Invited Commentary | Pediatrics

Comprehensive Genomic Sequencing–Based Screening for Hearing Loss in the Neonatal Intensive Care Setting—Is It Time?
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Zhu et al1 assessed the utility of combining expanded genomic sequencing with traditional physiological newborn hearing screening (NBHS) in the neonatal intensive care unit (NICU). The benefits associated with combining genetic and physiological screening, as illustrated by Zhu et al1 and elsewhere,2 include the identification of babies at risk for hearing loss who can benefit from early intervention yet are missed by NBHS, as well as genetic factors that may help improve the management of hearing loss in confirmed cases. In a cohort of 8078 patients admitted to the NICU, Zhu et al1 show that exome sequencing identified 7 patients with hearing loss who already had a negative NBHS test result (false negatives), thus increasing the total number of patients with confirmed hearing loss by 13.5% (7 of 52) in this setting. Furthermore, of all patients with confirmed hearing loss, 75.0% (39 of 52) had genetic findings, thus also providing important genetic information for a substantial proportion of patients.

Data from the general neonatal population show that current NBHS programs have a low positive predictive value (PPV). Of the 3 545 388 newborns who underwent NBHS by the US Early Hearing Detection and Intervention programs in 2019, the referral rate was 1.7% (n = 61 475). Of these 61 475 babies, 38 127 underwent confirmatory testing, which confirmed hearing loss in 5934 babies (0.2% of all screened newborns).3 Thus, the PPV was 15.6% (5934 of 38 127 babies). With the use of the combined screening approach by Zhu et al,1 the referral rate for those who had positive NBHS test results and/or positive genetic findings was 3.3% (265 of 8078). Of these babies, 240 were followed up, of whom 0.6% (52 of 8078) had confirmed hearing loss. Although the higher referral and diagnostic rates are more likely because of the higher risk of hearing impairment in the NICU setting, the overall combined PPV was 21.7% (52 of 240), while the PPV for genetic screening alone was 45.9%; that is, of the 90 babies who had positive genetic findings, 85 were followed up, of whom 39 (45.9%) had confirmed hearing loss. Although the remaining babies with positive genetic findings had normal hearing during the newborn period, it is possible that some, if not all, of those babies will have later-onset hearing loss, beyond the duration of this study.

Given the genetic and phenotypic heterogeneity associated with syndromic and nonsyndromic hearing loss,4 6 Zhu et al1 targeted 2742 genes for analysis in each patient. However, positive findings were restricted to 15 genes in this population, with most findings (83.3% [75 of 90]) limited to the 2 most common hearing loss genes, GJB2 (OMIM 220290) and SLC26A4 (OMIM 600791 and 274600). Specifically, 4 pathogenic variants in these 2 genes (GJB2 c.109G>A and c.235delC and SLC26A4 c.919-2A>G and c.1229C>T), in homozygosity or compound heterozygosity with other pathogenic variants, accounted for 77.7% (70 of 90) of all babies with pathogenic variants. This information has important implications for the implementation of a cost-effective and highly sensitive, targeted genetic hearing loss screening approach specific to this population. Although the cost of expanded sequencing continues to decrease, it is still prohibitive for population-based newborn screening. On the other hand, the pathogenic-variant landscape varies in each population, thus limiting the implementation of a universal variant screening in racial and ethnically diverse populations.2 With the continued sequencing and characterization of the genetic landscape of hearing loss across populations, it is possible to design population-specific genetic screening panels that balance cost-effectiveness with sensitivity.
An additional advantage of genetic screening is the identification of mild or later-onset hearing loss, which is usually missed by NHBS. In fact, of the 46 babies in the study by Zhu et al who had positive genetic findings and normal hearing within the short study period, 34 (73.9%) were homozygous or compound heterozygous for c.109G>A; p.Val37Ile in the \textit{GJB2} gene. This variant has an allele frequency of 8% in the East Asian population according to the Genome Aggregation Database, but it has been classified by the ClinGen Hearing Loss Expert Panel as a pathogenic variant for autosomal recessive nonsyndromic hearing loss with variable expressivity and incomplete penetrance. Homozygotes for this variant have been reported to lose hearing at a rate of approximately 1 dB per year, implicating an age-dependent penetrance that is estimated to be 17% by young adulthood. Other babies with normal hearing in the study by Zhu et al had pathogenic variants in autosomal dominant genes that are associated with postlingual and/or progressive hearing loss, such as \textit{COL11A1} (OMIM 120280) and \textit{KCNQ4} (OMIM 603537). Hence, it will be important to monitor those babies for longer periods because they are very likely to develop hearing loss later in life.

On the other hand, NBHS in the study by Zhu et al identified 13 patients with confirmed hearing loss owing to nongenetic factors, including an association with craniofacial anomalies, while congenital cytomegalovirus was associated with 15% of those cases. Despite the lowest PPV in this group (8.4% [13 of the 155 babies who had positive NBHS test results without genetic findings]), this finding illustrates the need for combinatory physiological, genetic, and cytomegalovirus testing to achieve a highly sensitive newborn screening approach.

Hearing loss is the most common sensory deficit in humans and is caused by both genetic and nongenetic factors. Unlike cystic fibrosis, which is caused by biallelic pathogenic variants in a single gene (\textit{CFTR}), more than 100 genes have been associated with syndromic and/or nonsyndromic hearing loss. Pathogenic sequence and copy number variants in those genes may cause dominant and/or recessive deafness, which is characterized by variable expressivity and complete or reduced penetrance. Furthermore, several hearing loss genes are associated with overlapping presentations obscuring specific genotype-phenotype correlations. Given such disease attributes, comprehensive genomic testing, in the form of expanded gene panels, has been the cornerstone of diagnostic testing for hearing loss and has successfully identified the molecular causes of deafness in a significant number of cases. However, such an approach is still challenging for population-based screening because it is relatively expensive, has an extended turnaround time spanning several weeks, and is associated with a significant burden of variant interpretation.

Although these limitations were not addressed by Zhu et al, their work implies that targeted genetic screening—using population-specific common pathogenic variants—combined with physiological and cytomegalovirus testing may be an effective newborn screening strategy for hearing loss, in critically ill neonates and beyond. This combinatory approach has the additional benefit of identifying mild and later-onset hearing loss and providing valuable genetic information that is often missed by traditional NHBS. However, additional work is needed to characterize the genetic landscape of hearing loss across populations and to define the optimal population-wide genetic screening method for deafness.
REFERENCES


