Utility of Genetic Testing in Detection of Late-Onset Hearing Loss

SUMMARY
Sponsor
Pediatrix Medical Group, Inc. and Pediatrix Screening, Inc.

Steering Committee
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Purpose
Two major limitations of existing audiorometric newborn hearing screening programs are their inability to detect forms of deafness that are not expressed at birth and the low compliance with obtaining recommended audiologic confirmation and/or follow-up. Molecular genetic tests on blood spots from all newborns will identify those at risk for the most frequent causes of late-onset hearing loss and to add these infants to the group who should receive continued audiologic monitoring.

The specific aims of this project are to:
- Demonstrate the utility of detecting four potentially important causes of delayed onset hearing loss by molecular tests at birth, which may be missed by current audiorometric screening tests.
- Document the frequency, clinical and genetic characteristics of hearing loss associated with each condition.

Dried blood spots (DBS) on filter paper will be obtained and be used for this project with parental informed consent from 6,000 newborn infants at approximately 25 hospitals. Pediatrix Screening, a subsidiary of Pediatrix Medical Group with long experience in high throughput neonatal testing, will perform genetic testing on the samples. The four genetic and environmental forms of deafness to be studied include:
- Prenatal/congenital cytomegalovirus (CMV) infection
  - Detecting the presence of CMV viral DNA in dried blood spots.
- Connexin Deafness - GJB2 and GJB6 mutations
- Pendred Syndrome - SLC26A mutations
  - L236P, 1001 +1G>A, T416P, E384G
- Mitochondrial Mutations

This panel of genetic and environmental risk factors will be identified as the “SoundGene™ Panel” in the rest of our protocol and in related documents.
Newborns found to be at risk for late-onset hearing loss (i.e., neonates with a positive SoundGene panel or an abnormal audiometric screening test) will be followed for at least two years. The study will establish the frequency of late-onset hearing loss associated with each of the four causes listed above and will also be used to identify relevant sources of phenotypic variation. The specific research objectives for the four forms of deafness each have merit, but the inclusion of all four in our protocol may actually result in the pre-symptomatic detection of most cases of delayed onset prelingual hearing loss. The study will also allow us to measure the effect of (1) Identifying a specific molecular genetic diagnosis or risk factor and (2) Changes in the testing protocol made possible by dramatic improvements in the outcome characteristics of the screening program on the level of compliance with recommended confirmatory diagnostic testing or monitoring.

**Summary of problem**

Because of demonstrated benefits of early detection of hearing loss on educational outcome of affected infants (1), universal audiometric hearing screening has been carried out in most parts of this country in the last 10 years. Two complementary neonatal screening techniques are now in widespread use: the automated auditory brain-stem response measures average neural response to a large number of repeated sound signals of the same pitch and intensity; whereas, measurement of spontaneous or sound-induced otoacoustic emissions detects sound produced by movements of outer hair cells of the cochlea.

Two major limitations of existing audiometric newborn hearing screening programs are their inability to detect forms of deafness that are not expressed at birth and the low compliance with obtaining recommended audiologic confirmation and/or follow-up. Molecular genetic tests on blood spots from all newborns will identify those at risk for the most frequent causes of late-onset hearing loss and to add these infants to the group who should receive continued audiologic monitoring.

Existing universal screening programs to identify hearing defects in newborns in the United States still do not possess the high follow-up rates for positive test results that characterize most metabolic screening programs for newborns. Another limitation is that some forms of late-onset hearing loss are not apparent at birth. Finally, most screening programs have lacked an etiologic focus, which may compromise meaningful interpretation of the results of early intervention.

Major benefits of genetic testing for common risk factors for hereditary hearing impairment include:

- Facilitating the establishment of an etiologic diagnosis.
- Improvement of the follow-up rate for hearing screening.
- Identification of late-onset hearing loss that will be missed by audiometric hearing screening.
- Timely diagnosis of some genetic/environmental conditions such as congenital CMV infection and mitochondrial mutation which may actually lead to prevention of hearing loss and allow for better treatment of asymptomatic CMV infection.
Study Type - Descriptive Study
Multicenter Study - 25 Sites

Study Enrollment Goal – 6,000 participants
Site Enrollment Goal - 240 participants

Eligibility - All newborns

Inclusion Criteria
1. Documentation of informed consent. Informed consent will be obtained by the principal investigator and/or designated research staff for each subject before enrollment or laboratory specimen is drawn.
2. Inborn
3. Ability to do ABR (auditory brainstem response screen technology) screening test. (Pediatrix Hearing Screen Program)
4. Age at enrollment less than 14 days or less than or equal to 336 hours. (Birth date is day 0.)
5. Gestational age > 34 0/7 weeks and above. (Late preterm infants and term infants)
6. No major anomalies
7. Ability to obtain blood sample prior to administration of any blood product transfusion.
8. Subjects' parents willing to provide follow-up data on their child. They will need to provide a telephone contact number and address for follow-up procedures.

Exclusion Criteria
1. Older than 14 days of age or 336 hours.
2. Receipt of a blood product prior to the ability to obtain blood sample for SoundGene panel.
3. Any major congenital anomaly. (chromosomal abnormalities, cyanotic congenital heart disease, gastroschisis, omphalocele, diaphragmatic hernia, or other major gastrointestinal anomalies, major neurological injury or anomaly, and multiple congenital anomalies).

Reference