Overview

Useful For
Establishing a diagnosis of a syndromic or nonsyndromic hereditary hearing loss disorder
Identifying variants within genes known to be associated with hereditary hearing loss, allowing for predictive testing of at-risk family members

Genetics Test Information
Hereditary hearing loss is a genetically heterogeneous condition that can be either syndromic or nonsyndromic in origin. This panel evaluates 160 genes related to both syndromic and nonsyndromic hereditary hearing loss.

The following genes are investigated in this panel test: ABHD12, ACTG1, ADCY1, ADGRV1, AIFM1, ALMS1, ATP6V1B1, BCS1L, BDP1, BND3, BTD, CABP2, CACNA1D, CATSPER2, CCDC50, CD164, CDC14A, CDH23, CEACAM16, CEP78, CHD7, CIB2, CIDS2, CLDN14, CLIC5, CLPP, CLRN1, COCH, COL2A1, COL4A3, COL4A4, COL4A5, COL4A6, COL9A1, COL9A2, COL9A3, COL11A1, COL11A2, CRYM, DCD2C, DFNA5 (GSDME), DIAIBL, DIAIP1, DIAIP3, DNM1T1, DSSP, EDN3, EDNRB, ELMD3, EPS8, EPS8L2, ESPN, ESRRB, EYA1, EYA4, FGFR3, FGFR2, FLNA, FOXC1, FOXI1, GATA3, GIPC3, GJB2, GJB6, GPSM2, GRHL2, GRXCR1, GRXCR2, HARS2, HGF, HOMER2, HOXA2, HSD17B4, ILDR1, JAG1, KARS, KNE1, KCN10, KCNQ1, KCNQ4, KITLG, LARS2, LHFPL5, LOXHD1, LRTOMT, MARVELD2, MCM2, MET, MIR96, MITF, MSRB3, MT-RNR1, MT-TS1, MYH14, MYH9, MYO3A, MYO7A, MYO15A, NARS2, NF2, NLRP3, OPA1, OSBP2L, OTOA, OTOF, OTOG, OTOL, P2RX2, PAX3, PCDH15, PDZD7, PEX1, PEX6, PHNY, PJVK, PNPT1, POLR1C, POLR1D, POU3F3, POU4F3, PRPS1, PTPRQ, RDX, RIPOR2, S1PR2, SERPINB6, SIXL, SLC17A8, SLC22A4, SLC26A4, SLC26A5, SLC52A2, SLC52A3, SLC52A4, SMPX, SNAI2, SOX10, STRC, SYNE4, TBC1D24, TCOF1, TECTA, TMEM8A, TIP2, TMEM12, TMEM132E, TMIE, TMEM33, TNC, TPRN, TRIOBP, TWNK, USH1C, USH1G, USH2A, WBP2, WFS1, and WHRN

Testing Algorithm
If skin biopsy is received, fibroblast culture and cryopreservation for biochemical studies will be added at an additional charge.

Special Instructions
• Informed Consent for Genetic Testing
• Informed Consent for Genetic Testing (Spanish)
• Molecular Genetics: Hereditary Hearing Loss Patient Information
• Targeted Genes and Methodology Details for the Hereditary Hearing Loss Panel

Reflex Tests

<table>
<thead>
<tr>
<th>Test Id</th>
<th>Reporting Name</th>
<th>Available Separately</th>
<th>Always Performed</th>
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<tbody>
<tr>
<td>FIBR</td>
<td>Fibroblast Culture</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>CRYOB</td>
<td>Cryopreserve for Biochem Studies</td>
<td>No</td>
<td>No</td>
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Method Name
Custom Sequence Capture and Targeted Next-Generation Sequencing (NGS)/Polymerase Chain Reaction (PCR)/Digital Droplet PCR (ddPCR)/qPCR/Sanger Sequencing/Gene Dosage Analysis by Multiplex Ligation-Dependent Probe Amplification (MLPA)

NY State Available
Yes
Specimen

Specimen Type
Varies

Ordering Guidance
Targeted testing for familial variants (also called site-specific or known mutations testing) is available for the genes on this panel. See FMTT / Familial Mutation, Targeted Testing, Varies.

Shipping Instructions
Specimen preferred to arrive within 96 hours of collection.

Specimen Required
Specimen Type: Whole blood

Patient Preparation: A previous bone marrow transplant from an allogenic donor will interfere with testing. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.

Container/Tube:
Preferred: Lavender top (EDTA) or yellow top (ACD)
Acceptable: Any anticoagulant

Specimen Volume: 3 mL

Collection Instructions:
1. Invert several times to mix blood.
2. Send specimen in original tube. Do not aliquot.

