Diagnostic yield of identifying a genetic cause of hearing loss in children after the introduction of the Next Generation Sequencing Panel R67 gene panel for monogenic hearing loss

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BACKGROUND

- 50% of permanent hearing loss in children can be due to genetic factors that can present as a hearing loss from birth, or of late onset.
- Identifying the correct aetiology can pre-empt the consequences of the hearing loss, provide crucial genetic counselling and improve therapeutic management and treatment.
- The next generation sequencing panel test (NGSP) analyses targeted human genomes.
- The R67 is a new NGSP monogenic sensorineural hearing loss (SNHL) panel.

AIMS AND OBJECTIVES

- To determine the diagnostic yield of NGSP R67 in identifying a genetic cause of SNHL in children with bilateral SNHL.
- Obtain a practical and a realistic idea about the diagnostic yield when compared with existing published evidence (25-33% yield).
- Establish new audit standards incorporating the yield, the logistics of genetic referrals and outcomes.
- Adopt the test as standard practice to investigate all cases of paediatric bilateral SNHL.

METHODS

- This was a local, retrospective cohort audit of children who received completed NGSP R67 reports from the tertiary Audiovestibular Department at Alder Hey Children's Hospital.
- NGSP reports from children with Permanent Childhood Hearing Impairment (PCHI) including mixed losses and auditory neuropathy spectrum disorder (ANSD) between 1st January 2022- 30th December 2022 were included.
- Used descriptive statistical analyses to calculate the diagnostic yield of NGSP R67.

- **The R67 panel is recommended for those with confirmed, bilateral sensorineural hearing loss (SNHL).**
- **Since the introduction of R67 in 2021 in UK, this is the first audit of its kind in an Audiovestibular Department to explore the diagnostic yield for bilateral PCHI in children.**

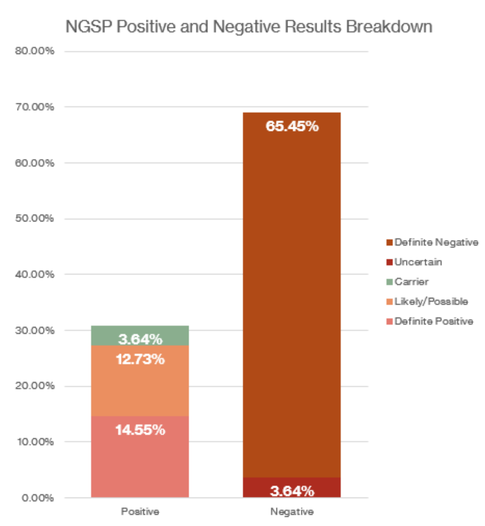
RESULTS

Results- Cohort Demographics

Total Number of Patients Received NGSP Report	**55**		
Age HL Detected	Newborn-17 Years		
Sex	Male: 28, Female: 27		50.91% : 49.09%
Route of Referral into Audiology	**NHSP**	20	36.36%
	SES	16	29.09%
	Other	19	34.55%

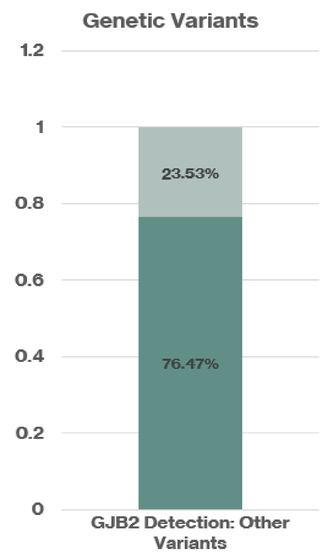
Results- Positive v Negative

Overall Positive	**17**	30.91%
Definite	8	47.06%
Likely/Possible	7	41.48%
Carrier	2	11.76%
Negative/Uncertain	38	69.09%



Results- Genetic Variants Identified

Pathogenic	Wolfram Syndrome
	Pendred Syndrome
	Autosomal Recessive Deafness 1A, 4, 8, 10, 12, ,21, 77, 84B
	Autosomal Recessive Usher Syndrome Type 1D, 2A
	Autosomal Recessive Neurodevelopmental Disorder with Hearing Loss, Seizures and Brain Abnormalities (NEDHSB)
Uncertain	Autosomal Recessive Bartter Syndrome Type 4a
	Autosomal Recessive Deafness 12
	Autosomal Recessive Usher Syndrome Type 1D



Results- Details of the Positive Patients

	Overall Positive	**17**	30.91%
Maximum Degree of Hearing Loss	**Profound**	**7**	**41.18%**
	Severe	4	23.53%
	Moderate	2	11.76%
	Mild	4	23.53%
Passed NHSP		4	**23.53%**
Syndromic		5	**29.41%**
Positive Family History		5	**29.41%**
Positive Scan Findings		*2/15*	***13.33%***
Abnormal Vestibular Function		*1/11*	***9.09%***

DISCUSSION AND CONCLUSION

- In our department, NGSP achieved 30.91% diagnostic yield.
- This is a high diagnostic yield, indicating the beneficial application of NGSP as a standard.
- Our reference papers for diagnostic yield came from two studies, one using single-gene and custom gene panels, and the other using whole-exome sequencing, which had diagnostic yields of 25 and 33% respectively.
- However, the most important observation was that it picked up rare and uncommon genes that would have been impossible to diagnose before NGSP.
- We suggest that NGSP is a beneficial tool to add to hospital guidelines, in a tiered approach to diagnosing HL aetiology. This should be used in combination with a comprehensive clinical history, examination, first-line investigations (audiology, neuro-otology and scans) and MDT advice from different specialties including Clinical Geneticists. Effective utilisation of R67 is recommended.

FUTURE STEPS

- **Re-audit** in another year to see if the diagnostic rates of the region increase for the year, after implementing NGSP as first line aetiological investigation alongside existing audiological and medical tests.
- **Share** this audit with national genetic services
- **Educate** and improve awareness and knowledge to improve HL clinical practice.
- **Publish** this audit.

References:

1.Korver AM, Smith RJ, Van Camp G, et al. Congenital hearing loss. Nat Rev Dis Primers. Jan 12 2017;3:16094. doi:10.1038/nrdp.2016.94

2.Van Camp G, Smith R. HHLH. Hereditary Hearing Loss Hereditary Hearing Loss. Accessed 07 May 2023, 2023. https://hereditaryhearingloss.org

3.Tropitzsch A, Schade-Mann T, Gamerdinger P, et al. Diagnostic Yield of Targeted Hearing Loss Gene Panel Sequencing in a Large German Cohort With a Balanced Age Distribution