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Genotype-phenotype correlations in childhood hearing loss: Audit of statewide tertiary genetic service testing

Dr Karen Liddle
Paediatrician and PhD Candidate

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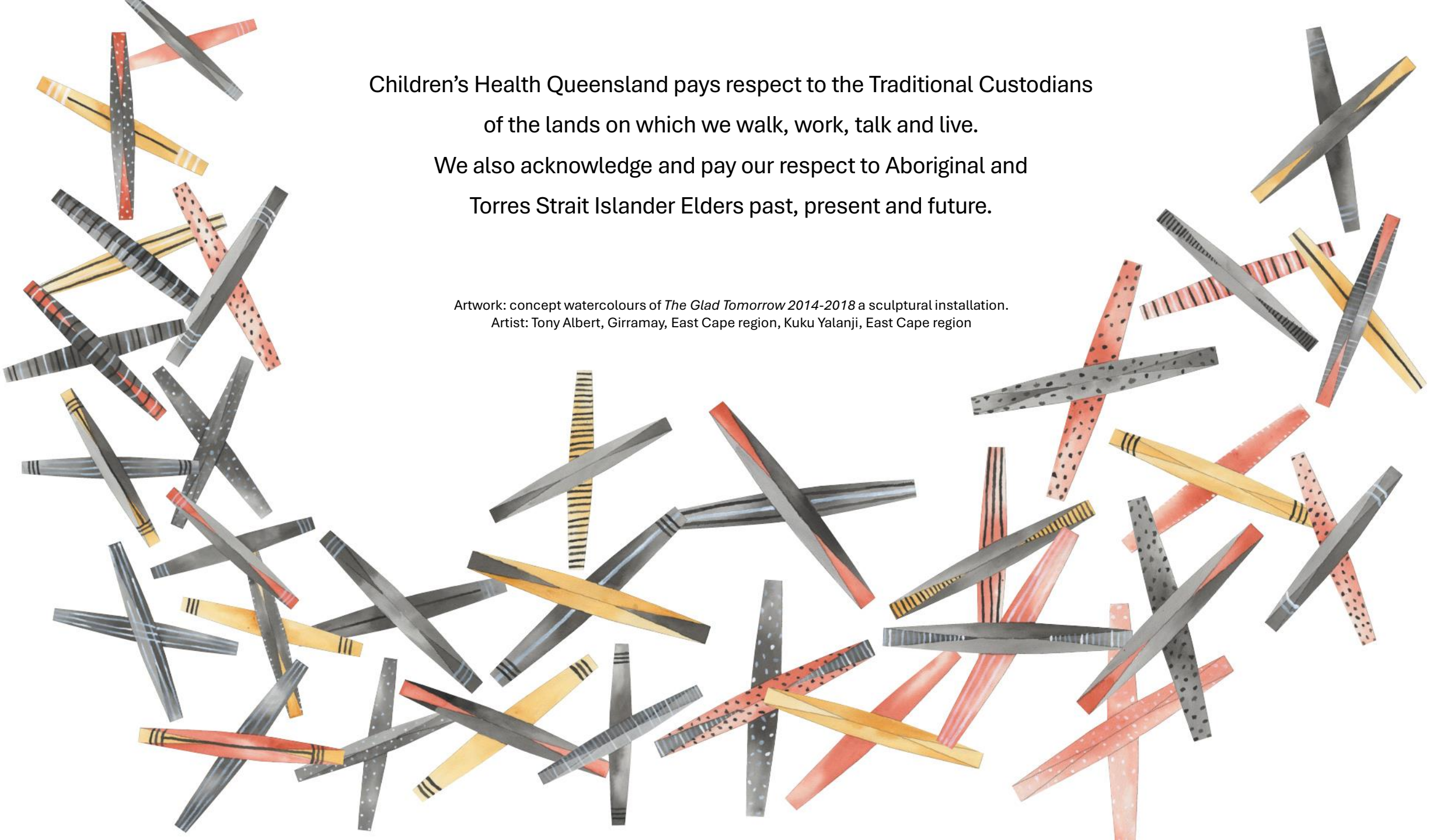
Children's Health Queensland pays respect to the Traditional Custodians of the lands on which we walk, work, talk and live.

We also acknowledge and pay our respect to Aboriginal and Torres Strait Islander Elders past, present and future.



Artwork: concept watercolours of *The Glad Tomorrow 2014-2018* a sculptural installation.
Artist: Tony Albert, Girramay, East Cape region, Kuku Yalanji, East Cape region

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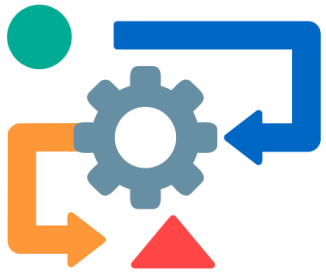
Importance of this study

Genetic tests



Methods

Cohort

Next steps

Usher syndrome

Key findings

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Why is this study important?

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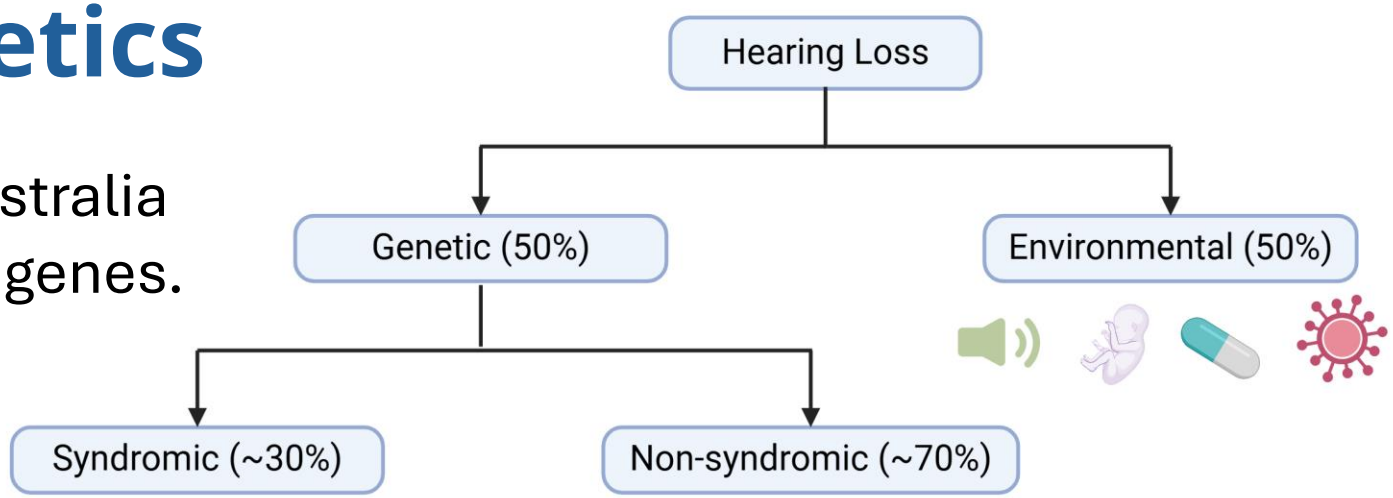
Hearing loss genetics

- Until recently, testing in Australia was limited to a handful of genes.



>400 genes

>120 genes

Diagram modified from Morgan et al. 2020.

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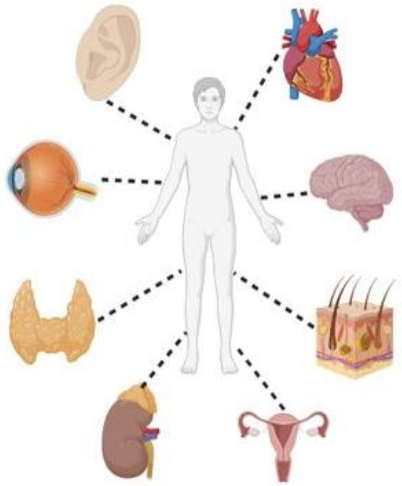
Benefits of genetic testing for hearing loss

Future of hearing loss



Syndromic diagnoses

Family information

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What types of genetic tests are available?

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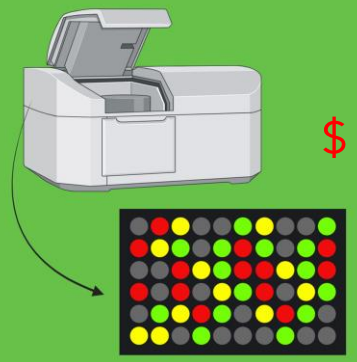
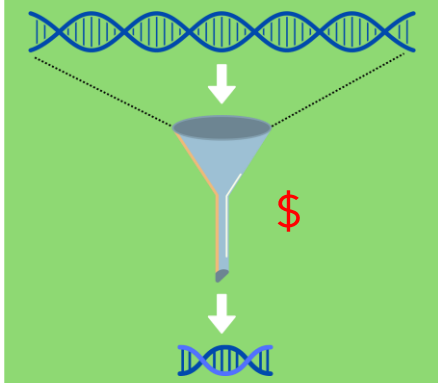
Types of genetic tests

Chromosomal Microarray



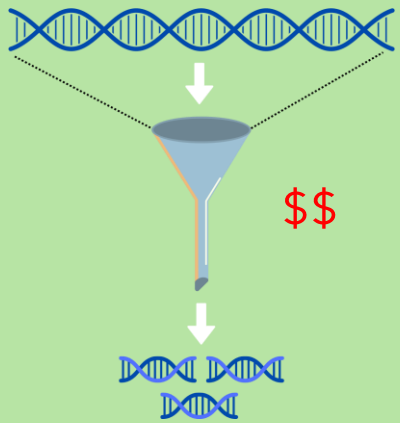
- Small deletions and duplications
- Results in 2-4 weeks

