Genes Tested

<table>
<thead>
<tr>
<th>CDH23</th>
<th>GJB6</th>
<th>OTOF</th>
<th>SLC26A4</th>
<th>USH1G</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLRN1</td>
<td>GPR98</td>
<td>PCDH15</td>
<td>TMC1</td>
<td>USH2A</td>
</tr>
<tr>
<td>EYA1</td>
<td>KCNJ10</td>
<td>POU3F4</td>
<td>TMIE</td>
<td>WHRN</td>
</tr>
<tr>
<td>FOXI1</td>
<td>MYO6</td>
<td>SIX1</td>
<td>TMPRSS3</td>
<td></td>
</tr>
<tr>
<td>GJB2</td>
<td>MYO7A</td>
<td>SIX5</td>
<td>USH1C</td>
<td></td>
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</tbody>
</table>

**Disorder:** Hearing loss affects about 1 in 500 newborns and a genetic etiology is suspected in two thirds of these patients. Hearing loss can be caused by mutations in many different genes which can be inherited in an autosomal dominant, autosomal recessive, X-linked or mitochondrial (maternal inheritance) manner.

**Rationale for Testing:** Identification of the specific cause of a child's hearing loss is an important part of a comprehensive hearing loss evaluation. Identification of a specific genetic mutation provides important information about long-term prognosis and medical management. It also provides very specific information on which to base genetic counseling for parents and other at-risk family members. Finally, identification of a genetic mutation, early in the evaluation process, may eliminate the need for further, more invasive and costly medical procedures and tests.

**OtoSeq* Hearing Loss Panel** is our next-generation sequencing panel of 23 genes (see above) associated with hearing loss. **OtoSeq* Hearing Loss Panel** is indicated for patients with sensorineural hearing loss of unknown etiology who have had no previous genetic testing. The **OtoSeq* Hearing Loss Panel** may also be used as follow-up testing in patients with normal GJB2 or Hearing Loss Panel Tier 1 test results. Please see our web site for complete information.

OtoSeq* was specifically designed to detect mutation(s) in the most common genes causing early onset sensorineural hearing loss, particularly those associated with other risk factors, while limiting the number of findings of uncertain clinical significance.

**Indications:**
- Nonsyndromic sensorineural hearing loss of unknown etiology
- Branchiootorenal spectrum disorder
- Pendred syndrome or cochlear defect
- Usher syndrome (types 1, 2, or 3)

**Specimen:** At least 5 mLs whole blood in a lavender top (EDTA) tube. Label each tube with patient’s name, birth date, and date of collection.

**Testing Methodology:** This test is performed by enrichment of the exons, flanking intronic and untranslated regions (5’ and 3’) of the genes specified above using microdroplet PCR technology followed by next-generation sequencing with > 20 fold coverage at every target base. All pathogenic and novel variants, as well as variants of unknown (indeterminate) significance, as determined bioinformatically, are confirmed by Sanger sequencing.
Test Sensitivity:
Clinical Sensitivity: OtoSeq® Hearing Loss Panel was designed to identify approximately 80% of the genetic causes of early onset sensorineural hearing loss. Over 80% of Usher syndrome, 50% of Pendred syndrome, and 30-40% of branchiootorenal (BOR/BOS) spectrum disorder will also be identified by OtoSeq® testing.

Analytical Sensitivity: The sensitivity of next-generation sequencing is over 99% for the detection of nucleotide base changes and small deletions and insertions (<10 bases) in the regions analyzed. Larger deletions, insertions and other complex genetic events, which are quite common in several of the genes on this panel, will not be identified using this test methodology. Rare primer site variants may lead to erroneous results.

Note: Single gene sequencing is available for all genes in the panel.

Turn-Around Time:
• 56 days for NGS of the panel
• Up to 42 days for analysis of any gene on the panel by Sanger sequencing

Cost: Please call 1-866-450-4198 for current pricing, insurance precertification, or with any billing questions.

CPT Codes:
• OtoSeq® Hearing Loss Panel by NGS: 81443
• Single gene sequencing of GJB2: 81252
• Single gene sequencing of GJB6: 81254
• Single gene sequencing of CLRN1, KCNJ10, USH1G: 81404
• Single gene sequencing of EYA1, SLC26A4: 81406
• Single gene sequencing of MYO7A, PCDH15, USH1C: 81407
• Single gene sequencing of CDH23, USH2A: 81408
• Single gene sequencing of any other panel gene: 81479

Results: Each OtoSeq® test report includes a detailed interpretation of the genetic findings, the clinical significance of the result, and specific recommendations for clinical management and additional testing, if warranted. Results will be reported to the referring physician or health care provider as specified on the test requisition form.

Shipping Instructions
Please enclose a completed test requisition, audiogram and MRI/CT report, if available with the sample. All information must be completed before the sample can be processed. Place samples in Styrofoam mailer and ship at room temperature by overnight Federal Express to arrive Monday through Friday.

Ship to:
Cytogenetics and Molecular Genetics Laboratories
3333 Burnet Avenue NRB 1042
Cincinnati, OH 45229
513-636-4474

Additional information and test requisitions are available at: www.cchmc.org/hearing-loss
References:

Nonsyndromic hearing loss

Branchio-oto-renal (BOR/BOS) spectrum

Usher syndrome

Pendred syndrome
Stephens & M. P. Adam (Eds.), GeneReviews. Seattle (WA).