Overview

Useful For
Confirms a diagnosis of primary hyperoxaluria type 1

Carrier testing for individuals with a family history of primary hyperoxaluria type 1 in the absence of known mutations in the family

Testing Algorithm
See Hyperoxaluria Diagnostic Algorithm in Special Instructions

Special Instructions
- Molecular Genetics: Congenital Inherited Diseases Patient Information
- Informed Consent for Genetic Testing
- Hyperoxaluria Diagnostic Algorithm
- Informed Consent for Genetic Testing (Spanish)

Method Name
Polymerase Chain Reaction (PCR) Followed by DNA Sequence Analysis and Gene Dosage Analysis by Multiplex Ligation-Dependent Probe Amplification (MLPA)

NY State Available
Yes

Specimen

Specimen Type
Varies

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: Lavender top (EDTA) or yellow top (ACD)

Specimen Volume: 3 mL

Collection Instructions:
1. Invert several times to mix blood.
2. Send specimen in original tube.

Additional Information: Specimen preferred to arrive within 96 hours of draw.

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)

2. **Molecular Genetics: Congenital Inherited Diseases Patient Information** (T521) in Special Instructions

3. If not ordering electronically, complete, print, and send a **Renal Diagnostics Test Request** (T830) with the specimen.

**Specimen Minimum Volume**

1 mL

**Reject Due To**

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

**Specimen Stability Information**

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<th>Temperature</th>
<th>Time</th>
<th>Special Container</th>
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**Clinical and Interpretive**

**Clinical Information**

Primary hyperoxaluria type 1 (PH1) is a hereditary disorder of glyoxylate metabolism caused by deficiency of alanine:glyoxylate-aminotransferase (AGT), a hepatic enzyme that converts glyoxylate to glycine. Absence of AGT activity results in conversion of glyoxylate to oxalate, which is not capable of being degraded. Therefore, excess oxalate is excreted in the urine, causing kidney stones (urolithiasis), nephrocalcinosis, and kidney failure. As kidney function declines, blood levels of oxalate increase markedly, and oxalate combines with calcium to form calcium oxalate deposits in the kidney, eyes, heart, bones, and other organs, resulting in systemic disease. Pyridoxine (vitamin B6), a cofactor of AGT, is effective in reducing urine oxalate excretion in some PH1 patients.

Presenting symptoms of PH1 include nephrolithiasis, nephrocalcinosis, or end-stage kidney disease with or without a history of urolithiasis. Age of symptom onset is variable; however, most individuals present in childhood or adolescence with symptoms related to kidney stones. In some infants with a more severe phenotype, kidney failure may be the initial presenting feature. Less frequently, affected individuals present in adulthood with recurrent kidney stones or kidney failure. End-stage kidney disease is most often seen in the third decade of life, but can occur at any age.

The exact prevalence and incidence of PH1 are not known, but prevalence rates of 1 to 3 per million population and incidences of 0.1 per million/year have been estimated from population surveys.

Biochemical testing is indicated in patients with possible primary hyperoxaluria. Measurement of urinary oxalate is strongly preferred, with correction to adult body surface area in pediatric patients (HYOX / Hyperoxaluria Panel, Urine; OXU / Oxalate, 24 Hour, Urine). Abnormal urinary excretion of oxalate is strongly suggestive of, but not diagnostic for, this disorder, as there are other forms of inherited (type 2 and non-PH1/PH2) hyperoxaluria and secondary hyperoxaluria that may result in similarly elevated urine oxalate excretion rates. An elevated urine glycolate in the presence of hyperoxaluria is suggestive of PH1. Historically, the diagnosis of PH1 was confirmed by
AGT enzyme analysis performed on liver biopsy; however, this has been replaced by molecular testing, which forms the basis of confirmatory or carrier testing in most cases.

PH1 is inherited as an autosomal recessive disorder caused by mutations in the AGXT gene, which encodes the enzyme AGT. Several common AGXT mutations have been identified including c.33dupC, p.Gly170Arg (c.508G->A), and p.Ile244Thr (c.731T->C). These mutations account for at least 1 of the 2 affected alleles in approximately 70% of individuals with PH1. Direct sequencing of the AGXT gene is predicted to identify 99% of alleles in individuals who are known by enzyme analysis to be affected with PH1.

While age of onset and severity of disease is variable and not necessarily predictable by genotype, a correlation between pyridoxine responsiveness and homozygosity for the p.Gly170Arg mutation has been observed. (Note: testing for the p.Gly170Arg mutation only is available by ordering AGXTG / Alanine:Glyoxylate Aminotransferase [AGXT] Mutation Analysis [G170R], Blood). Pyridoxine (vitamin B6) is a known cofactor of AGT and is effective in reducing urine oxalate excretion in some PH1 patients treated with pharmacologic doses. Individuals with 2 copies of the p.Gly170Arg mutation have been shown to normalize their urine oxalate when treated with pharmacologic doses of pyridoxine and those with a single copy of the mutation show reduction in urine oxalate. This is valuable because not all patients have been shown to be responsive to pyridoxine, and strategies that help to identify the individuals most likely to benefit from such targeted therapies are desirable.

Reference Values
An interpretive report will be provided.

Interpretation
All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Cautions
A small percentage of individuals who are carriers or have a diagnosis of primary hyperoxaluria type 1 (PH1) may have a mutation that is not identified by this method (eg, promoter mutations). The absence of a mutation, therefore, does not eliminate the possibility of positive carrier status or the diagnosis of PH1 disease. For carrier testing, it is important to first document the presence of a PH1-gene mutation in an affected family member.

In some cases, DNA alterations of undetermined significance may be identified.

In addition to disease-related probes, this test utilizes probes localized to other chromosomal regions as internal controls. In certain circumstances, these control probes may detect other diseases or conditions for which this test was not specifically intended. Results of the control probes are not normally reported. However, in cases where clinically relevant information is identified, the ordering physician will be informed of the result and provided with recommendations for any appropriate follow-up testing.

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

Test results should be interpreted in the context of clinical findings, family history, and other laboratory data. Errors in our interpretation of results may occur if information given is inaccurate or incomplete.

Clinical Reference


8. Communique April 2007: Laboratory and Molecular Diagnosis of Primary Hyperoxaluria and Oxalosis

**Performance**

**Method Description**

Bidirectional sequence analysis is performed to test for the presence of a mutation in all coding regions and intron/exon boundaries of the AGXT gene. Additionally, gene dosage analysis (multiplex ligation-dependent probe amplification) is used to test for the presence of large deletions and duplications in this gene. (Unpublished Mayo method)

**PDF Report**

No

**Day(s) and Time(s) Test Performed**

Performed weekly; Varies

**Analytic Time**

14 days

**Maximum Laboratory Time**

20 days

**Performing Laboratory Location**

Rochester

**Fees and Codes**

**Fees**

- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their Regional Manager. 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. This test has not been cleared or approved by the U.S. Food and Drug Administration.

**CPT Code Information**
81479-Unlisted molecular pathology procedure

**LOINC® Information**

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