Single Gene



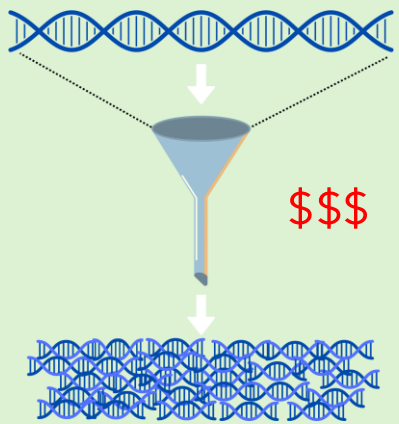
- Clear indication of the gene involved
- Known family history
- Results in 2-6 weeks

Multigene Panel



- Targeted panel of 2-1000+ genes
- Condition / phenotype specific
- Results in 2-6 weeks

WES / WGS



- **Whole exome**: coding regions (1% of genome)
- **Whole genome:** coding + non-coding + CNVs
- Agnostic approach
- Results in 3-6 months

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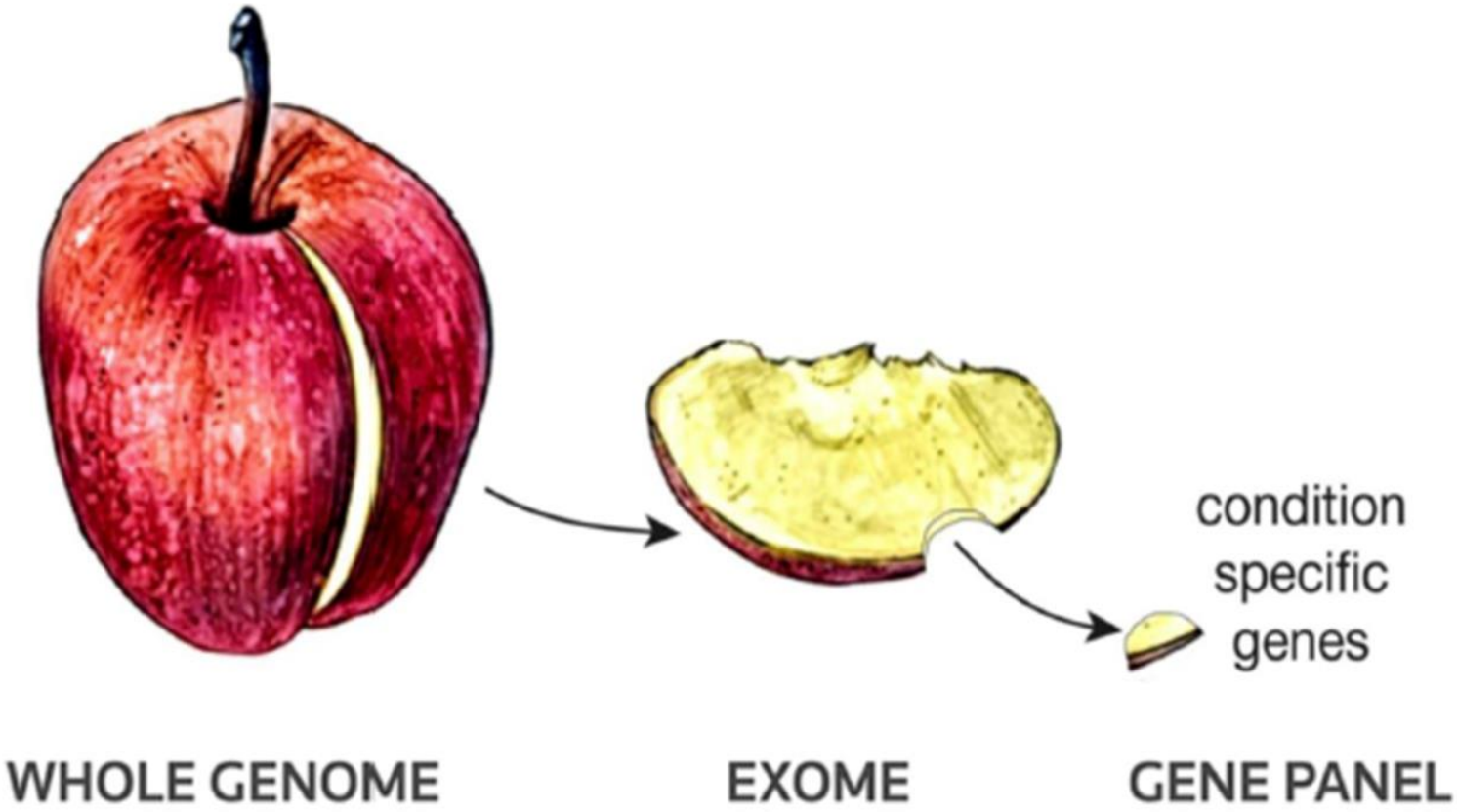

Image modified courtesy of University of Washington

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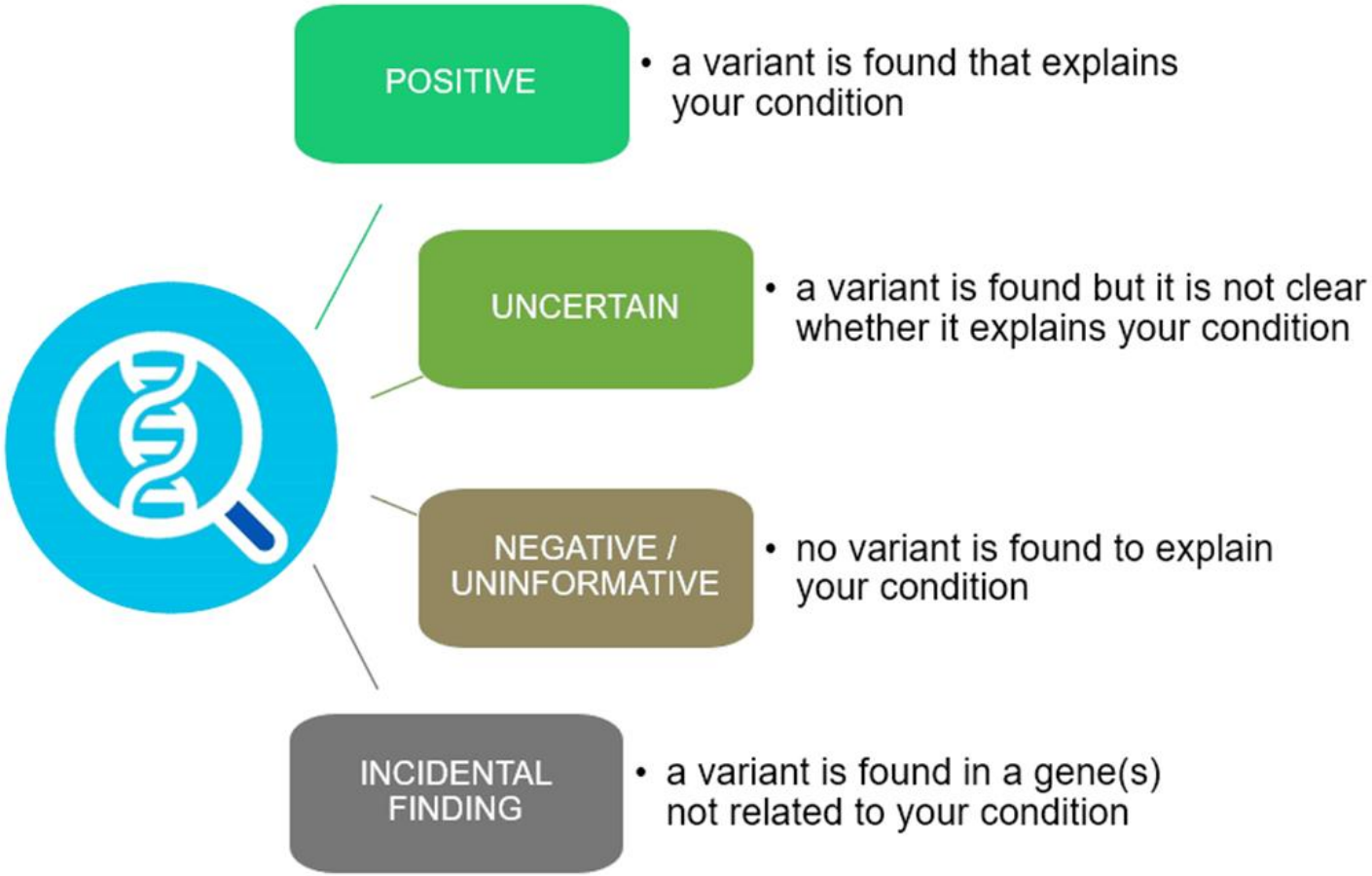
Possible results



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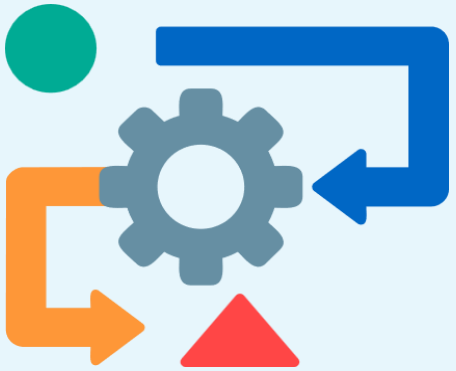
What did we do?



