

## Overview

### Useful For

Identifying individuals who are at increased risk of adverse drug reactions with drugs that are metabolized by *UGT1A1*, including irinotecan, atazanavir, nilotinib, pazopanib, and belinostat

Identifying individuals who are at risk of hyperbilirubinemia

Follow-up testing for individuals with a suspected *UGT1A1* variant, who had negative TA repeat region testing

Establishing a diagnosis of Gilbert, Crigler-Najjar syndrome type I or type II

Establishing carrier status for Gilbert, Crigler-Najjar syndrome type I or type II

### Genetics Test Information

This is a full gene sequencing test for *UGT1A1* that includes the TA repeat region of the promoter and all intron/exon boundaries. Results are interpreted for the purposes of *UGT1A1* drug metabolism and hereditary hyperbilirubinemia syndromes (Gilbert syndrome and Crigler-Najjar syndrome).

### Testing Algorithm

See [UGT1A1 Test-Ordering Algorithm](#) in Special Instructions.

### Special Instructions

- [Informed Consent for Genetic Testing](#)
- [UGT1A1 Gene Testing Patient Information](#)
- [UGT1A1 Test-Ordering Algorithm](#)
- [Multiple Whole Blood EDTA Genotype Tests](#)
- [Pharmacogenomic Associations Tables](#)
- [Informed Consent for Genetic Testing \(Spanish\)](#)

### Highlights

This test screens for *UGT1A1* gene variants associated with increased risk of adverse drug reactions when taking *UGT1A1*-metabolized drugs. These drugs include irinotecan, atazanavir, nilotinib, pazopanib, and belinostat

This test screens for *UGT1A1* gene variants associated with congenital hyperbilirubinemia conditions including Gilbert syndrome, Crigler-Najjar syndrome type I and type II

### Method Name

Polymerase Chain Reaction (PCR) followed by DNA Sequence Analysis

### NY State Available

Yes

## Specimen

### Specimen Type

Varies

### Ordering Guidance

If analysis of only the *UGT1A1* promoter TA repeat region (\*28, \*36, \*37 alleles) is desired, see U1A1Q /

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UDP-Glucuronosyl Transferase 1A1 TA Repeat Genotype, UGT1A1, Varies.

**Shipping Instructions**

If submitting microtube, place inside a larger tube or vial for transport.

**Necessary Information**

[UGT1A1 Gene Testing Patient Information](#) (T664) is recommended, but not required, to be filled out and sent with the specimen.

**Specimen Required**

Multiple whole blood EDTA tests can be performed on a single specimen after a single extraction. See [Multiple Whole Blood EDTA Genotype Tests](#) in Special Instructions for a list of tests that can be ordered together.

**Patient Preparation:** A previous bone marrow transplant from an allogenic donor or a recent (ie, <6 weeks from time of sample collection) heterologous blood transfusion will interfere with testing. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.

**Submit only 1 of the following specimens:**

**Specimen Type:** Whole blood

**Container/Tube:**

Adults: Lavender top (EDTA)

Pediatrics: Purple microtube

**Specimen Volume:**

Adults: 3 mL

Pediatrics: 1 mL

**Collection Instructions:**

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

**Specimen Stability Information:** Ambient (preferred) 9 days/Refrigerated 30 days

**Specimen Type:** Saliva

**Patient Preparation:** Patient should not eat, drink, smoke, or chew gum 30 minutes prior to collection.

**Supplies:** Saliva Swab Collection Kit (T786)

**Container/Tube:** Saliva Swab Collection Kit

**Specimen Volume:** One swab

**Collection Instructions:** Collect and send specimen per kit instructions.

**Specimen Stability Information:** Ambient 30 days

**Specimen Type:** Extracted DNA

**Container/Tube:** 2 mL screw top tube

**Specimen Volume:** 100 mL (microliters)

**Collection Instructions:**

1. The preferred volume is 100 mL at a concentration of 50 ng/mL.
2. Include concentration and volume on tube.

**Specimen Stability Information:** Frozen (preferred)/Ambient/Refrigerated

**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. [UGT1A1 Gene Testing Patient Information](#) (T664) is requested but not required. See Special Instructions.
3. If not ordering electronically, complete, print, and send 1 of the following forms with the specimen:
  - [Oncology Test Request](#) (T729)
  - [Therapeutics Test Request](#) (T831)

### Reject Due To

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

### Specimen Minimum Volume

Blood: 0.45 mL

Saliva: 1 swab

### Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Varies (preferred)		

## Clinical & Interpretive

### Clinical Information

The *UGT1A1* gene is part of a gene complex located on chromosome 2 that encodes several enzymes called uridine diphosphate (UDP)-glycosyl transferases. These enzymes perform a chemical reaction called glucuronidation, a major pathway that enhances the elimination of small lipophilic molecules, such as steroids, bilirubin, hormones, and drugs, into water-soluble metabolites that can be excreted from the body.

