commentary

Genetic testing as part of the Early Hearing Detection and Intervention (EHDI) process

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Hearing loss is the most common human birth defect occurring in 1 to 3 per thousand infants.[1] Recent evidence for a critical period for language acquisition[2,3] promoted the adoption of Early Detection and Hearing Intervention (EHDI) programs in nearly every state.[1] Universal newborn hearing screening by bedside audiometric testing is rapidly becoming standard of care.[4]

Concurrent with the adoption of EHDI programs, an explosion of knowledge occurred in the field of genetics with the identification of over 100 genes associated with hearing impairment.[5] However, more than half of infants with nonsyndromic hearing loss will have identifiable mutations in only two genes, *GJB2*[6] and *GJB6*[7–9] making this the most common world wide cause of hereditary hearing impairment.[10]

Genetic testing for *GJB2/GJB6* performed as part of the EHDI process can be of benefit to parents of children with hearing impairment by removing the mystery as to why their child has hearing impairment, helping with treatment decisions, and providing an accurate recurrence chance.[11,12] There is considerable interest in genetic testing for hearing impairment. A survey of parents of deaf children found that 96% approved of genetic testing for hearing impairment[12] and a survey of hearing, deaf, and hard-of-hearing adults in the broader community found support for genetic testing for hearing impairment specifically in the newborn period.[13] Furthermore, a large percentage of these individuals would avail themselves of genetic counseling as part of the testing process.

Mutations in *GJB2* were first identified in 1997,[14] and remarkably, a few common mutations account for the majority of deafness causing alleles.[15] Three major mutations have been identified in *GJB2* and one in *GJB6*. In *GJB2*, the common mutation in the European population is 35delG; in the Ashkenazim, 167delT, and in the Asian population 235delC.[6] A 342-Kb deletion in *GJB6* can occur in trans with a *GJB2* mutation as a major cause of hearing impairment.[7,8,16] This small number of mutations in relatively small genes that are responsible for the majority of affected individuals creates a technically facile situation, allowing incorporation of genetic testing into the EHDI process.[7,17–19]

The phenotype of individuals with mutations in *GJB2/GJB6*-related hearing impairment is typically characterized as profound to moderate prelingual/congenital and nonprogressive.[20] Much of the variability can be attributed to *GJB2/GJB6* genotype. Profound hearing impairment is more commonly associated with presence of the 35delG mutation.[21] In a study of 166 individuals homozygous for 35delG, a range of phenotypes from mild to profound with the median severity in the profound range has been demonstrated.[21] Additionally, although rare, there have been reports of later onset hearing loss or unilateral hearing loss in patients with *GJB2*-related hearing impairment.[22,23]

Not only would augmentation of the EHDI process through *GJB2/GJB6* mutation analysis determine an etiology for many infants with nonsyndromic hearing impairment, it would eliminate unnecessary and often invasive testing because individuals with *GJB2/GJB6*-related hearing impairment do not have other physical conditions.[20] About 30% of infants with hearing impairment will have one of the more than 400 genetic syndromes associated with hearing impairment[24] and many will have associated physical abnormalities. There are syndromes in this group whose features may be hidden in the newborn period, including Pendred syndrome (hearing impairment, inner ear deformities, and thyroid goiter), Jervell and Lange-Nelson syndrome (hearing impairment and cardiac arrhythmias), Usher syndrome (hearing impairment, retinitis pigmentosa, and variable vestibular dysfunction), Alport syndrome (hearing impairment and renal tubular dysfunction), and Branchiootorenal syndrome (renal malformations, branchial arch malformations, and hearing impairment). Importantly, the morbidities associated with these syndromes require additional medical studies and ongoing surveillance as they typically go undetected for a number of years after birth. Knowing the *GJB2/GJB6* mutation status at the outset in a child with hearing impairment will save the time, effort and cost involved with performing electrocardiograms, serial ophthalmological evaluations, renal ultrasounds, urine testing, and complicated thyroid studies.[25]

Because *GJB2/GJB6* genetic testing offers clinical and informational benefits, it is a near certainty that it will become an important addition to current EDHI protocols. In this commentary, we discuss issues to be considered before there is widespread inclusion of genetic testing into the EHDI process,

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incorporating some of our experience from our current study on the impact of genetic testing for hearing impairment on individuals and families as part of the EHDI process.