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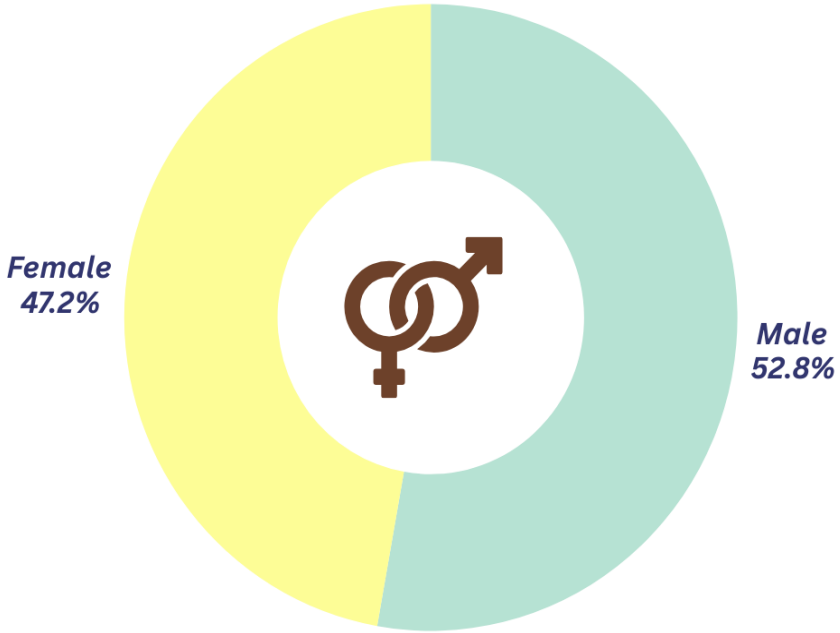
Genetic Health Queensland (GHQ) audit

- Statewide audit of children referred to GHQ for indication of hearing loss
- Diagnostic cohort: 82 in total positive genetic result
- Date range: 2014-2024



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Context: Cohort details

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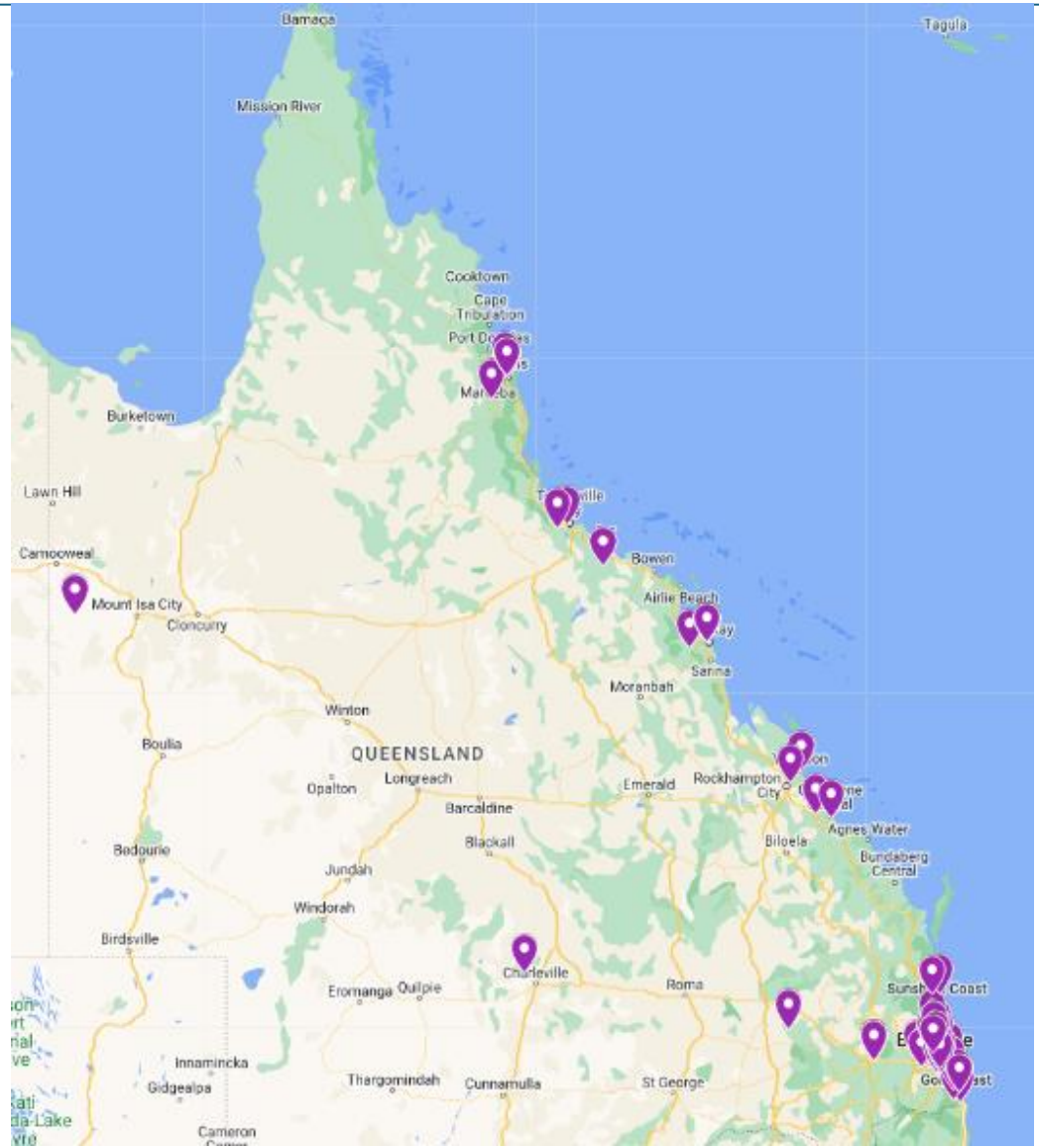
Cohort - location

N=82



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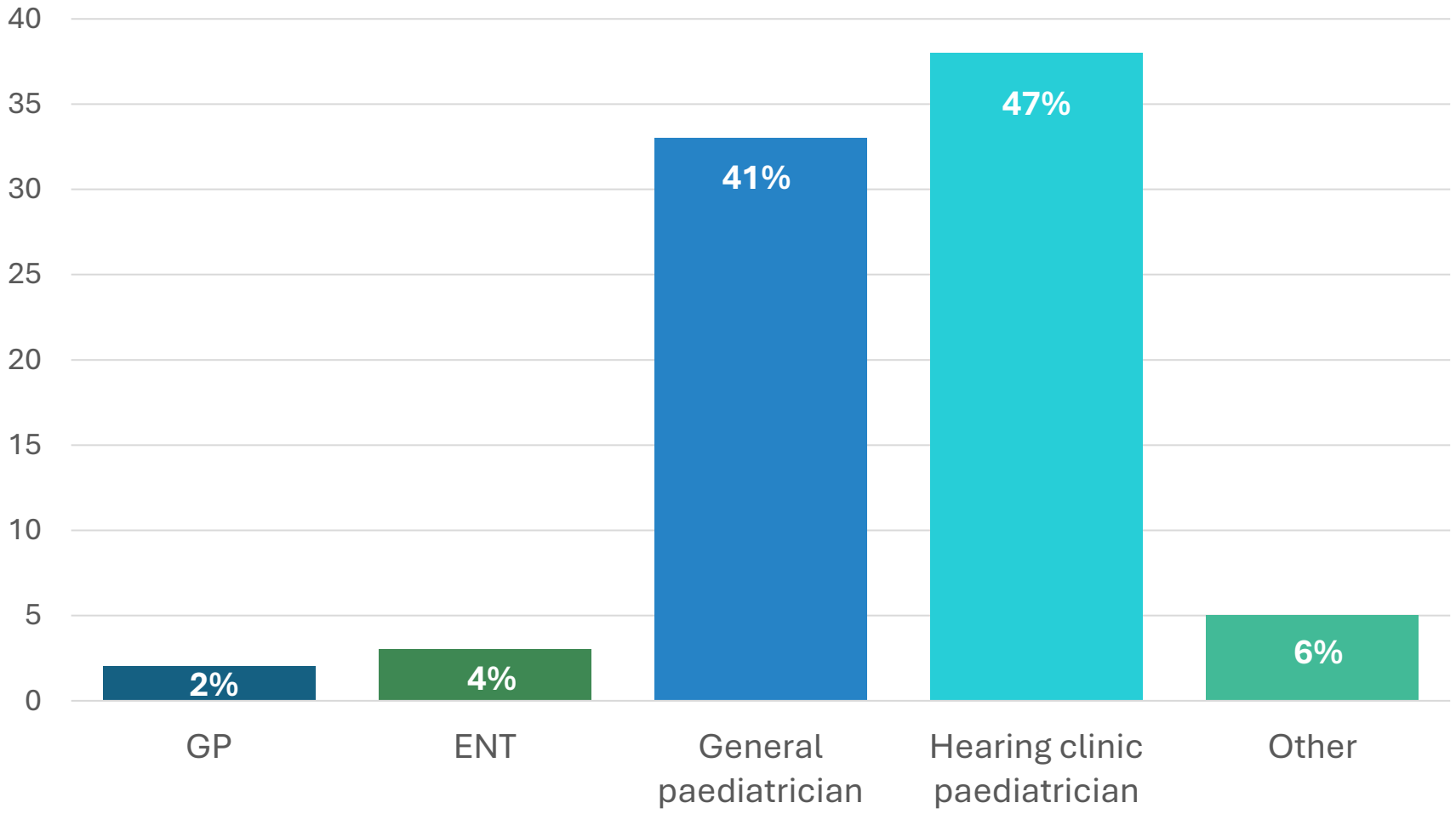
Referral source