The UGT1A1 enzyme, primarily found in the liver, is responsible for the glucuronidation of bilirubin, converting it from the toxic form of bilirubin (unconjugated bilirubin) to its nontoxic, water-soluble form (conjugated bilirubin). Genetic variants in *UGT1A1* may cause reduced or absent UGT1A1 enzymatic activity, resulting in conditions associated with unconjugated hyperbilirubinemia including Gilbert syndrome and Crigler-Najjar syndromes types I and II.

Gilbert syndrome is the most common hereditary cause of increased bilirubin and is characterized by total serum bilirubin levels of 1 to 6 mg/dL. Gilbert syndrome is generally considered to be an autosomal recessive disorder, although autosomal dominant inheritance has been suggested in some cases.(1) Gilbert syndrome is caused by a 25% to 50% reduction in glucuronidation activity of the UGT1A1 enzyme and is characterized by episodes of mild intermittent jaundice and the absence of liver disease.

Crigler-Najjar syndromes types I and II (CN1 and CN2) are autosomal recessive disorders caused by more severe reductions in UGT1A1 glucuronidation activity. CN1 is the most severe form, with complete absence of enzyme activity and total serum bilirubin levels of 20 to 45 mg/dL. Infants with CN1 present with jaundice shortly after birth that persists thereafter.(2) CN2 is milder than CN1, with at least partial UGT1A1 activity and total serum bilirubin ranging from 6 to 20 mg/dL. Phenobarbital, a drug that induces synthesis of a number of hepatic enzymes, is effective in decreasing serum bilirubin levels by approximately 25% in patients with CN2; CN1 does not respond to phenobarbital treatment. If left untreated, the buildup of bilirubin in a newborn can cause bilirubin-induced brain damage, known as kernicterus. In addition to phenobarbital, treatments of CN may include phototherapy, heme oxygenase inhibitors, oral calcium phosphate and carbonate, and liver transplantation.

In addition to the role of UGT1A1 in bilirubin metabolism, this enzyme also plays a role in the metabolism of several drugs. UGT1A1 is involved in the metabolism of irinotecan, a topoisomerase I inhibitor. Irinotecan is a chemotherapy

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drug used to treat solid tumors including colon, rectal, and lung cancers. It is a prodrug that forms an active metabolite, SN-38. SN-38 is normally inactivated by conjugation with glucuronic acid followed by biliary excretion into the gastrointestinal tract. If UGT1A1 activity is impaired or deficient, SN-38 fails to become conjugated with glucuronic acid, increasing the concentration of SN-38. This can result in severe neutropenia. The combination of neutropenia with diarrhea can be life-threatening.(3,4)

Additional drugs have also been associated with an increased risk for adverse outcomes in patients with reduced UGT1A1 enzyme activity. The FDA drug labels for nilotinib, pazopanib, and belinostat all contain warnings for an increased risk (incidence) of adverse outcomes in patients who have *UGT1A1* variants associated with reduced activity. The Clinical Pharmacogenetics Implementation Consortium (CPIC) released guidelines for atazanavir treatment, indicating that patients with homozygous *UGT1A1* alleles associated with reduced activity or decreased expression should consider an alternate medication due to a significant risk for developing hyperbilirubinemia (jaundice). The *UGT1A1* gene maps to chromosome 2q37 and contains 5 exons. In this assay, the promoter, exons, and exon-intron boundaries are assessed for variants.(5)

### Reference Values

An interpretive report will be provided.

### Interpretation

An interpretive report will be provided that includes assessment of risk for UGT1A1-associated adverse drug reactions as well as interpretation for hyperbilirubinemia syndromes.

