

## Overview

### Useful For

Diagnostic confirmation of Wilson disease

### Genetics Test Information

Ceruloplasmin, serum copper, and urine copper studies are recommended prior to submitting sample. Test includes next-generation sequencing of exons 1 through 21 and for the common Sardinian promoter mutation. Sanger sequencing may be performed to confirm detected variants.

### Testing Algorithm

See [Wilson Disease Testing Algorithm](#) in Special Instructions.

### Special Instructions

- [Molecular Genetics: Congenital Inherited Diseases Patient Information](#)
- [Informed Consent for Genetic Testing](#)
- [Wilson Disease Testing Algorithm](#)
- [Informed Consent for Genetic Testing \(Spanish\)](#)

### Method Name

Custom Sequence Capture and Targeted Next-Generation Sequencing (NGS) followed by Polymerase Chain Reaction (PCR) and Sanger Sequencing when appropriate

### NY State Available

Yes

## Specimen

### Specimen Type

Varies

### Shipping Instructions

Specimen preferred to arrive within 96 hours of collection.

### 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.

**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.

**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 1 of the following forms with the specimen:

[-Inborn Errors of Metabolism Test Request](#) (T798)

[-Gastroenterology and Hepatology Client Test Request](#) (T728)

**Specimen Minimum Volume**

1 mL

**Reject Due To**

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

**Specimen Stability Information**

Specimen Type	Temperature	Time	Special Container
Varies	Ambient (preferred)		
	Frozen		
	Refrigerated		

**Clinical and Interpretive**

**Clinical Information**

Wilson disease (WD) is an autosomal recessive disorder that results from the body's inability to excrete excess copper. Typically, the liver releases excess copper into the bile. Individuals with WD lack the necessary enzyme that facilitates clearance of copper from the liver to bile. As a result, copper accumulates first in the liver and gradually in other organs. The brain, kidneys, bones, and corneas can also be affected. WD affects approximately 1 in 30,000 people worldwide, with a carrier frequency of approximately 1 in 90 individuals.

The primary clinical manifestations of WD are hepatic and neurologic. Hepatic disease can be quite variable, ranging from hepatomegaly or other nonspecific symptoms that mimic viral hepatitis to severe liver damage, such as cirrhosis. Neurologic symptoms of WD can include poor fine-motor coordination, ataxia, and dysphagia. Psychiatric

---

manifestations are reported in approximately 20% of individuals with WD. A characteristic ophthalmologic finding is the Kayser-Fleischer ring. Individuals with WD typically begin to show symptoms of liver dysfunction or neurologic disease in the first or second decade of life. If not treated, WD can cause liver failure, severe brain damage, and even death.

A variety of laboratory tests are recommended in the initial evaluation for WD. In approximately 95% of cases, serum ceruloplasmin is below normal. Additionally, patients with WD show decreased copper in serum, increased copper in urine, and significantly elevated copper on liver biopsy. While liver biopsy is not recommended as a first-tier screening test for WD, it can be useful to help interpret discrepant biochemical or molecular results. The other tests should be performed prior to sequence analysis of the *ATP7B* gene, the gene responsible for WD. More than 300 disease-causing mutations have been identified in the *ATP7B* gene. Most mutations are family-specific with the exception of the H1069Q mutation, which accounts for greater than 50% of identified disease alleles in the Northern European Caucasian population.

See [Wilson Disease Testing Algorithm](#) in Special Instructions for additional information.

### Reference Values

An interpretive report will be provided.

### Interpretation

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

### Cautions

Clinical Correlations:

A small percentage of individuals who are carriers or have a diagnosis of Wilson disease (WD) may have a mutation that is not identified by this method (eg, large genomic deletions, promoter mutations, deep intronic mutations). The absence of a mutation, therefore, does not eliminate the possibility of positive carrier status or the diagnosis of WD. For carrier testing, it is important to first document the presence of an *ATP7B* gene mutation in an affected family member.

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.

Technical Limitations:

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

Due to the limitations of next-generation sequencing, small deletions and insertions may not be detected by this test. If a diagnosis is still suspected, contact a molecular genetic counselor in the Genomics Laboratory at 800-533-1710 for more information regarding follow-up testing options.

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.

Evaluation Tools:

Multiple in-silico evaluation tools were used to assist in the interpretation of these results. These tools are updated regularly; therefore changes to these algorithms may result in different predictions for a given alteration. Additionally, the predictability of these tools for the determination of pathogenicity is currently unvalidated.

Unless reported or predicted to cause disease, alterations that do not result in an amino acid substitution are not reported.

#### Reclassification of Variants-Policy:

All detected alterations are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. At this time, it is not standard practice for the laboratory to systematically review likely pathogenic alterations or variants of uncertain significance that are detected and reported. 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.

### Supportive Data

Ninety-six normal Caucasian specimens were screened for the presence of benign polymorphisms in the *ATP7B* gene. Selected exons from 21 of these specimens were confirmed by direct sequencing to have at least a single polymorphism. One normal specimen was found to be a carrier of an *ATP7B* mutation (IVS11-2A>G). Five Wilson disease patients with known *ATP7B* mutations were sequenced with 100% concordance.

### Clinical Reference

1. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015 May;17(5):405-424
2. European Association for Study of Liver. EASL Clinical Practice Guidelines: Wilson's disease. *J Hepatol* 2012 Mar;56(3):671-685
3. Roberts EA, Schilsky ML, American Association for Study of Liver Diseases (AASLD): Diagnosis and treatment of Wilson disease: an update. *Hepatology* 2008;47(6):2089-2111
4. Mak CM, Lam CW: Diagnosis of Wilson's disease: a comprehensive review. *Crit Rev Clin Lab Sci* 2008;45(3):263-290
5. Bandmann O, Weiss KH, Kaler SG: Wilson's disease and other neurological copper disorders. *Lancet Neurol* 2015 Jan;14(1):103-113

### Performance

#### Method Description

Next-generation sequencing is used to test for the presence of a mutation in all coding exons and intron/exon boundaries, as well as a portion of the 5' untranslated region (UTR), of the *ATP7B* gene. Sanger sequencing is used to confirm alterations detected by next-generation sequencing when appropriate. (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

**Specimen Retention Time**

Whole Blood: 2 weeks (if available) Extracted DNA: 3 months

**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**

81406

**LOINC® Information**

Test ID	Test Order Name	Order LOINC Value
WDZ	Wilson Disease Full Gene Analysis	95781-1

Result ID	Test Result Name	Result LOINC Value
54048	Result Summary	50397-9
54049	Result	82939-0
54050	Interpretation	69047-9
54051	Additional Information	48767-8
54052	Specimen	31208-2
54053	Source	31208-2
54054	Released By	18771-6