Specimen Stability Information: Ambient (preferred) 4 days/Refrigerated 14 days

Additional Information: To ensure minimum volume and concentration of DNA is met, the preferred volume of blood must be submitted. Testing may be canceled if DNA requirements are inadequate.

Specimen Type: Skin biopsy

Supplies: Fibroblast Biopsy Transport Media (T115)

Container/Tube: Sterile container with any standard cell culture media (eg, minimal essential media, RPMI 1640). The solution should be supplemented with 1% penicillin and streptomycin.

Specimen Volume: 4-mm punch

Specimen Stability Information: Refrigerated (preferred)/Ambient

Additional Information: A separate culture charge will be assessed under FIBR / Fibroblast Culture, Tissue. An additional 4 weeks is required to culture fibroblasts before genetic testing can occur.

Specimen Type: Cultured fibroblast

Container/Tube: T-25 flask

Specimen Volume: 2 Flasks

Collection Instructions: Submit confluent cultured fibroblast cells from a skin biopsy from another laboratory. Cultured cells from a prenatal specimen will not be accepted.

Specimen Stability Information: Ambient (preferred)/Refrigerated (<24 hours)

Additional Information: A separate culture charge will be assessed under FIBR / Fibroblast Culture, Tissue. An additional 4 weeks is required to culture fibroblasts before genetic testing can occur.

Forms
1. New York Clients-Informed consent is required. Document on the request form or electronic order that a copy is on
file. The following documents are available in Special Instructions:
- Informed Consent for Genetic Testing (T576)
- Informed Consent for Genetic Testing (Spanish) (T826)
3. Targeted Genes and Methodology Details for the Hereditary Hearing Loss Panel in Special Instructions.
4. If not ordering electronically, complete, print, and send a Neurology Specialty Testing Client Test Request (T732) with the specimen.

Reject Due To

All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

Specimen Minimum Volume

3 mL

Specimen Stability Information

<table>
<thead>
<tr>
<th>Specimen Type</th>
<th>Temperature</th>
<th>Time</th>
<th>Special Container</th>
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<tbody>
<tr>
<td>Varies</td>
<td>Varies (preferred)</td>
<td></td>
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Clinical & Interpretive

Clinical Information
Hereditary hearing loss encompasses a heterogeneous group of syndromic and nonsyndromic conditions. A comprehensive diagnostic genetic test is useful to help determine a molecular etiology for hearing loss and, therefore, identify other organ systems that may be involved, establish long-term prognosis, and ascertain the inheritance pattern and recurrence risk within a family.

Individuals with syndromic hearing loss typically have involvement of other organs or organ systems and may have malformations of the external ear. Individuals with nonsyndromic hearing loss may have abnormalities of the middle ear and/or inner ear but typically do not have visible abnormalities of the external ear and often do not have additional organ system involvement or other related medical problems.

Approximately 50% of individuals with hearing loss have a genetic etiology that can be identified. Of those, approximately 70% of individuals have a nonsyndromic condition, and the remaining 30% have 1 of over 400 syndromes involving hearing loss. Of the individuals with nonsyndromic hearing loss, at least three-quarters have an autosomal recessive condition, approximately 25% of whom have variants in the GJB2 or GJB6 genes.

Reference Values
An interpretive report will be provided.

Interpretation
Variant curation is performed using published American College of Medical Genetics and Genomics and the Association for Molecular Pathology recommendations as a guideline.(1) Other gene-specific guidelines may also be considered. Variants are classified based on known, predicted, or possible pathogenicity, and reported with interpretive comments detailing their potential or known significance.

Cautions
Clinical Correlations:
Test results should be interpreted in the context of clinical findings, family history, and other laboratory data. Misinterpretation of results may occur if the information provided is inaccurate or incomplete.
If testing was performed because of a clinically significant family history, it is often useful to first test an affected family member. Detection of at least one reportable variant in an affected family member would allow for more informative testing of at-risk individuals.
To discuss the availability of additional testing options or for assistance in the interpretation of these results, contact the Mayo Clinic Laboratory genetic counselors at 800-533-1710.