When is the right time to perform testing? Birth? Those who did not pass the newborn screen? Only after the diagnosis of hearing impairment?

The first natural time point to introduce genetic testing for hearing impairment is at birth. If testing is performed at birth, then all children regardless of audiometric hearing screening status will be tested. There are several advantages to performing genetic testing at birth (Table 1). First, it allows for the possibility of performing DNA-based testing on neonatal blood spots currently used to test for inborn errors of metabolism.[17,19,26,27] Second, the mutation results will be available at the time that hearing impairment is diagnosed, offering an immediate piece of information that will influence subsequent medical workup and habilitation options. Concern for syndromic or infectious causes of hearing impairment has prompted the practice of performing a number of medical studies in all newborns with hearing impairment, which would include newborns with *GJB2/GJB6*-related hearing impairment unless the etiology of their hearing impairment is known.[23,28,29] Such workups will be eliminated in newborns/infants with *GJB2/GJB6*-related hearing impairment if genetic testing is performed in the newborn period. Additionally, preliminary data suggests that children who have *GJB2*-related hearing impairment will benefit from cochlear implantation, thus suggesting a therapeutic option from the knowledge of *GJB2/GJB6* status.[30,31] Therefore, knowledge of the genetic status of a newborn with hearing impairment could streamline the evaluation process and avoid additional testing and recurrent evaluations for syndromic forms of hearing impairment. Third, genetic testing on all newborns will identify hearing impairment-causing *GJB2/GJB6* mutations in some small percentage of babies who pass their newborn hearing screening, either as a false negative or because of hearing impairment that manifested after newborn hearing screening.[22] In these cases, parents and physicians can be alerted so that the baby's hearing status is reevaluated.

There also are disadvantages to testing all newborns. The costs of adding new tests to a blood spot–based newborn screen may be an issue. Parental interest may be an issue. With a carrier frequency of 3% for common *GJB2* mutations in the Caucasian population, numerous carriers will be identified.[32] Are we prepared to share this kind of result with parents of unaffected infants? Do we have the trained manpower that will be needed to provide unanticipated genetic testing results to families?

Another possible time point to introduce genetic testing is when the newborn is at heightened risk for hearing impairment because they did not pass the newborn bedside audiometric screening. As with testing all newborns, one advantage will be identification of mutation status at about the time of identification of hearing status, providing immediate informa-

Table 1
Table comparing three time points when genetic testing can be performed in the EHDI process

Time of genetic testing	Advantages	Disadvantages	Estimated number of patients that would be screened
Birth	(1) Nearly all newborns will be tested. (2) Can utilize the newborn blood spot. (3) Information regarding need for additional medical workup nearly concurrent with diagnosis of hearing impairment (4) Identify babies at genetic risk who pass the hearing screening. (5) No need to perform other medical workup if *GJB2/GJB6* testing is diagnostic.	(1) Test result may not be in congruence with audiometric phenotype. (2) False positives from audiometric screening will also undergo genetic testing. (3) Large numbers of carriers may need to be told results. (4) Potential lack of parental interest.	The entire U.S. birth cohort: ≈4 million in 2002[38]
After failed inpatient audiometry screening	(1) Fewer newborns will need to be tested. (2) Possibility of obtaining a sample in an inpatient setting or reporting to the state to use the newborn bloodspot. (3) No need to perform other medical workup if *GJB2/GJB6* testing is diagnostic.	(1) Test result may not be in congruence with audiometric phenotype. (2) False positives from audiometric screening will also undergo genetic testing. (3) Large numbers of carriers may need to be told results. (4) Potential lack of parental interest. (5) Some infants who are at genetic risk for hearing impairment may be missed.	2–8 per 100 infants[39,40]
After diagnosis of hearing impairment	(1) Testing will be specific to the phenotype of hearing impairment. (2) No need to perform other medical workup if *GJB2/GJB6* testing is diagnostic. (3) Parental interest potentially high.	(1) Test result may not be in congruence with audiometric phenotype. (2) Some infants who are at genetic risk for hearing impairment may be missed. (3) Need to obtain a new tissue or blood specimen for genetic testing. (4) Delay in information regarding need for additional medical workup.	1 in 500 infants

tion regarding medical workup and habilitation options. Testing at the time of bedside audiometry is complicated by the lack of uniformity for implementing hearing screening between states or even between hospitals within each state. Although, most facilities screen newborns at least twice using either OAE (otoacoustic emissions) or ABR (automated brainstem response), some facilities only screen once before proceeding to referral to an audiologist to make the final diagnosis of hearing impairment, thus increasing the false-positive referral rate.