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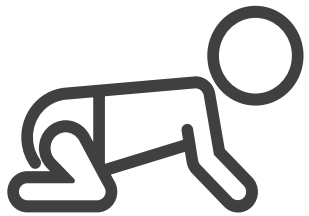
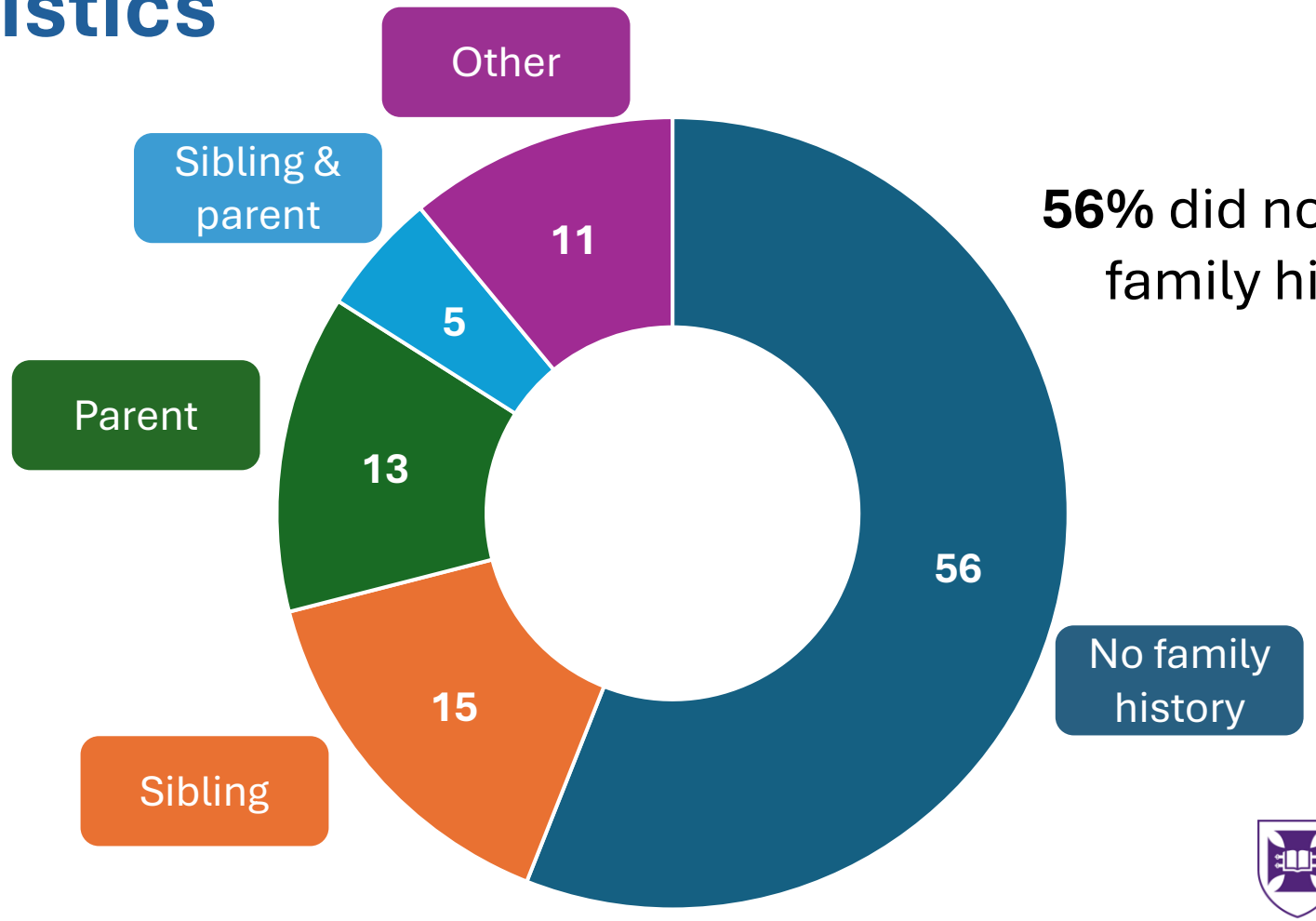
Cohort characteristics



Most **(84.2%)** were born at term.



56% did not have a family history.

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What did our results show?

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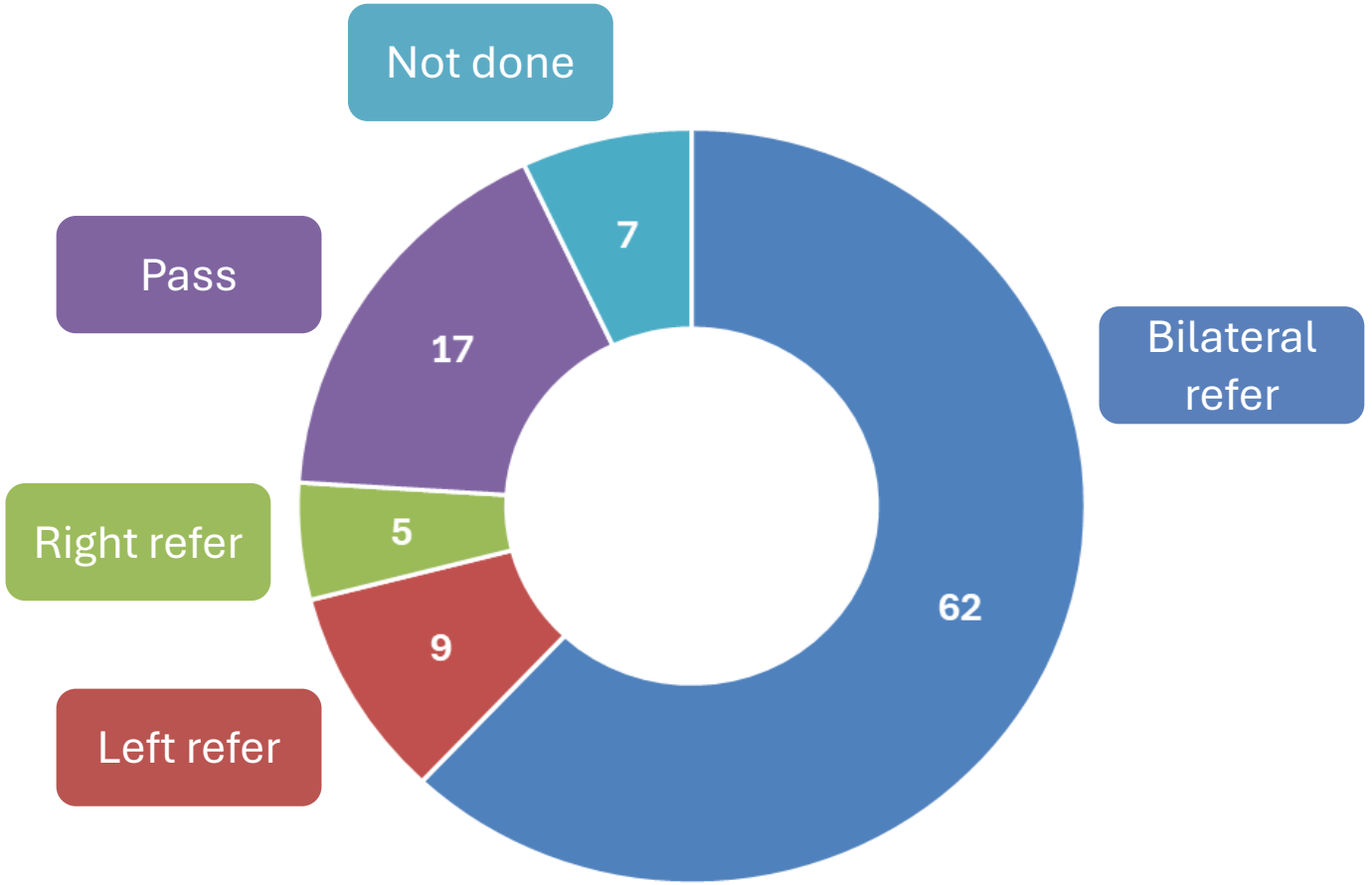
Newborn hearing screening

17 % **(14/82)** passed UNHS



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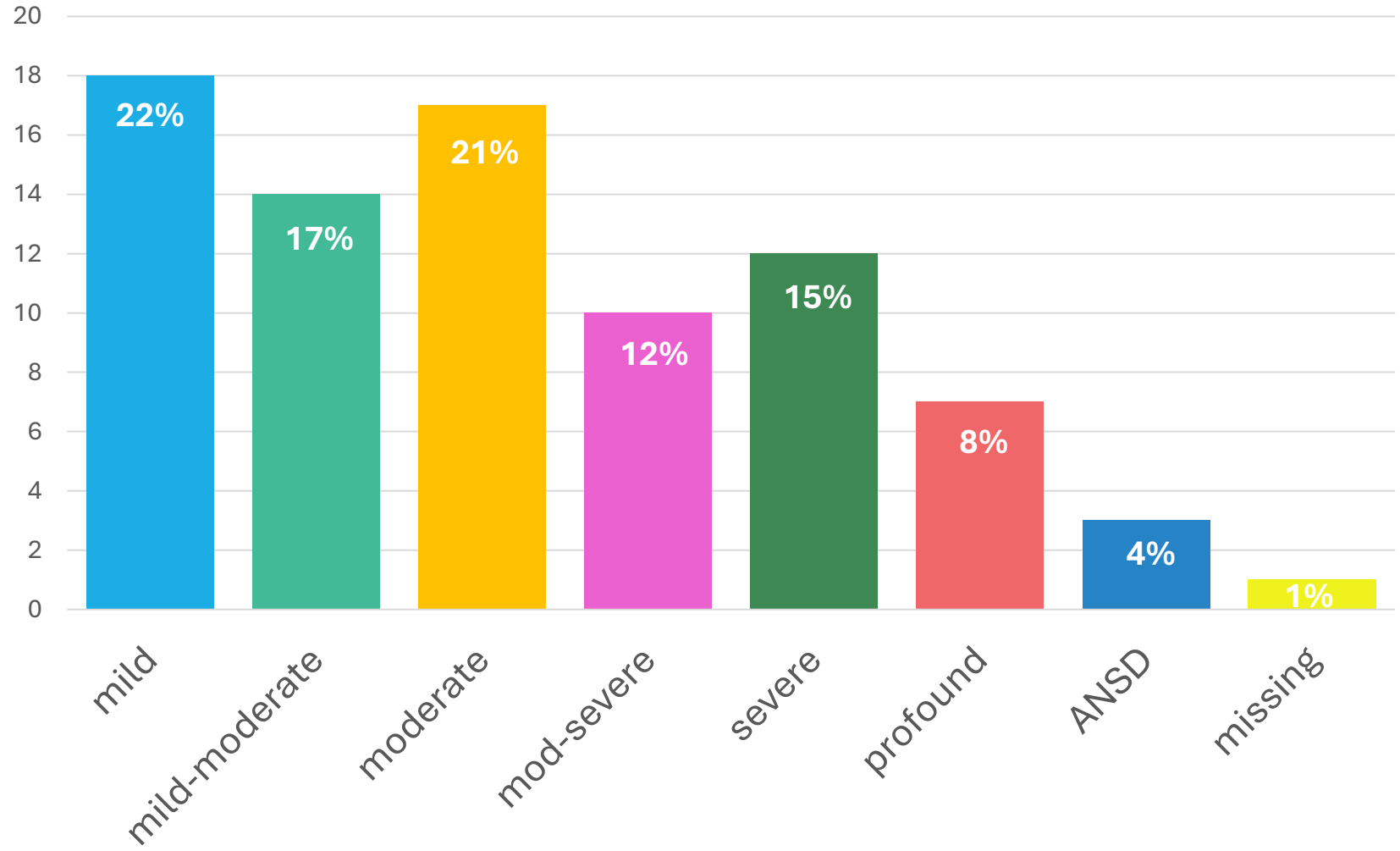
Audiology (at HL diagnosis)



