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

Ordering Guidance
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
**Test Definition: UGTFG**

**UGT1A1 Full Gene Sequencing**

**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**

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**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)-glycuronosyl 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 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**


**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
Test Definition: UGTFG
UGT1A1 Full Gene Sequencing


PDF Report
No

Day(s) Performed
Tuesday

Report Available
7 to 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

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