However, compared to testing all newborns, one advantage of testing after a newborn does not pass bedside audiometric screening will be testing fewer babies. The disadvantage will be missing the rare infant with a false-negative hearing screening result.[22] There also have been reports of patients with *GJB2*-related hearing impairment that were not congenitally deaf, suggesting that some infants will be missed by screening.[22] Coupling genetic testing with tests performed on the newborn blood spots would be more complicated at this point and would possibly require a new blood or tissue sample. We found that parents at this stage are not as interested in genetic testing as their child has not yet been diagnosed with hearing impairment (Palmer and Schimmenti, unpublished data, 2004) and this lack of interest likely would generalize to testing immediately at birth, as well.

The final time point is to introduce genetic testing once the diagnosis of hearing impairment has been established. The advantages of introducing testing at this time point are that only babies with hearing impairment will be tested, and in our experience, parental interest in genetic testing will be greater compared to earlier time points in the EHDI process (unpublished data, 2004). Identification of mutation status will occur sometime subsequent to identification of hearing status, hence information regarding medical workup and habilitation options will be delayed relative to the earlier testing time points. Coupling genetic testing with tests performed on the newborn blood spots would be logistically challenging at this point, and likely would require a new blood or tissue sample.

What type of testing should be done: common mutations or sequencing of the entire gene?

There are currently two ways to go about testing for mutations in *GJB2/GJB6*: common mutation testing or complete sequencing. The rapidity and ease of common mutation testing was recently demonstrated in a study from New York.[19] A potentially significant disadvantage is that common mutation identification studies have been limited by geography and to only certain populations, so these common mutations may not be representative of populations in many areas of the United States.[6] By limiting the panel of mutations to only the most common, it is possible that a significant proportion of babies will not be accurately identified as having *GJB2/GJB6*-related hearing impairment. This issue may also have informational consequences if providers and parents do not fully appreciate that if a common disease-causing allele is not identified, *GJB2/GJB6*-related hearing impairment has not been conclusively ruled out. Sequencing both exons of *GJB2* and deletion testing in *GJB6* for the majority of possible alleles would be an exhaustive means for mutation identification; however, both testing and interpretation could be costly to perform. Also, those interpreting the sequencing must be expert in understanding the significance of certain sequence variations including novel polymorphisms.

Who will order the testing? The state? Primary care providers? ENT specialists? Clinical geneticists? Audiologists?

In one scenario, testing could be provided through the state newborn screening program via DNA testing of blood spots. If genetic testing is provided by the state as part of a universal screen or a directed screen for babies that have failed the newborn audiometric screen, pre- and post-test genetic counseling would need to be incorporated into the protocols. How states will do this and ensure an understanding of testing by parents is unclear.

Genetic testing could be ordered by a medical contact, most likely a caregiver providing primary care, otolaryngology, audiology, or genetic services. Extensive training of the physician and audiology workforce would be required to provide genetic testing and pretest counseling. Evidence suggests that nongenetics professionals, including physicians and audiologists, are not yet ready to provide genetic information to patients and do not understand the implications of genetic testing and how to discuss results in the context of genetic counseling.[33,34] Do specialty services outside the realm of genetics have the interest or time to provide genetic counseling, evaluation, and follow-up to families and patients with hearing impairment?

How will the results be explained? Will genetic counseling be part of the EHDI process?

Results of genetic testing would need to be provided in the context of genetic counseling so that parents and caregivers can interpret the results.[11] Our preliminary results suggest that in a setting where genetic testing is performed in the context of genetic counseling that 100% of the parents whose infants had biallelic *GJB2/GJB6*-related hearing impairment knew that their infant had hearing impairment caused by mutations in *GJB2/GJB6*, understood the recurrence chance, and felt that the testing helped them understand why their child had hearing impairment.[35] Additionally, these parents have increased sense of perceived personal control.[36] Therefore, genetic testing for hearing impairment where parents are given diagnostic results has benefits in the context of genetic counseling.