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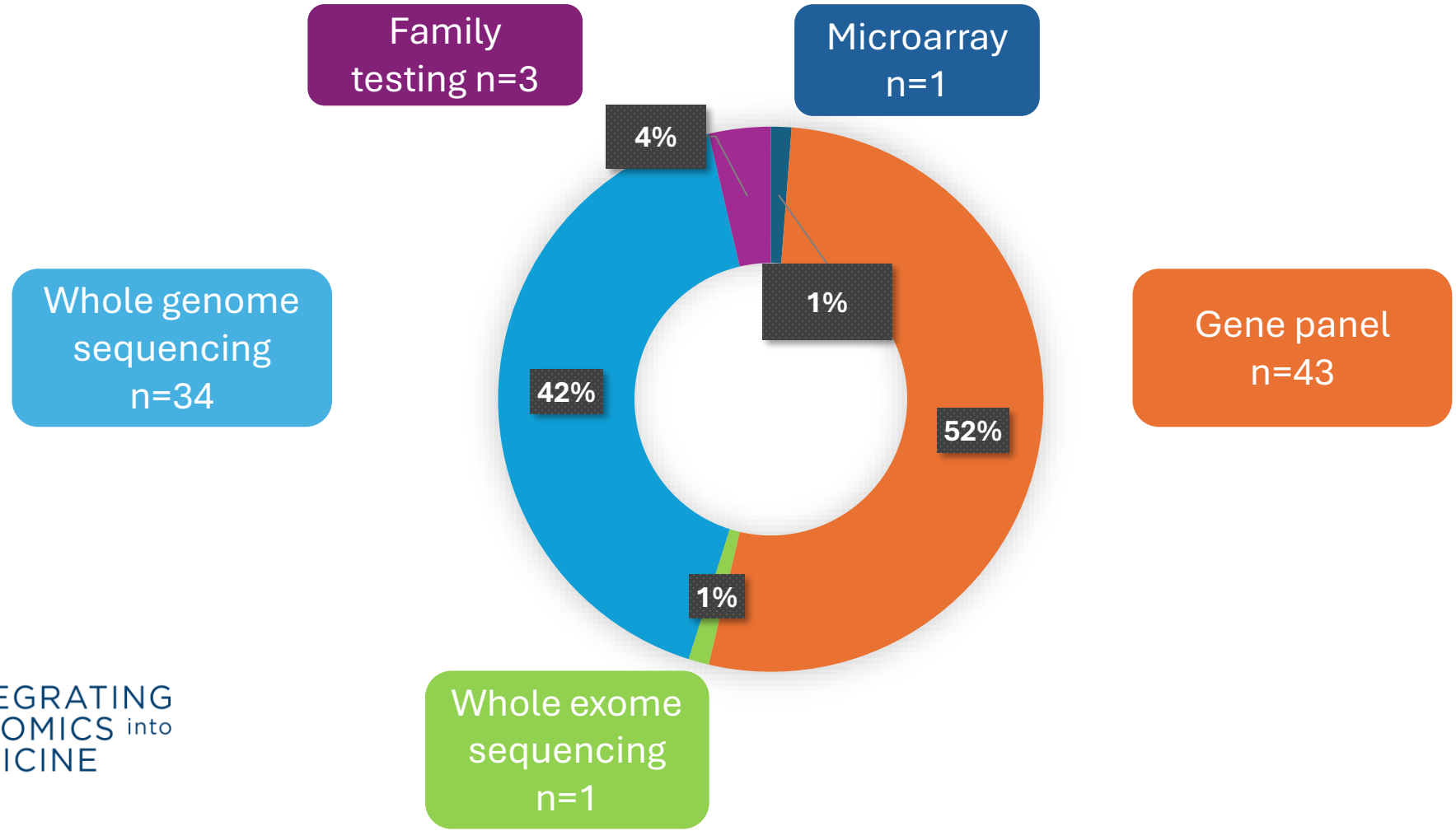
Genetic testing positive n=82



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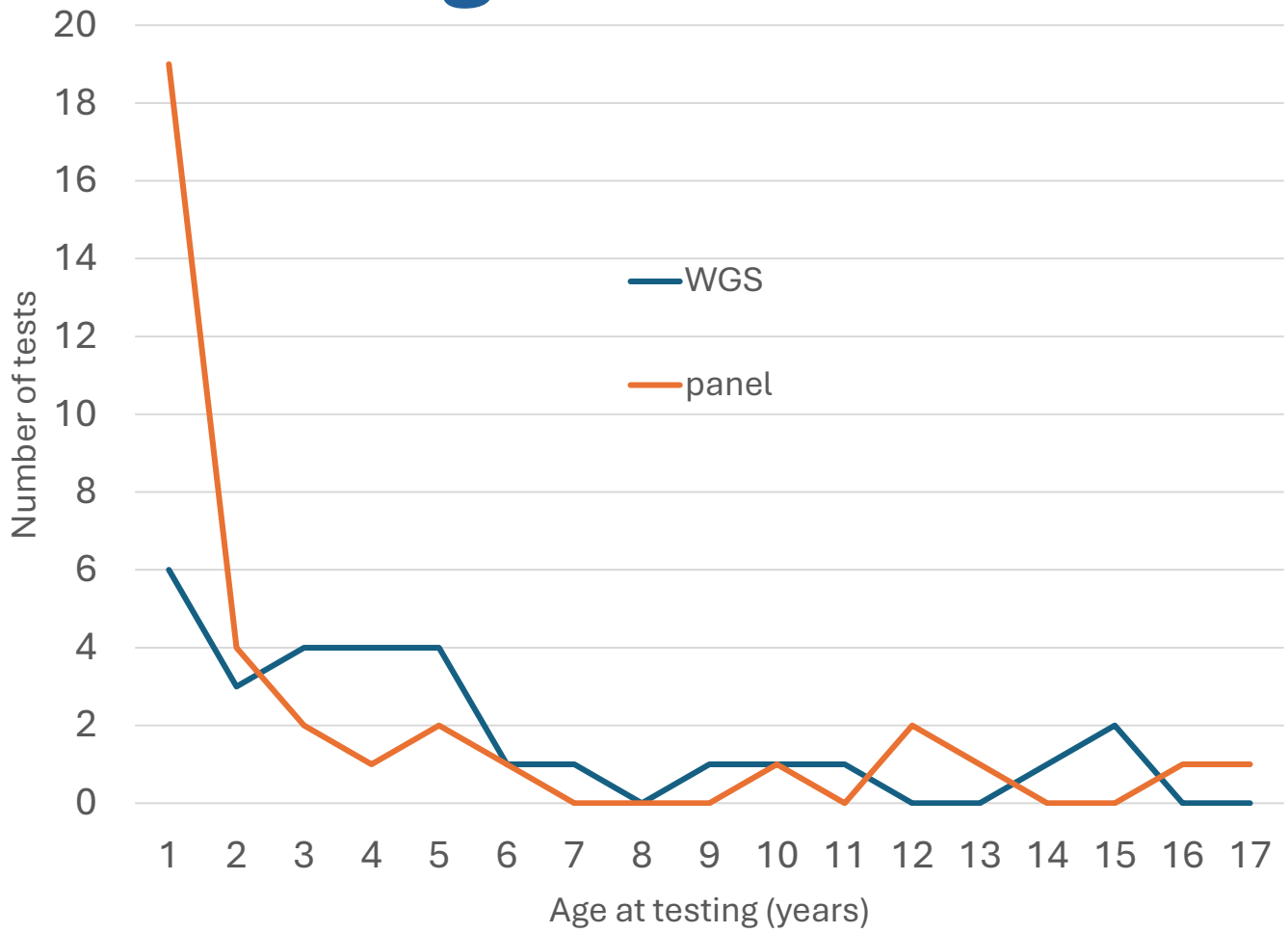
Age at genetic testing



