries ○ Proven/suspected congenital infections (e.g. CMV/toxoplasmosis/HSV/rubella/syphilis) ○ Exposure to ototoxic medications (e.g. aminoglycosides, loop diuretics, cisplatin) ○ Cranial irradiation ○ Motor delay/balance issues (consider vestibular dysfunction) ○ Haematuria (Alport syndrome)

Family history: three-generation family tree	○ Audiograms from first-degree relatives ○ Consanguinity ○ Family history of hearing loss, goitre (Pendred syndrome), pigment abnormalities (Waardenburg syndrome, neurofibromatosis type 2), congenital renal anomalies, renal failure (Alport syndrome, branchio-oto-renal syndrome BOR), short stature (Stickler syndrome, 22q deletion), cardiac malformations (22q deletion, CHARGE), arrhythmias/sudden death (Jervell Lange Nielson), vision issues (Usher syndrome), ear and neck malformations, developmental delay/regression, neurological conditions
Social history	○ Other specialists/services involved, access to financial supports/service pathways (including Carer allowance, National Disability Insurance Scheme) ○ Migration history (including risk factors for congenital infection) ○ Language, family structure, employment ○ Adjustment, impact on family, resilience and coping factors, including supports

Table 4: Key characteristics on physical examination

Examination systems	Physical features	Examples of diagnoses to consider
Growth (weight, length, head circumference percentiles)	Microcephaly Low birth weight	Congenital infections
Development	Developmental delay/regression Gross motor delay*	Congenital infections / metabolic disorders Neurological causes (e.g. prematurity, hypoxic ischaemia encephalopathy) *Gross motor delay may be an early manifestation of vestibular dysfunction (consider Pendred, Usher)
General	Dysmorphology	Syndromic causes

	Pigmentation: skin / hair /eyes	Waardenburg syndrome
	Coarse features	Metabolic / storage disorders
	Blood pressure	Renal causes
Head and neck	Facial asymmetry	Developmental causes (especially with unilateral hearing loss e.g. branchio-oto-renal syndrome)
	Abnormal external ears	
	Abnormal ear canals	
	Preauricular sinuses / pits / tags	
	Bifid uvula	
	Cleft palate / submucous cleft	
	Tympanic membrane status	Middle ear fluid

	Goitre	Pendred (goitre onset usually in mid-late childhood)
Eyes	Cataracts	Congenital infections
	Retinal scarring (fundoscopy)	
	Microphthalmia	Syndromic causes
	Hypertelorism	Waardenburg
	Heterochromia iridium	
	Retinitis pigmentosa (fundoscopy)	Usher (retinitis pigmentosa onset usually in mid-late childhood; electroretinography best screening tool)

Neurologic	Hypotonia	Neurological causes (e.g. prematurity, hypoxic ischaemia encephalopathy, space occupying lesions)
	Ataxia	
	Focal neurological signs	
Cardiac	Murmur	Cardiac causes
Skeletal	Spine	Bony dysplasias
	Digits	Connective tissue disorders
	Nails	
	Hyperextendable joints	
Abdominal	Organomegaly	Storage disorders

Urine dipstick / microscopy	Haematuria	Alport (onset usually late childhood)

Table 5: Investigations for childhood sensorineural hearing loss and auditory neuropathy

	Bilateral hearing loss (HL)	Unilateral hearing loss (HL)	Strength of recommendation for Tier 1 investigations
Tier 1: First-line recommendations[†]			
CMV saliva PCR	• For all infants within 21 days of birth		B ++++
CMV dried blood spot PCR	• Beyond 21 days if saliva PCR not available		B +++

MRI brain & parasagittal sections of internal acoustic canal	• Early 'feed and wrap' +/- sedation for all where possible, especially for severe to profound HL, asymmetric, or auditory neuropathy • Under general anaesthetic if cochlear implant candidate, progression of HL, bilateral auditory neuropathy or other indications for MRI brain • Without general anaesthetic at school entry for all if cause unknown	• Early 'feed and wrap' +/- sedation for all • Under general anaesthetic if unilateral auditory neuropathy, cochlear implant candidate, progression of HL or other indications for MRI brain • Without general anaesthetic for all at school entry if cause unknown	B ++

Connexin 26/30 (GJB2/GJB6)	• All bilateral HL according to parental wish	• Not recommended	B +++
Family audiograms	• For all first degree family members		C +++
Ophthalmology examination	• Visual acuity assessment before school (Tier 1) • At any stage if features of congenital infections, syndromic features, or concerns about vision, night vision, hypotonia, poor coordination, clumsiness, or where hearing loss is profound or progressive (Tier 2) • At 18 months if not yet walking (Tier 2) • At 7-9 years if cause unknown (+/- electroretinography for Usher syndrome) (Tier 3)		B ++++

