MAYO CLINIC LABORATORIES

Test Definition: U1A1Q

Uridine Diphosphate (UDP) Glucuronosyltransferase 1A1 TA Repeat Genotype, UGT1A1, Varies

Overview

Useful For

Identifying individuals who are at increased risk of adverse drug reactions with drugs that are metabolized by uridine diphosphate glucuronosyltransferase (UGT1A1); especially irinotecan but also atazanavir, nilotinib, pazopanib, and belinostat

Identifying individuals with Gilbert syndrome due to the presence of homozygous *UGT1A1*6* (c.211G>A, based on NM_000463.2) allele, TA7, homozygous TA8, or compound heterozygous *6, TA7 or TA8

This test is **not useful for** assessment of Crigler-Najjar syndrome.

Genetics Test Information

This pharmacogenomic test interrogates the thymine-adenine (TA) repeat in the TATA-box of the promoter region of *UGT1A1*. In addition, this test evaluates the *UGT1A1*6* (c.211G>A) allele. TA repeat number may vary from 5 to 8 TA repeats, with 6 TA repeats representing the most common (normal) number of repeats.

Individuals with more than 6 TA repeats may have an increased risk for adverse drug reactions to drugs metabolized by uridine diphosphate glucuronosyltransferase 1A1, especially atazanavir, irinotecan, nilotinib, pazopanib, and belinostat.

Homozygosity for TA7, TA8, or compound heterozygosity for TA7/TA8 is also consistent with the Gilbert syndrome phenotype.

Note: This testing uses a tagging single nucleotide variant strategy for the TA5 and for the TA7 and TA8 repeats. This testing is not able to distinguish between TA7 and TA8, so both are reported as TA7; however, the function and clinical significance of TA7 and TA8 repeats are thought to be the same.

Special Instructions

- Informed Consent for Genetic Testing
- UGT1A1 Test-Ordering Algorithm
- Pharmacogenomic Association Tables
- Multiple Genotype Test List
- Informed Consent for Genetic Testing (Spanish)

Method Name

Real-Time Polymerase Chain Reaction (PCR) with Allelic Discrimination Analysis

NY State Available

Yes

Specimen

Specimen Type
Varies

Ordering Guidance
This test does not detect or report variants other than the *1 (TA6), *28 (TA7), *36 (TA5), and *6 (c.211G>A) alleles. The *37 (TA8) allele cannot be distinguished from *28 (TA7) and will be reported as *28 (TA7) by this methodology. Numerous variants outside of the TA repeat region have been described that impair UGT1A1 activity. Sequencing of the full gene is available for detection of variants outside of the TA repeat region; order UGTFZ / UDP-Glucuronosyltransferase 1A1 (UGT1A1), Full Gene Sequencing, Varies.

If Crigler-Najjar syndrome is suspected, order UGTFZ / UDP-Glucuronosyltransferase 1A1 (UGT1A1), Full Gene Sequencing, Varies.

For more information on test ordering, see *UGT1A1* Test-Ordering Algorithm.

Specimen Required
Multiple genotype tests can be performed on a single specimen after a single extraction. See Multiple Genotype Test List for a list of tests that can be ordered together.

Patient Preparation: A previous hematopoietic stem cell transplant from an allogenic donor will interfere with testing. For information about testing patients who have received a hematopoietic stem cell transplant, call 800-533-1710.

Submit only 1 of the following specimens:

Specimen Type: Whole blood
Container/Tube: Lavender top (EDTA)
Specimen Volume: 3 mL
Collection Instructions:
1. Invert several times to mix blood.
2. Send whole blood specimen in original tube. **Do not aliquot**.
3. Whole blood collected postnatal from an umbilical cord is also acceptable. See Additional Information
Specimen Stability Information: Ambient (preferred) 4 days/Refrigerated 4 days/Frozen 4 days
Additional Information:
1. Specimens are preferred to be received within 4 days of collection. Extraction will be attempted for specimens received after 4 days, and DNA yield will be evaluated to determine if testing may proceed.
2. To ensure minimum volume and concentration of DNA is met, the requested volume must be submitted. Testing may be canceled if DNA requirements are inadequate.
3. For postnatal umbilical cord whole blood specimens, maternal cell contamination studies are recommended to ensure test results reflect that of the patient tested. A maternal blood specimen is required to complete maternal cell

contamination studies. Order MATCC / Maternal Cell Contamination, Molecular Analysis, Varies on both the cord blood and maternal blood specimens under separate order numbers.

Specimen Type: Saliva
Patient Preparation: Patient should not eat, drink, smoke, or chew gum 30 minutes prior to collection.
Supplies:
DNA Saliva Kit High Yield (T1007)
Saliva Swab Collection Kit (T786)
Container/Tube:
Preferred: High-yield DNA saliva kit
Acceptable: Saliva swab
Specimen Volume: 1 Tube if using T1007 or 2 swabs if using T786
Collection Instructions: Collect and send specimen per kit instructions.
Specimen Stability Information: Ambient (preferred) 30 days/Refrigerated 30 days
Additional Information: Saliva specimens are acceptable but not recommended. Due to lower quantity/quality of DNA yielded from saliva, some aspects of the test may not perform as well as DNA extracted from a whole blood sample. When applicable, specific gene regions that were unable to be interrogated will be noted in the report. Alternatively, additional specimen may be required to complete testing.