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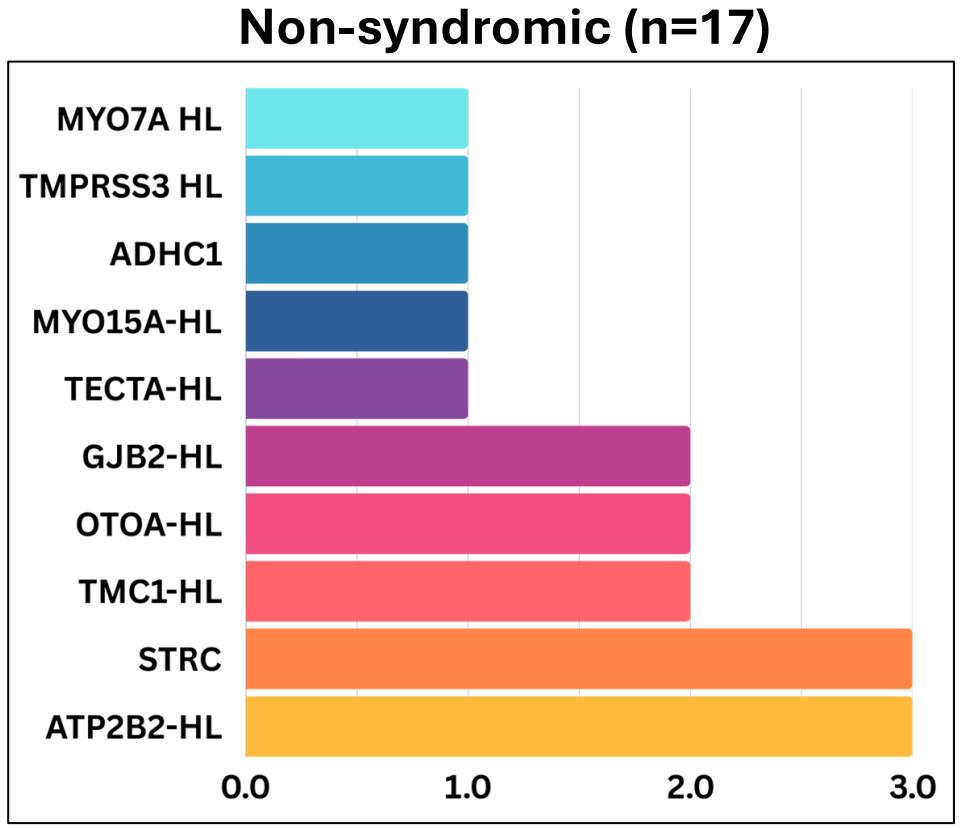
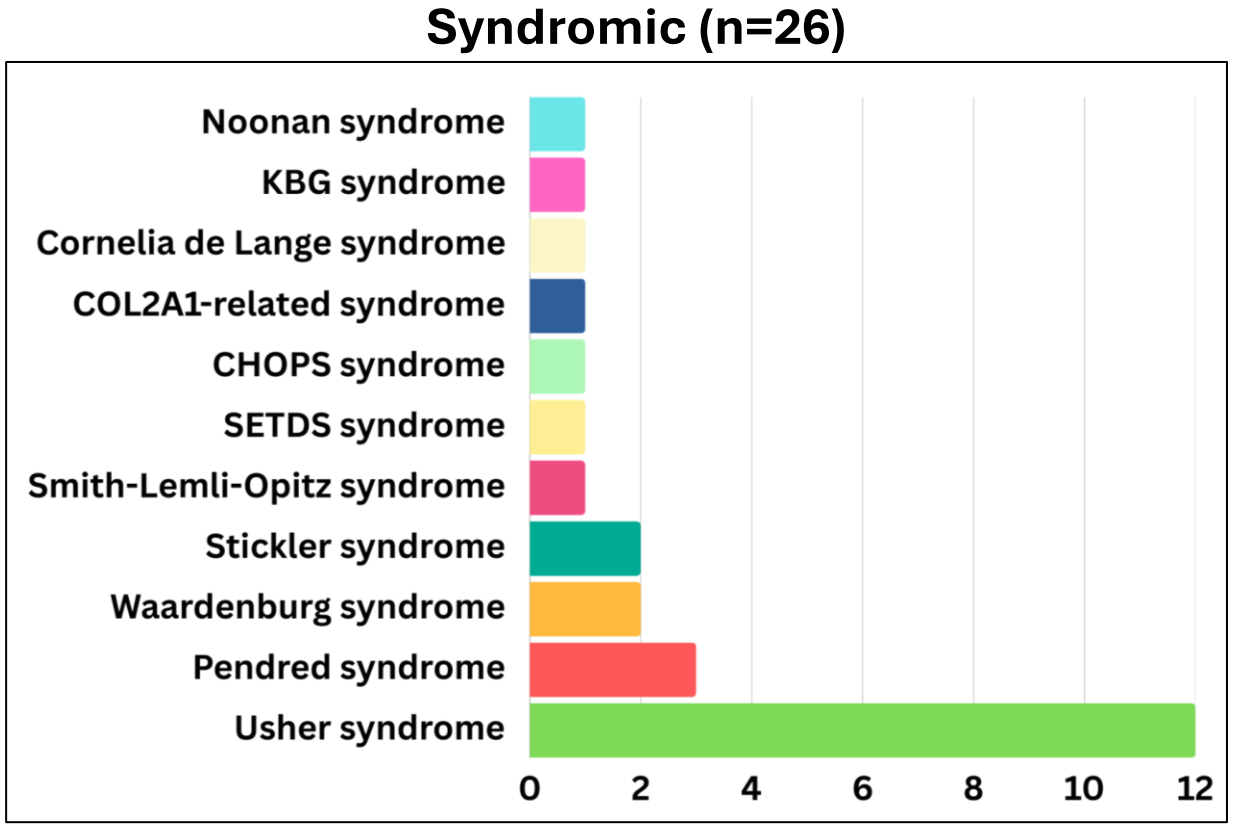
Gene Panel (n=43)





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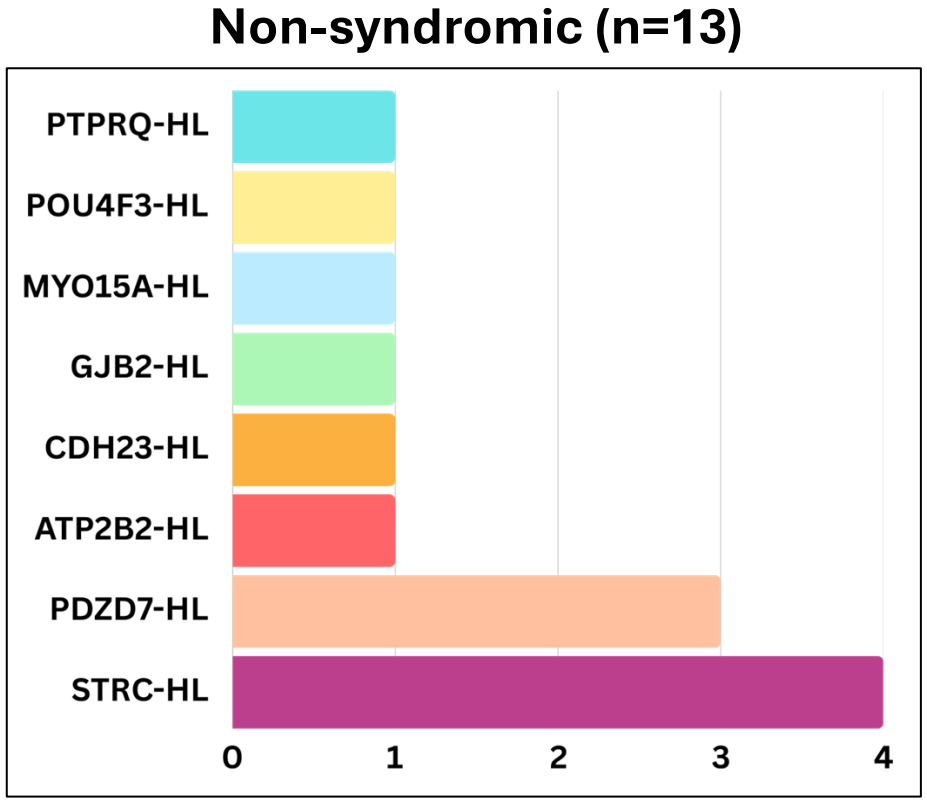
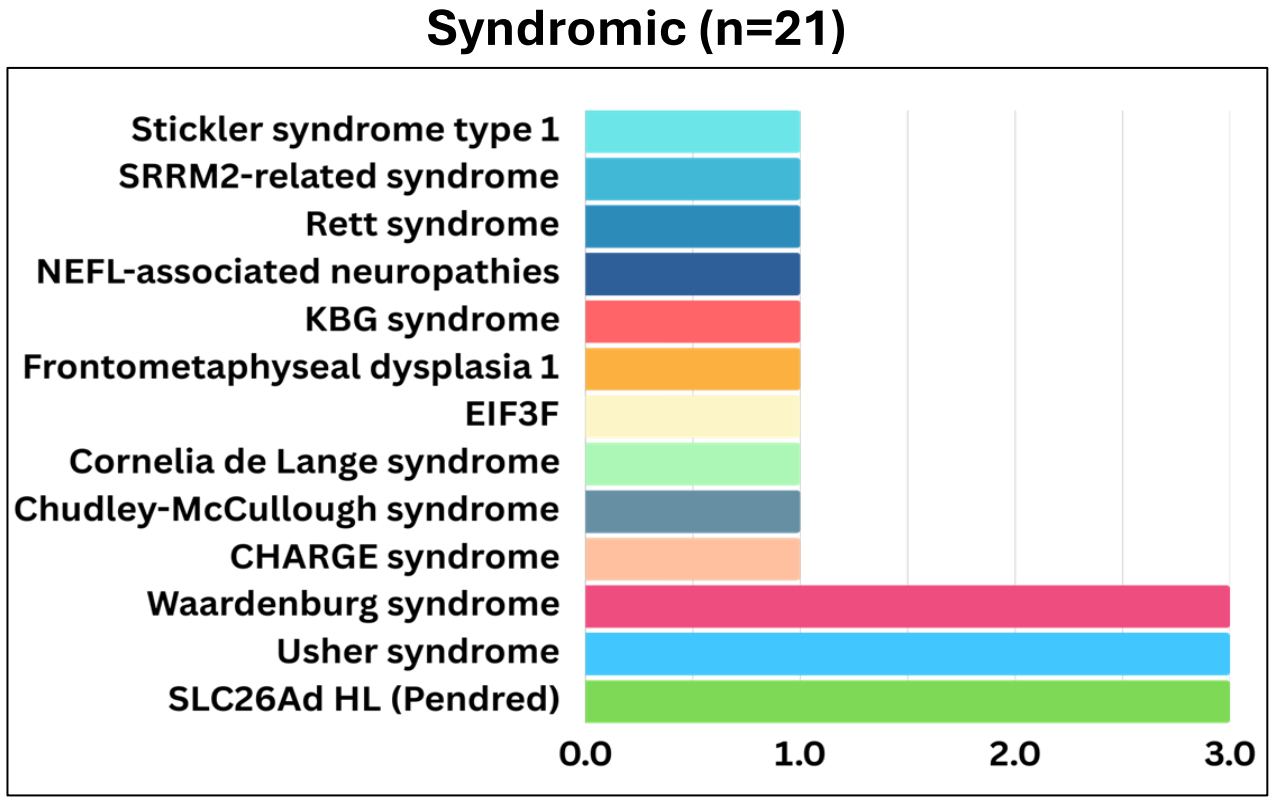
Whole Genome Sequencing (n=34)