Tier 2: recommended for specific clinical indications[†]		
Chromosome microarray	• Developmental delay/regression or complex phenotype • If connexin testing negative (Tier 3)	• Developmental delay/regression or complex phenotype

Whole exome sequencing or hearing loss gene panel	• Syndromic features or complex phenotype • If connexin / microarray testing negative (Tier 3)	• Syndromic features or complex phenotype
Thyroid function	• Poor growth, developmental delay, goitre, newborn blood screen completed early (before 48 hours of age) • From 10 years of age if LEDS/EVA/LVAS or genetic mutation indicative of Pendred syndrome	
Resting ECG	• Bilateral severe–profound HL, or • Syncopal episodes, or • Family history of unexplained sudden death, arrhythmias or	• Not recommended

	syncope
CT scan	• Permanent conductive HL, or • Further information beyond MRI: e.g. bony anatomy (possible surgical correction), major cochlear abnormality
Perinatal infection testing	• 'At risk' babies i.e. known maternal infection (serological or clinical evidence), ophthalmology findings
Metabolic testing	• Genetic testing for mitochondrial DNA variants (MT-RNR1) to be considered if: o Family history of HL with matrilineal inheritance, or

- Children with HL following aminoglycoside administration, or
- History or family history suggestive of maternally inherited diabetes and deafness (MIDD, HL and diabetes usually in mid-adulthood)

- As clinically indicated, including: developmental regression, encephalopathy, intellectual disability, autism, features of storage disorders, hepatosplenomegaly, progressive HL, family history of progressive HL or auditory neuropathy with suspected Brown Vialetto-Van Laere syndrome

Renal ultrasound	• Multi-system abnormalities, or • Family history of renal malformations associated with hearing loss, or • Isolated preauricular pits, cup ears or other ear anomaly accompanied by one or more of the following: cochlear/vestibular malformations (seen on imaging, e.g. LEDS/EVA/LVAS, Mondini deformity of the cochlea or dysplasia of the semicircular canals), other branchial abnormalities (e.g. branchial cleft fistulae or cysts), family history of HL or maternal history of gestational diabetes

Urinalysis for haematuria / proteinuria	• Family history of renal disease (Alport syndrome, MYH9-related disorders with progressive high frequency hearing loss, Fabry disease, Charcot-Marie-Tooth disease, Cockayne syndrome, cystic kidney disease, Bardet-Biedl syndrome, Alstrom syndrome, tubulopathies including Bartter syndrome, Pendred syndrome and distal renal tubular acidosis) • Delayed onset or progressive HL, or branchio-oto-renal syndrome • Around 10 years of age if cause unknown (Tier 3)

HL = hearing loss; CMV = cytomegalovirus; MRI = magnetic resonance imaging; GA = general anaesthetic; LEDS/EVA/LVAS = large endolymphatic ducts and sacs / enlarged vestibular aqueducts / large vestibular aqueduct syndrome; CT = computerised tomography; ECG = electrocardiogram

† Includes lower tier investigations where indicated

Table 6: Suggested referrals for children with hearing loss

Service / health profession	Timing and referral reasons
Audiology	All – at the following time-points and as clinically indicated: • At diagnosis • At around 6-9 months for behavioural testing • 6-monthly to yearly until age 5 years (more frequently if known congenital CMV, LEDS/EVA/LVAS, progressive loss or concurrent middle ear fluid) • Yearly thereafter, unless clinical deterioration identified

Otolaryngology (Ear Nose and Throat (ENT) surgeon)	• Consideration of cochlear implant • Progressive loss • Permanent conductive hearing loss including microtia • Middle ear disease / consideration of ventilation tubes (grommets) • Family request

Paediatrician	All – at following time-points and as clinically indicated:
	• At diagnosis if not already seeing ENT (or together with ENT)
	• Around 9 months after behavioural testing confirmation
	• At key developmental stages to monitor development:
	  ○ 15-18 months
	  ○ 2 years
	  ○ 3 years
	• 4 years (prepare for school entry)
	• 5 years (school entry: review services with school transition, organise MRI to exclude LEDS/EVA/LVAS and give advice on contact sports; consider referral to ophthalmology for Usher)
	• 10-11 years (primary school exit: urine dipstick, TFTs if LEDS/EVA/LVAS, refer to ophthalmology for Usher)
	• 12 years (secondary school entry: review services with school transition)

