

Aminoglycoside-Induced Hearing Loss, Targeted Variant Testing, Droplet Digital PCR, Varies

#### Overview

#### **Useful For**

Identification of individuals who may be at risk for aminoglycoside-induced hearing loss (AIHL)

Establishing a diagnosis of late-onset sensorineural hearing loss associated with aminoglycoside exposure

Identifying mitochondrial variants associated with AIHL, allowing for predictive testing of at-risk family members

#### **Genetics Test Information**

This test detects 2 mitochondrial gene *RNR1* (MT-RNR1) variants, m.1555A>G and m.1494C>T, which are the most common variants associated with aminoglycoside induced ototoxicity.

#### **Special Instructions**

- Informed Consent for Genetic Testing
- Informed Consent for Genetic Testing (Spanish)
- Molecular Genetics: Hereditary Hearing Loss Patient Information

#### Highlights

This test uses droplet digital polymerase chain reaction to evaluate for the presence of 2 mitochondrial variants associated with aminoglycoside-induced hearing loss.

#### Method Name

Droplet Digital Polymerase Chain Reaction (ddPCR)

#### NY State Available

Yes

## Specimen

#### Specimen Type

Varies

#### Ordering Guidance

The preferred genetic test for diagnosis in individuals with suspicion of syndromic or non-syndromic hereditary hearing loss is HHLP / AudioloGene Hereditary Hearing Loss Panel, Varies.

#### **Shipping Instructions**

Specimen preferred to arrive within 96 hours of collection.



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## **Specimen Required**

**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.

Specimen Type: Whole blood 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.

Specimen Stability Information: Ambient/Refrigerated/Frozen

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: Saliva

Patient Preparation: Patient should not eat, drink, smoke, or chew gum 30 minutes prior to collection.
Supplies: Saliva Collection Kit (T786)
Specimen Volume: 1 swab
Collection Instructions: Collect and send specimen per kit instructions.
Specimen Stability Information: Ambient

#### 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:

-Informed Consent for Genetic Testing (T576)

-Informed Consent for Genetic Testing (Spanish) (T826)

2. Molecular Genetics Hereditary Hearing Loss Patient Information

3. If not ordering electronically, complete, print, and send a <u>Therapeutics Test Request</u> (T831) with the specimen.

## **Specimen Minimum Volume**

See Specimen Required

## **Reject Due To**

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

## Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Varies		



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## **Clinical & Interpretive**

## **Clinical Information**

Aminoglycosides (tobramycin, streptomycin, and gentamicin, etc) are a group of broad-spectrum antibiotics commonly prescribed for infections caused by Gram-negative bacteria. In the United States alone, approximately 4 million courses of aminoglycosides are administered each year with approximately 2% to 5% of patients treated developing clinically significant hearing loss. Mitochondrial gene *RNR1* (MT-RNR1) variants m.1555A>G and m.1494C>T are the most common variants associated with aminoglycoside-induced ototoxicity. Hearing loss associated with aminoglycoside exposure can occur even after a single dose and may be bilateral, irreversible, and often severe to profound. Avoidance of aminoglycoside antibiotics reduces the risk of developing hearing loss for individuals carrying one of these 2 variants.

The severity and onset of hearing loss in individuals with the associated pathogenic mitochondrial variants range from profound congenital deafness to mild to moderate late-onset hearing loss. Evidence demonstrates that this variance can often be explained by variant load in an individual. In contrast to variants in nuclear genes, which are present in either 0, 1, or 2 copies, mitochondrial variants can be present in any fraction of the total organelles, a phenomenon known as heteroplasmy. Penetrance of hearing loss without exposure to aminoglycosides is thought to be a function of the degree of heteroplasmy, with a correlation between higher fraction of altered mitochondria and higher penetrance. Hearing loss is believed to be 100% penetrant in homoplasmic individuals who receive aminoglycoside antibiotics.

## **Reference Values**

An interpretive report will be provided.

## Interpretation

An interpretive report will be provided.

## Cautions

Clinical Correlations:

Test results should be interpreted in 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 a reportable variant in an affected family member would allow for more informative testing of at-risk individuals.

## Technical Limitations:

This assay will not detect all variants or genes that cause mitochondrial nonsyndromic hearing loss and deafness. Therefore, the absence of a detectable variant does not rule out the possibility that an individual is a carrier of or affected with mitochondrial non-syndromic hearing loss and deafness.

Some individuals who are a carrier or have a diagnosis of mitochondrial nonsyndromic hearing loss and deafness may have a variant that is not identified by this assay. The absence of a variant, therefore, does not eliminate the possibility of a hereditary hearing loss disorder. For predictive testing of asymptomatic individuals, it is important to first document



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the presence of a gene variant in an affected family member.

Of note, absence of the mitochondrial variants MT-RNR1 m.1494C>T or MT-RNR1 m.1555A>G does not rule out the presence of these variants below the limits of detection of this assay (<5% heteroplasmy).

Rare alterations exist that could lead to false-negative or false-positive results. If results obtained do not match clinical findings, additional testing should be considered.

## **Clinical Reference**

1. Gao Z, Chen Y, Guan MX: Mitochondrial DNA mutations associated with aminoglycoside induced ototoxicity. J Otol. 2017 Mar;12(1):1-8

2. Krause KM, Serio AW, Kane TR, Connolly LE: Aminoglycosides: An overview. Cold Spring Harb Perspect Med. 2016 Jun 1;6(6):a027029

3. Qian Y, Guan MX: Interaction of aminoglycosides with human mitochondrial 12S rRNA carrying the deafness-associated mutation. Antimicrob Agents Chemother. 2009 Nov;53(11):4612-4618

4. Usami S, Nishio S: Nonsyndromic hearing loss and deafness, mitochondrial. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2004. Updated June 14, 2018. Accessed March 15, 2021. Available at www.ncbi.nlm.nih.gov/books/NBK1422/

## Performance

## **Method Description**

This test is a droplet digital polymerase chain reaction method for the detection of MT-RNR1 m.1494C>T and MT-RNR1 m.1555A>G associated with aminoglycoside-induced hearing loss. Variant nomenclature is based on the following GenBank Accession number (build GRCh37 [hg19]): NC\_012920.1.(Unpublished Mayo method)

## PDF Report

No

## Day(s) Performed

Monday through Saturday

## **Report Available**

1 to 7 days-Specimens must arrive in the performing laboratory by 12 p.m. for the report to be available 1 day from specimen receipt.

## **Specimen Retention Time**

Whole Blood: 2 weeks (if available); Extracted DNA: Indefinitely

## **Performing Laboratory Location**

Rochester



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## Fees & Codes

#### Fees

- Authorized users can sign in to <u>Test Prices</u> for detailed fee information.
- Clients without access to Test Prices can contact <u>Customer Service</u> 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact Customer Service.

#### **Test Classification**

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

#### **CPT Code Information**

81401

#### LOINC<sup>®</sup> Information

Test ID	Test Order Name	Order LOINC <sup>®</sup> Value
AIHL	Aminoglycoside-Induced Hearing	In Process
	Loss	

Result ID	Test Result Name	Result LOINC <sup>®</sup> Value
609786	Specimen	31208-2
609787	Source	31208-2
609788	Result Summary	50397-9
609789	Result	82939-0
609790	Interpretation	69047-9
609791	Additional Information	48767-8
609792	Method	85069-3
609793	Disclaimer	62364-5
609794	Released By	18771-6