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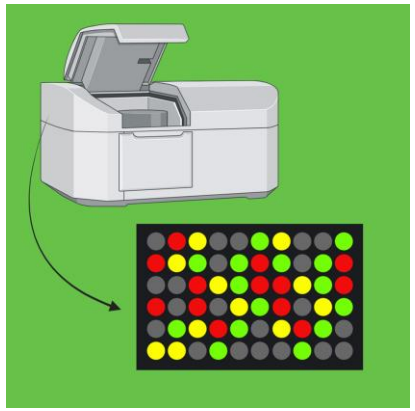
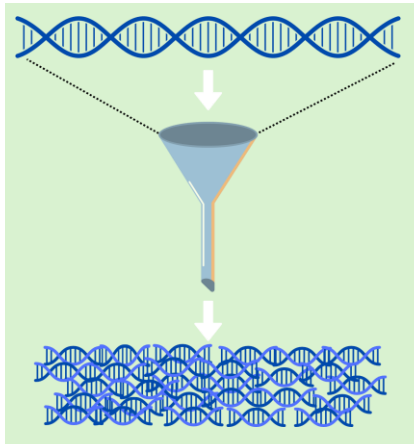
Microarray and Whole Exome Sequencing

Microarray



- **n=6** pathogenic or likely pathogenic results
- No cases did microarray result alone make the diagnosis
- One case of STRC hearing loss diagnosed with MPLA

WES



- **n=1**
- Diagnosis of Cockayne syndrome

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Usher syndrome

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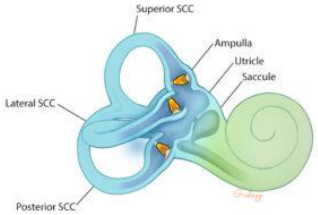
Usher syndrome

	Hearing	vestibular	retinitis pigmentosa	
				
Type 1	Severe to profound congenital	areflexia	First decade	~1/3
Type 2	Mod to severe congenital	normal	2nd decade	>50%
Type 3	Progressive	sporadic	Variable onset	~2%

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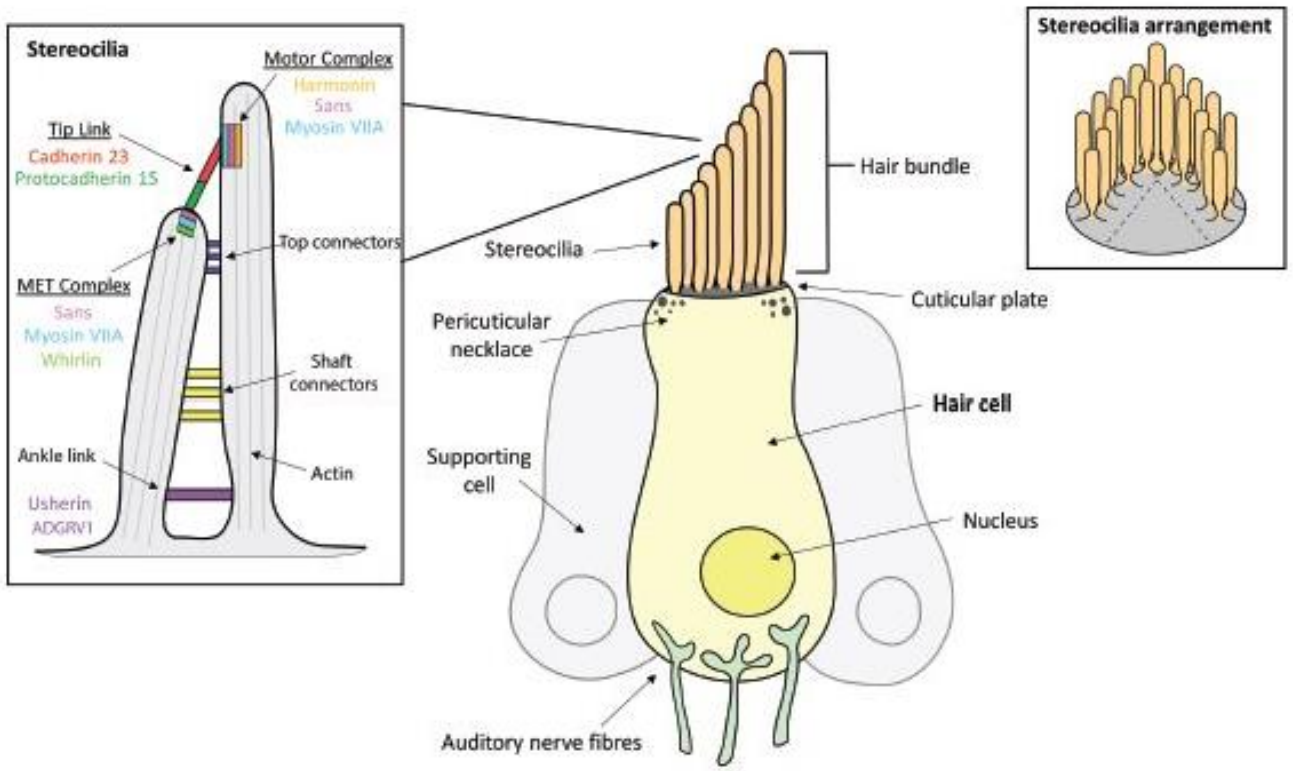
Usher syndrome - genetics

Table 1. Clinical features and genes

Usher subtype	Causative genes
Usher 1	*MYO7A, USH1C, CDH23, PCDH15, USH1G, CIB2*
Usher 2	*USH2A, ADGRV1, WHRN*
Usher 3	*CLRN1*



Toms et al, Ther Adv Ophthalmol, 2020 12: 1-19

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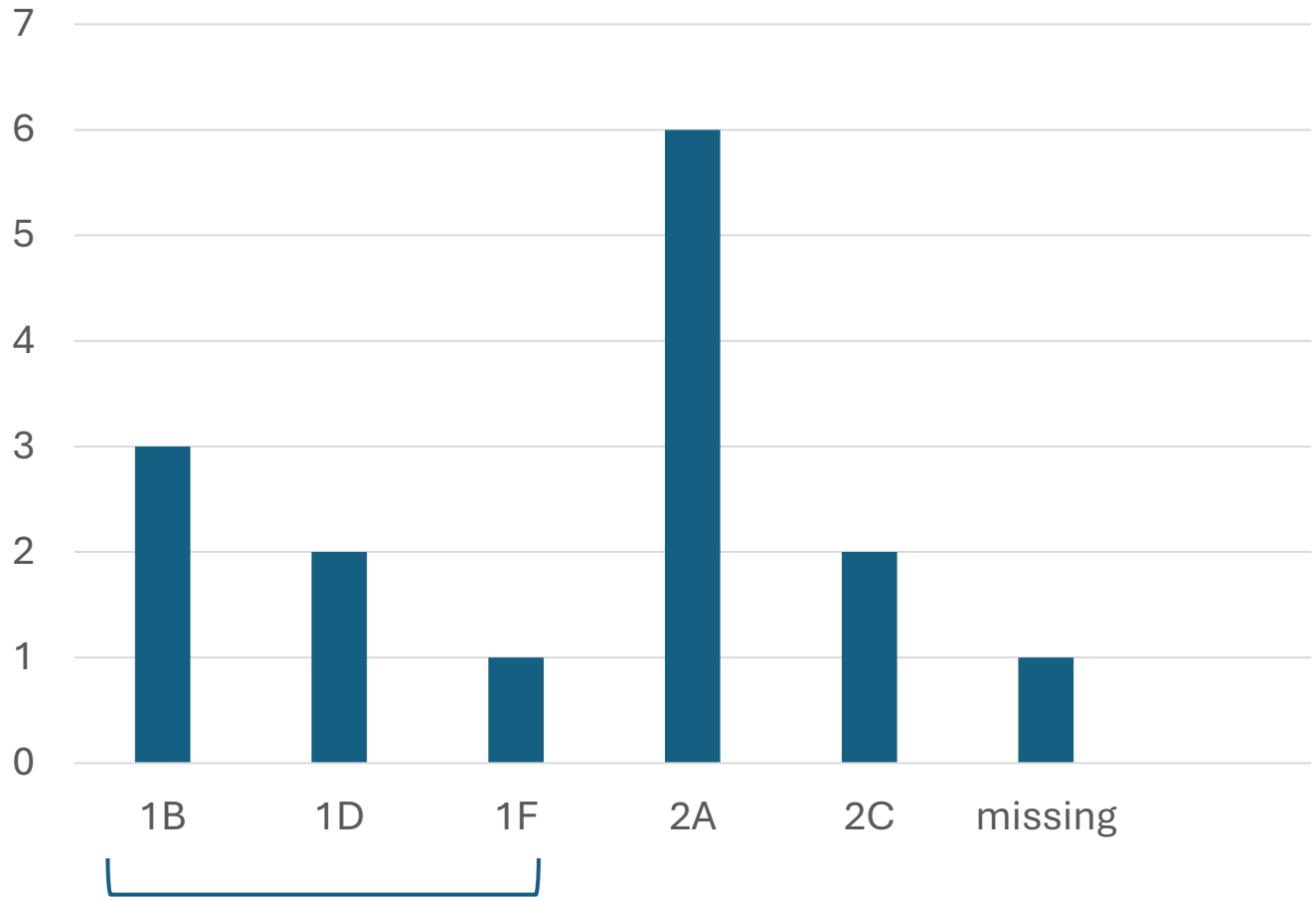
Usher syndrome genetics: Type