Early intervention services	• All moderate-severe bilateral hearing loss • Mild and unilateral hearing loss: refer as indicated; should be offered if available • General early intervention services for children with global developmental issues • Vision support services for children with dual sensory issues • Consider services that offer signing and/or spoken language support depending on the child's developmental progress and family preferences
Other allied health	• Consider psychology and other allied health supports according to the child's needs
Genetics	• For bilateral hearing loss, according to parental wishes • Especially important if dysmorphic/syndromic features (>400 syndromes with hearing loss)
Ophthalmology	• See Table 3

Neurology	• Children with neurological impairment or abnormal MRI (e.g. 'non-specific white matter changes') • Auditory neuropathy (associated with mitochondrial disorders, Charcot-Marie-Tooth, Friedrich ataxia) • Family history of peripheral neuropathy
Cardiology	• Cardiology review if clinical features suggesting cardiac disease, ECG abnormal, syndromic diagnosis associated with cardiac abnormalities, or a family history of cardiomyopathy
Vestibular assessment	• Consider for children with gross motor delay or balance issues

LEDS/EVA/LVAS = large endolymphatic ducts and sacs / enlarged vestibular aqueducts / large vestibular aqueduct syndrome

Figure 1: Aetiology of childhood hearing loss

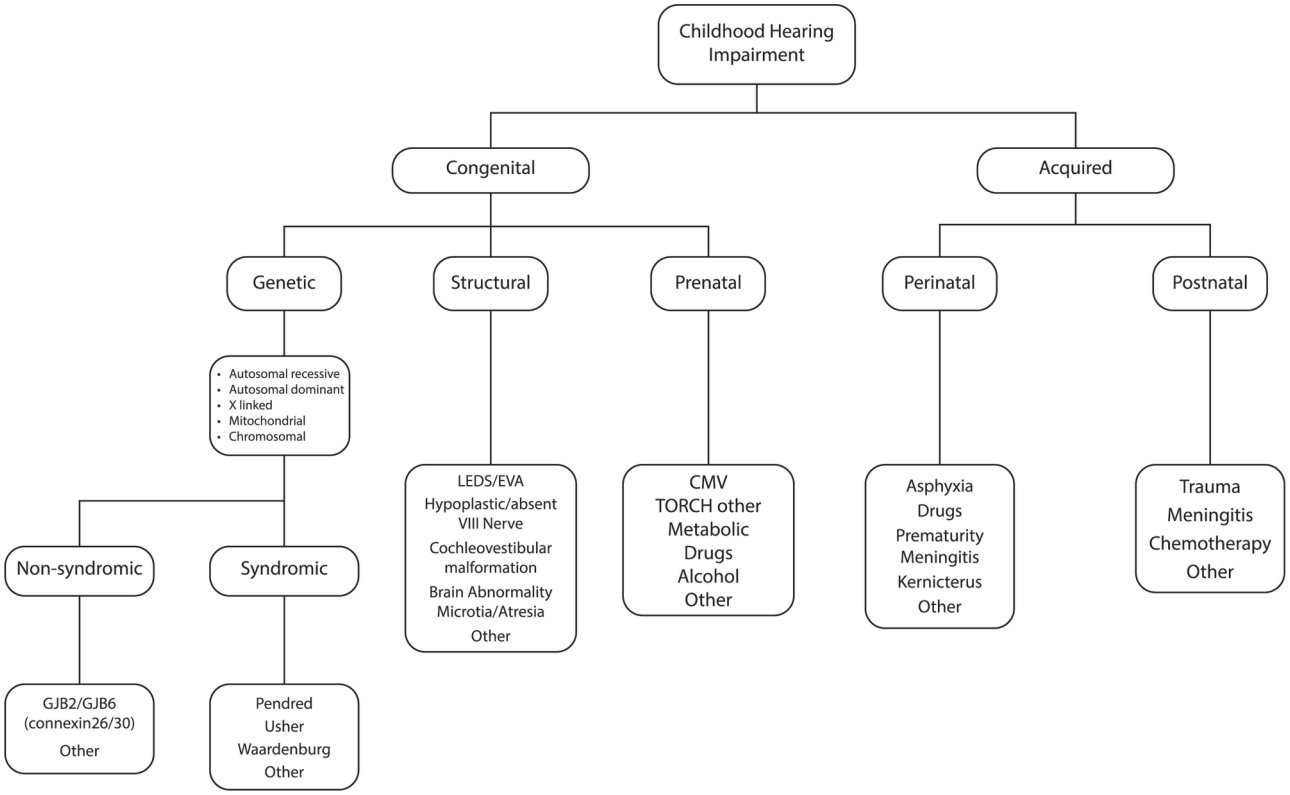
Abbreviations for Figure 1

LEDS = large endolymphatic ducts and sacs

EVA = enlarged vestibular aqueducts

CMV = cytomegalovirus

TORCH = **T**oxoplasmosis, **O**ther (syphilis, varicella, parvovirus B19), **R**ubella, **C**ytomegalovirus, **H**erpes simplex virus