However, preliminary data from our study shows that parents who were given nondiagnostic results, i.e., the child's hearing impairment was not clearly explained by the *GJB2/GJB6* results, had greater difficulty understanding the meaning of test results and demonstrated considerable variability in their understanding of recurrence chance.[35] They also were less likely to feel that the test helped them understand their child's cause of hearing impairment.[35] This points to the complexity of providing negative test results and the need for the develop-

ment of genetic counseling strategies to enhance parental understanding of nondiagnostic test results.

Depending on the timing of *GJB2/GJB6* genetic testing for hearing impairment, there are up to six possible outcomes based on genotype and phenotype. For an infant with hearing impairment and two mutations in *GJB2/GJB6* or a child without hearing impairment and no mutation identified, the situation is fairly unambiguous and genetic counseling straightforward. (Rarely an infant will be born without congenital hearing impairment that has biallelic or double heterozygosity for mutations in *GJB2/GJB6*. Those infants will need longitudinal follow-up for the development of hearing impairment.) However, for the two situations where nondiagnostic information is given (a baby with hearing impairment and either no mutations or only one mutation identified), conveying information to families can prove more challenging and in our experience, even in the context of genetic counseling, families given nondiagnostic information fare more poorly in understanding the meaning of the genetic test results.[35] Additionally, families who have children with hearing impairment and nondiagnostic *GJB2/GJB6* testing may be erroneously left with the impression that if this single test is negative, then the hearing loss in their child is not genetic.[12,35] Further complexity will be added by identification of novel alleles or polymorphisms as well as the presence of family history of hearing impairment in some families that would need to be considered in the determination of recurrence chance.

Who will oversee follow-up based on the results?

For patients who have mutations in *GJB2/GJB6*, follow-up by audiologists and otolaryngologists can focus on care and habilitation of hearing impairment with less worry about other physical abnormalities. Geneticists should follow-up as required to assure understanding as well as for counseling purposes. All subspecialists should have close communications with the primary care provider or medical home.

For patients who do not have *GJB2/GJB6* mutations, the need for follow-up is complex and compelling. Infants in this group need careful clinical genetic evaluations to evaluate for the possibility of a syndromic diagnosis[25] as well a follow-up studies based on the differential diagnosis outlined earlier and as recommended by the American College of Medical Genetics.[29] Current protocols suggest a workup that includes CT scanning for cochlear and vestibular anomalies, studies to determine prenatal infections such as the toxoplasmosis, rubella, cytomegalovirus, herpes virus, and syphilis, renal ultrasound, urine analysis, electrocardiogram, thyroid studies, and ophthalmological surveillance.[24,28,29]

Should parental informed consent be part of genetic testing for hearing impairment?

In most states, newborn screening is performed with parental notification but not informed consent.[37] The informing process appears to lack uniformity between birthing centers. As genetic testing is not without risks, including discovery of nonpaternity, use of informed consent should be explored and offered in the context of genetic counseling. Because hearing impairment does not share the same morbidity and mortality as metabolic disorders, one could argue that an informing process, be it consent or assent, would be appropriate as this would allow the family to be prepared to receive results they will need to act upon. Additionally privacy issues in genetic testing including HIPAA compliance and prevention of genetic discrimination should be addressed.

Regardless of the final answers to these questions, the issues must be addressed to be able to successfully incorporate genetic testing into the EHDI process. First, we can be reasonably certain that genetic testing will become part of the EHDI process and that to be effective must be performed in the context of genetic counseling. Without genetic counseling, the significance of the genetic testing results, especially nondiagnostic results will be lost to families and care providers. A genetics evaluation is an integral part of the workup of a child with hearing impairment and should be incorporated into the EHDI process. A genetics evaluation with careful attention to syndromic forms of hearing impairment will guide the management of children with hearing impairment and streamline the process so as to limit extensive follow-up testing to only those children who need it.

As members of the genetics community, we have much to offer individuals and families with hearing impairment; we must take this opportunity to be available to them to offer the best services possible in coordination with primary care, audiology, and otolaryngology providers.

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