N=15

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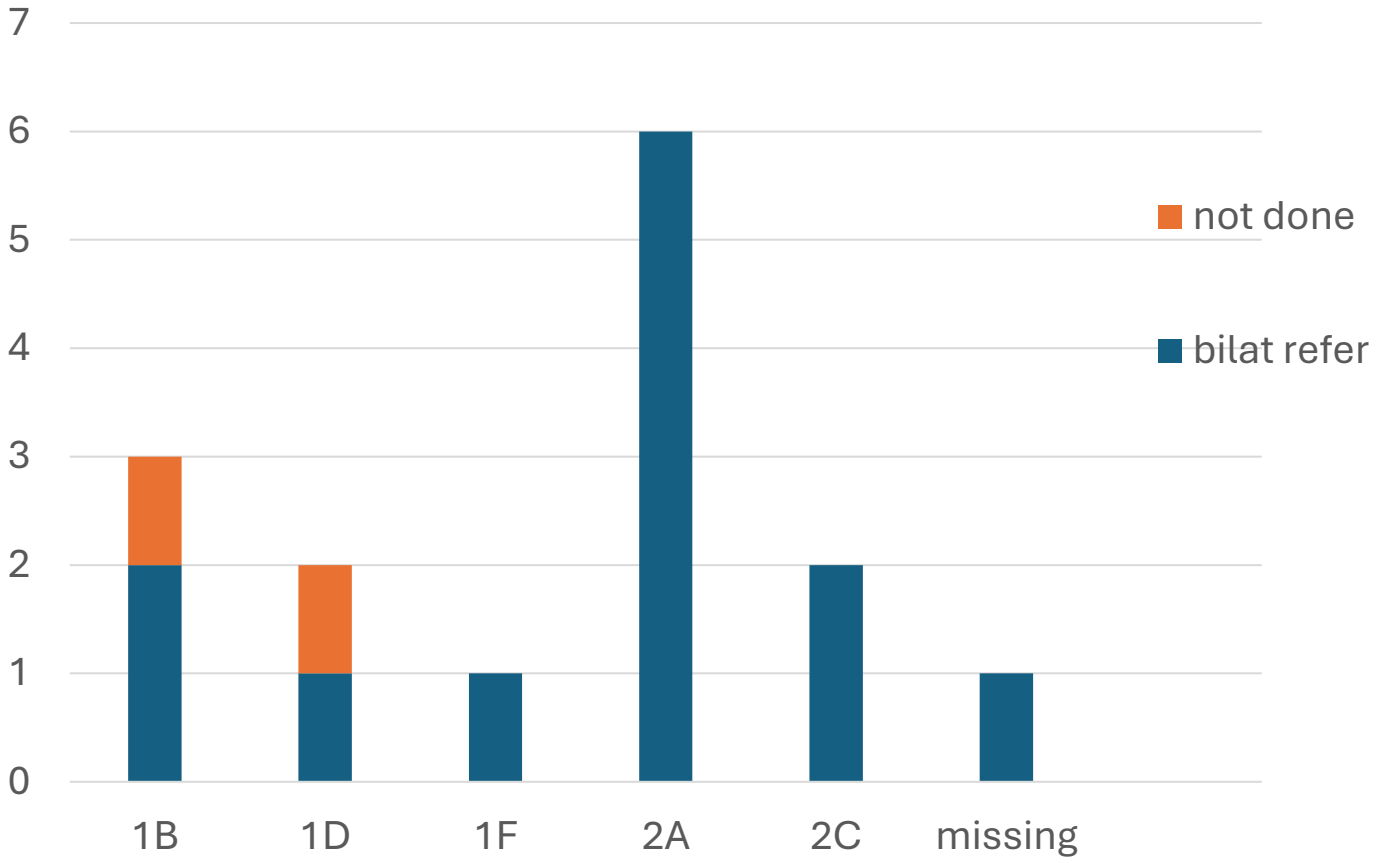
Usher syndrome – Newborn screening by type



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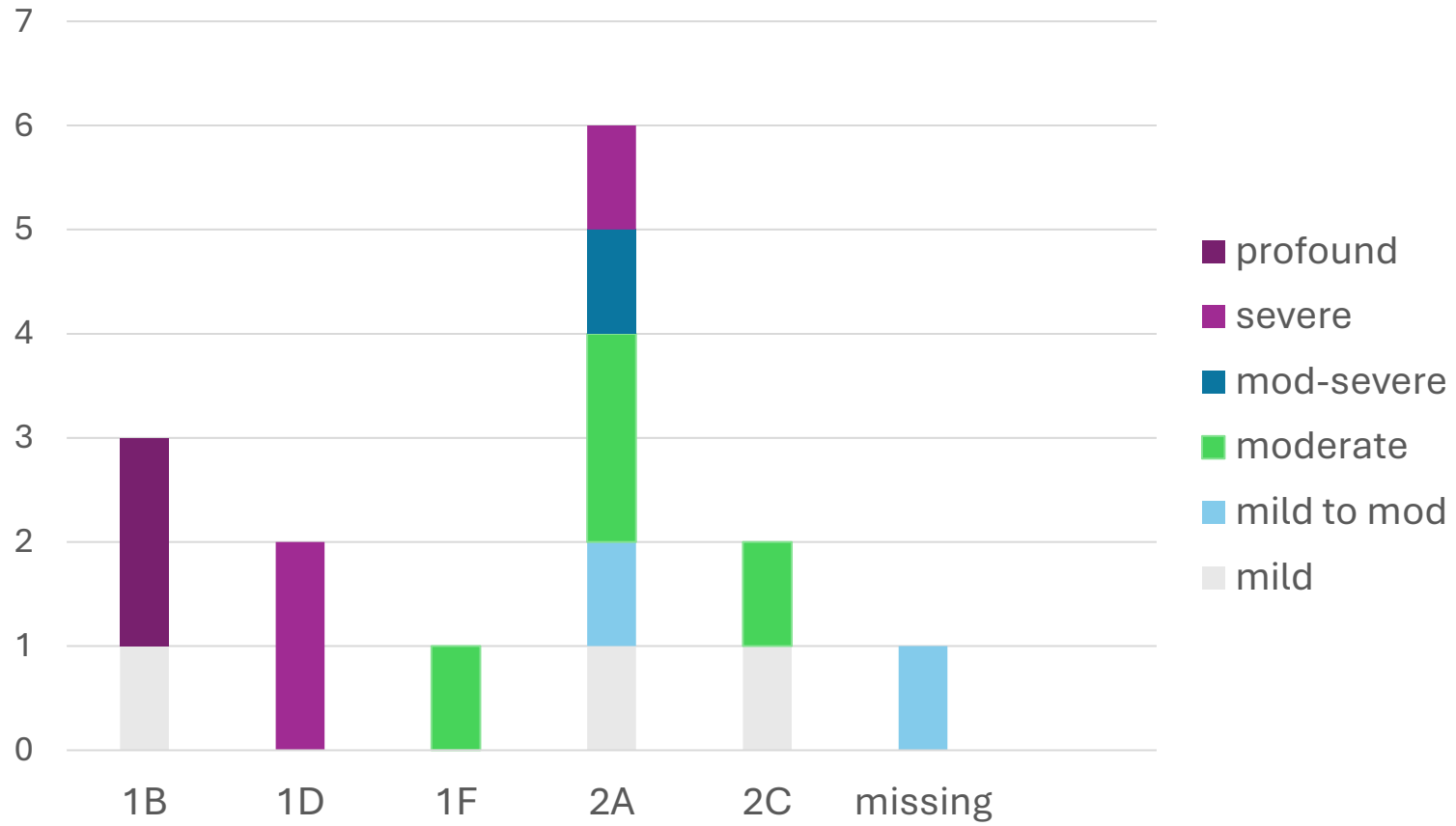
Usher syndrome – Initial HL degree by type



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Where to from here?

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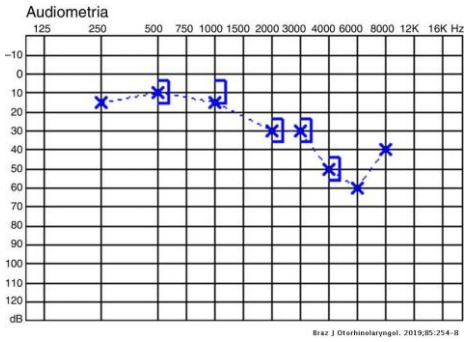
Next steps



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Acknowledgements

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Dr Chirag Patel

Ms Lucy Burbury

Ms Ming Wai (Jasmine) Lee

Dr E Jane Fitzgibbons

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Thank you

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