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Full names of authors:

1. Valerie Sung
   - Murdoch Children's Research Institute, 50 Flemington Road, Parkville, VIC, 3052
   - Royal Children's Hospital, 50 Flemington Road, Parkville, VIC, 3052
   - Department of Paediatrics, University of Melbourne, Parkville, VIC, 3052

2. Lilian Downie
   - Murdoch Children's Research Institute, 50 Flemington Road, Parkville, VIC, 3052
   - Royal Children's Hospital, 50 Flemington Road, Parkville, VIC, 3052
   - Victorian Clinical Genetics Service, 50 Flemington Road, Parkville, VIC, 3052
   - Department of Paediatrics, University of Melbourne, Parkville, VIC, 3052

3. Georgia A. Paxton
   - Murdoch Children's Research Institute, 50 Flemington Road, Parkville, VIC, 3052
   - Royal Children's Hospital, 50 Flemington Road, Parkville, VIC, 3052
   - Department of Paediatrics, University of Melbourne, Parkville, VIC, 3052

4. Karen Liddle
   - Queensland Children's Hospital, Stanley St, South Brisbane, QLD, 4101
   - University of Queensland, Herston Rd, Herston, QLD, 4006

5. Catherine S. Birman

- The Children's Hospital at Westmead, Corner Hawkesbury Road and Hainsworth Street, Westmead, NSW, 2145
- Sydney Cochlear Implant Centre, PO Box 188, Gladesville, NSW, 2111
- Sydney Medical School, The University of Sydney, Camperdown, NSW, 2006
- Macquarie University, NSW, 2109

6. Wei Wei Chan
   - Department of Paediatrics, Gold Coast University Hospital, 1 Hospital Boulevard, Southport, QLD, 4215
   - School of Medicine, Griffith University, Parklands Drive, Southport, QLD, 4215

7. Carolyn Cottier
   - Sydney Children's Hospital, High Street, Randwick, NSW, 2031
   - University of New South Wales, Sydney, NSW, 2052

8. Alison Harris
   - Queensland Children's Hospital, Stanley St, South Brisbane, QLD, 4101
   - University of Queensland, Herston Rd, Herston, QLD, 4006

9. Matthew Hunter
   - Monash Genetics, Monash Health, Clayton, VIC, 3168
   - Department of Paediatrics, Monash University, Clayton, VIC, 3168

10. Elizabeth Peadon
    - Deafness Centre, The Children's Hospital at Westmead, Corner Hawkesbury Road and Hainsworth Street, Westmead, NSW, 2145

11. Kenneth Peacock
    - Deafness Centre, The Children's Hospital at Westmead, Corner Hawkesbury Road and Hainsworth Street, Westmead, NSW, 2145

12. Laurence Roddick

- John Hunter Children's Hospital, Locked Bag 1, HRMC, NSW, 2310
- University of Newcastle, University Drive, Callaghan, NSW, 2308

13. Elizabeth Rose
    - Royal Children's Hospital, 50 Flemington Road, Parkville, VIC, 3052
    - Department of Otolaryngology, University of Melbourne, Parkville, VIC, 3052
    - Murdoch Childrens Research Institute, 50 Flemington Road, Parkville, VIC, 3052
    - Royal Victorian Eye and Ear Hospital, 32 Gisborne Street, East Melbourne VIC, 3002

14. Kerryn Saunders
    - Paediatric Hearing Services, Monash Children's Hospital, Clayton, VIC, 3168
    - Department of Paediatrics, Monash University, Clayton, VIC, 3168

15. David J Amor
    - Murdoch Children's Research Institute, 50 Flemington Road, Parkville, VIC, 3052
    - Royal Children's Hospital, 50 Flemington Road, Parkville, VIC, 3052
    - Victorian Clinical Genetics Service, 50 Flemington Road, Parkville, VIC, 3052
    - Department of Paediatrics, University of Melbourne, Parkville, VIC, 3052

Corresponding author

Dr Valerie Sung

Valerie.sung@rch.og.au

Murdoch Children's Research Institute

Royal Children's Hospital

50 Flemington Road, Parkville, VIC, 3052, Australia

Ph: +613 9345 4363

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Conflicts of Interest

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