

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).

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

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 \(Spanish\)](#)

Method Name

Polymerase Chain Reaction (PCR) Followed by DNA Sequence Analysis

NY State Available

Yes

Specimen

Specimen Type

Varies

Advisory Information

[If analysis of **only** the *UGT1A1* promoter TA repeat region \(*28, *36, *37 alleles\) is desired, see U1A1V / UDP-Glucuronosyl Transferase 1A1 TA Repeat Genotype, *UGT1A1*.](#)

Shipping Instructions

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

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.

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.

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: DNA

Container/Tube: 2 mL screw top tube

Specimen Volume: 100 mcL (microliters)

Collection Instructions:

1. The preferred volume is 100 mcL at a concentration of 50 ng/mcL.
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)

Specimen Minimum Volume

Blood: 0.45 mL

Saliva: one swab

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		

Clinical and Interpretive

Clinical Information

The *UGT1A1* gene is part of a gene complex located on chromosome 2 that encodes several enzymes called uridine diphosphate (UDP)-glyucuronosyl 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 gluronidation 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 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
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
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
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 Pharm 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
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
10. UDP-Glucuronosyltransferase Alleles Nomenclature page. Accessed March 2018. Available at www.pharmacogenomics.pha.ulaval.ca/ugt-alleles-nomenclature/

Performance

Method Description

Genomic DNA is extracted from whole blood. The *UGT1A1* gene is amplified by 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 Molecular Diagnostics: Techniques and Applications for the Clinical Laboratory. Edited by WW Grody, RM Nakamura, FL Kiechle, CM Strom. Academic Press 2010, pp 409-420)

PDF Report

No

Day(s) and Time(s) Test Performed

Tuesday; 8 a.m.

Analytic Time

7 days (Not reported on Saturday or Sunday)

Maximum Laboratory Time

14 days

Specimen Retention Time

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

81404

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
UGTFG	UGT1A1 Full Gene Sequencing	93844-9

Result ID	Test Result Name	Result LOINC Value
91972	Result Summary	50397-9
91977	TA Repeat Result	95143-4
BA0266	Full Gene Sequence Result	82939-0
91993	Interpretation	69047-9



Result ID	Test Result Name	Result LOINC Value
92007	Additional Information	48767-8
92008	Method	49549-9
92009	Disclaimer	62364-5
92010	Reviewed By	18771-6