Technical Limitations:
Next-generation sequencing may not detect all types of genomic variants. In rare cases, false-negative or false-positive results may occur. The depth of coverage may be variable for some target regions, but assay performance below the minimum acceptable criteria or for failed regions will be noted. Given these limitations, negative results do not rule out the diagnosis of a genetic disorder. Additionally, low level mosaic variants may not be detected. If a specific clinical disorder is suspected, evaluation by alternative methods can be considered.
If the patient has had an allogeneic hematopoietic stem cell transplant or a recent heterologous blood transfusion, these results may be inaccurate due to the presence of donor DNA.
There may be regions of genes that cannot be effectively amplified for sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. Confirmation of select reportable variants will be performed by alternate methodologies based on internal laboratory criteria.
Of note, absence of the mitochondrial variants MT-RNR1 m.1494C>T, MT-RNR1 m.1555A>G, or MT-TS1 m.7445A>G on the report does not rule out the presence of these variants below the limits of detection of this assay (<5% heteroplasmy).
This test is not designed to differentiate between somatic and germline variants. If there is a possibility that any detected variant is somatic, additional testing may be necessary to clarify the significance of results.
Reclassification of Variants Policy:
At this time, it is not standard practice for the laboratory to systematically review previously classified variants on a regular basis. The laboratory encourages health care providers to contact the laboratory at any time to learn how the status of a particular variant may have changed over time.

Variant Evaluation:
Evaluation and categorization of variants is performed using published American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) recommendations as a guideline.(1) Other gene-specific guidelines may also be considered. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Variants classified as benign or likely benign are not reported.
Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and periodic updates to these tools may cause predictions to change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Clinical Reference
Performance

Method Description
Next-generation sequencing (NGS) and/or Sanger sequencing is performed to test for the presence of a sequence variant in all genes analyzed. Additionally, digital droplet polymerase chain reaction (ddPCR) is performed to test for 3 mitochondrial variants included in this panel.

Finally, NGS or multiplex ligation-dependent probe amplification (MLPA) is used to test for the presence of large deletions and duplications in the majority of genes. There may be regions of genes that cannot be effectively amplified for sequencing or large deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC)-rich content, and repetitive sequences. MLPA, PCR, qPCR, array comparative genomic hybridization (aCGH) or Sanger sequencing may be used to confirm alterations detected by NGS when appropriate.(Unpublished Mayo method)

Genes analyzed: ABHD12, ACTG1, ADCY1, ADGRV1, ALMS1, ATP6V1B1, BCS1L, BDP1, BSND, BTD, CABP2, CACNA1D, CATSPER2, CCDC50, CD164, CDC14A, CDH23, CEACAM16, CEP78, CHD7, CIB2, CISD2, CLDN14, CLICS, CLPP, CLRN1, COCH, COL2A1, COL4A3, COL4A4, COL4A5, COL4A6, COL9A1, COL9A2, COL11A1, COL11A2, CYRM, DCDC2, DFNAS (GSDME), DIABLO, DIAPH1, DIAPH3, DNMT1, DPP, EDN3, EDNRB, ELMOD3, EPS8, EPS8L2, ESPN, ESRRB, EYA1, EYAF, FGFR3, FGFR2, FLNA, FOXC1, FOXI1, GATA3, GIPC3, GJB2, GJ16, GMPM2, GRHL2, GRXCR1, GRXCR2, HARS2, HGF, HOMER2, HOXA2, HS17B4, ILDR1, JAG1, KARS, KCNE1, KCNJ10, KCNQ1, KCNQ4, KITLG, LARS2, LHFPL5, LOXHD1, LRTOMT, MARVELD2, MCM2, MET, MIR96, MTF, MSTRB3, MT-RNR1, MT-TS1, MYH14, MYH9, MYO3A, MYO6, MYO7A, MYO15A, NARS2, NF2, NLGRP3, OPA1, OSBPL2, OTOA, OTOF, OTOGL, P2RX2, PAX3, PCDH15, PDZD7, PEX1, PEX6, PHHY, PIVK, PNPT1, POLR1C, POLR1D, POLR3F, POLR3F, PRPS1, PTPN11, PTPQ, RXD, RIPOR2, S1PR2, SERPINB6, SIX1, SLC17A8, SLCC2A4, SLCC26A4, SLCC26A5, SLCS2A2, SLCS2A3, SLTRK6, SMPX, SNAI2, SOX10, STRC, SYNE4, TBC1D24, TCOF1, TECTA, TIMM8A, TJP2, TMC1, TMEM132E, TMIE, TMPRS53, TNC, TPRN, TRIOPB, TWNK, USH1C, USH1G, USH2A, WB2, WFS1, and WHRN

PDF Report
Supplemental

Specimen Retention Time
Whole Blood: 2 weeks (if available) Extracted DNA: Indefinitely

Performing Laboratory Location
Rochester
**Test Definition: HHLP**  
**Hereditary Hearing Loss Panel**

### Fees & Codes

**Test Classification**  
This test was developed, and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the US Food and Drug Administration.

**CPT Code Information**  
81430  
81431