For additional information regarding pharmacogenomic genes and their associated drugs, see the [Pharmacogenomic Associations Tables](#) in Special Instructions. This resource includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

### Cautions

Samples may contain donor DNA if obtained from patients who received heterologous blood transfusions or allogeneic hematopoietic stem cell transplantation. Results from samples obtained under these circumstances may not accurately reflect the recipient's genotype. For individuals who have received blood transfusions, the genotype usually reverts to that of the recipient within 6 weeks. For individuals who have received allogeneic hematopoietic stem cell, a pretransplant DNA specimen is recommended for testing.

*UGT1A1* genetic test results in patients who have undergone liver transplantation may not accurately reflect the patient's *UGT1A1* status.

Absence of a detectable gene variant does not rule out the possibility that the patient may have a genetic cause for increased unconjugated bilirubin.

Rare variants 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.

### Clinical Reference

1. Innocenti F, Grimsley C, Das S, et al: Haplotype structure of the UDP-glucuronosyltransferase 1A1 promoter in different ethnic groups. *Pharmacogenetics*. 2002;12:725-733. doi: 10.1097/00008571-200212000-00006
2. Costa E, Vieira E, Martins M, et al: Analysis of the UDP-glucuronosyltransferase gene in Portuguese patients with a clinical diagnosis of Gilbert and Crigler-Najjar syndromes. *Blood Cells Mol Dis*. 2006;36:91-97. doi: 10.1016/j.bcmd.2005.09.002
3. Goetz MP, Safgren S, Goldberg RM, et al: A phase I dose escalation study of irinotecan (CPT-11), oxaliplatin (Oxal), and capecitabine (Cap) within three UGT1A1 TA promoter cohorts (6/6, 6/7, and 7/7). ASCO 2005 ASCO Annual Meeting Abstract No:2014
4. NDA 20-571/S-024/S-027/S-028. Camptosar (Irinotecan HCL) Final Label. July 21, 2005. Pfizer

5. Kitagawa C, Ando M, Ando Y, et al: Genetic polymorphism in the phenobarbital-responsive enhancer module of the UDP-glucuronosyltransferase 1A1 gene and irinotecan toxicity. *Pharmacogenet Genomics*. 2005;15:35-41. doi: 10.1097/01213011-200501000-00006
6. Guilemette C: Pharmacogenomics of human UDP-glucuronosyltransferase enzymes. *Pharmacogenomics J*. 2003;3:136-158
7. Gammal R, Court M, Haidar C, et al: Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for UGT1A1 and atazanavir prescribing. *Clin Pharmacol Ther*. 2015 doi: 10.1002/cpt.269
8. Shibata T, Minami Y, Mitsuma A, et al: Association between severe toxicity of nilotinib and UGT1A1 polymorphisms in Japanese patients with chronic myelogenous leukemia. *Int J Clin Oncol*. 2014;19:391-396. doi: 10.1007/s10147-013-0562-5
9. US Food and Drug Administration, Pharmacogenomic Biomarkers in Drug Labeling. Accessed November 2015. Available at [www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm](http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm)
10. UDP-Glucuronosyltransferase Alleles Nomenclature page. Accessed March 2018. Available at [www.pharmacogenomics.pha.ulaval.ca/ugt-alleles-nomenclature/](http://www.pharmacogenomics.pha.ulaval.ca/ugt-alleles-nomenclature/)

## Performance

### Method Description

Genomic DNA is extracted from whole blood. The UGT1A1 gene is amplified by polymerase chain reaction (PCR). The PCR product is then purified and sequenced in both directions using fluorescent dye-terminator chemistry. Sequencing products are separated on an automated sequencer and trace files analyzed for sequence variants in the exons and intron/exon boundaries using variant detection software and visual inspection. (Skierka J, O'Kane D: UDP-glucuronosyltransferase 1A1 and the glucuronidation in oncology applications and hyperbilirubinemia. In: Grody WW, Nakamura RM, Kiechle FL, Strom CM, eds. *Molecular Diagnostics: Techniques and Applications for the Clinical Laboratory*. Academic Press; 2010:409-420)

### PDF Report

No

### Specimen Retention Time

Whole blood/Saliva Swab: 2 weeks; Extracted DNA: 2 months

### Performing Laboratory Location

Rochester

## 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

81404