Specimen Type: Extracted DNA
Container/Tube:
Preferred: Screw Cap Micro Tube, 2 mL with skirted conical base
Acceptable: Matrix tube, 1 mL
Collection Instructions:
1. The preferred volume is at least 100 mcL at a concentration of 75 ng/mcL.
2. Include concentration and volume on tube.
Specimen Stability Information: Frozen (preferred) 1 year/Ambient/Refrigerated
Additional Information: DNA must be extracted in a CLIA-certified laboratory or equivalent and must be extracted from a specimen type listed as acceptable for this test (including applicable anticoagulants). Our laboratory has experience with Chemagic, Puregene, Autopure, MagnaPure, and EZ1 extraction platforms and cannot guarantee that all extraction methods are compatible with this test. If testing fails, one repeat will be attempted, and if unsuccessful, the test will be reported as failed and a charge will be applied. If applicable, specific gene regions that were unable to be interrogated due to DNA quality will be noted in the report.

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:
-Informed Consent for Genetic Testing (T576)
-Informed Consent for Genetic Testing-Spanish (T826)
2. If not ordering electronically, complete, print, and send 1 of the following forms with the specimen:
-Therapeutics Test Request (T831)
-Oncology Test Request (T729)

Specimen Minimum Volume

See Specimen Required

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 & Interpretive

Clinical Information

Following primary metabolism by the phase I enzymes (by oxidation, reduction, dealkylation, and cleavage in the intestines and liver), many drugs and their metabolites are further modified for excretion by a group of conjugative, phase II enzymes. One of these phase II enzymes, uridine diphosphate (UDP) glucuronosyltransferase 1A1 (UGT1A1), is responsible for phase II conjugation of certain drugs, like atazanavir, irinotecan, nilotinib, pazopanib, and belinostat. UGT1A1 is additionally responsible for glucuronide conjugation of bilirubin, which renders the bilirubin water soluble and permits excretion of the bilirubin-glucuronide conjugates in urine. Reduced *UGT1A1* gene transcription due to variation in the number of thymine-adenine (TA) repeats in the TATA box of the gene promoter and c.211G>A (*6) results in reduced enzymatic activity and an increased risk for adverse outcomes in response to drugs metabolized by UGT1A1. These variants are also associated with Gilbert syndrome (unconjugated hyperbilirubinemia).

The TA repeat number may vary from 5 to 8 TA (TA5-TA8) repeats, with 6 TA (TA6) repeats being the most common allele. TA6 is the reference allele and is considered to have normal *UGT1A1* expression. In addition, the rare TA5 repeat (*36: c.-41_-40delTA) has normal or possibly increased *UGT1A1* expression. Individuals with TA7 repeat (*28: c.-41_-40dup) or the rare TA8 repeat (TA8 or *37: c.-43_-40dup, which is not distinguished from TA7 with this assay) have decreased expression of *UGT1A1.* Approximately 10% to 15% of White and African American populations are homozygous for the TA7 repeat (*28/*28).

Uridine diphosphate glucuronosyltransferase 1A1 is involved in the metabolism of irinotecan, a chemotherapy drug used to treat solid tumors including colon, rectal, and lung cancers. If UGT1A1 activity is reduced or deficient, the active irinotecan metabolite (SN-38) is less efficiently conjugated with glucuronic acid, which leads to an increased concentration of SN-38. This in turn can result in severe neutropenia and diarrhea, which in some cases can be life-threatening. Individuals who are homozygous for *28 (TA7) have a 50% higher risk of experiencing severe (grade 4 or 5) neutropenia following the administration of irinotecan. Approximately 40% of individuals are heterozygous for the TA7 repeat allele (ie, TA6/TA7 or heterozygous *28). Heterozygous individuals are also at increased risk of grade 4 neutropenia. The drug label for irinotecan indicates that individuals homozygous or heterozygous for TA repeat variants have a higher risk for severe or life-threatening neutropenia. The risk is thought to be greatest in individuals who receive irinotecan once every 3 weeks.

Additional drugs have also been associated with an increased risk for adverse outcomes if the patient has reduced UGT1A1 enzyme activity. The US Food and Drug Administration drug labels for atazanavir, nilotinib, pazopanib, and belinostat all contain warnings for an increased risk (incidence) of adverse outcomes in patients who have reduced activity alleles. Recently, the Clinical Pharmacogenetics Implementation Consortium (CPIC) released guidelines for atazanavir treatment that indicate patients who are homozygous for a reduced activity (decreased expression) allele should be considered for an alternate medication due to the significant risk for developing hyperbilirubinemia (jaundice).(1)

Gilbert syndrome (GS), found in 5% to 10% of the population, is the most common hereditary cause of increased bilirubin and is associated with usually benign, mild hyperbilirubinemia (bilirubin levels are typically around 3 mg/dL). Gilbert syndrome is caused by a 25% to 50% reduced glucuronidation activity of the UGT1A1 enzyme and characterized by episodes of mild intermittent jaundice and the absence of liver disease. Homozygosity for the reduced activity alleles, *UGT1A1*6* (c.211G>A) allele, TA7, and TA8, or compound heterozygosity (*6, TA7, or TA8) is consistent with Gilbert syndrome. Heterozygosity for *6, TA7 or TA8 is consistent with carrier status for Gilbert syndrome.

Reference Values

UGT1A1 Phenotype: Normal (extensive) metabolizer

An interpretive report will be provided.

Interpretation

The interpretive report includes an overview of the findings as well as the associated clinical significance. Drug-drug interactions must be considered when predicting the *UGT1A1* phenotype, especially in individuals heterozygous for the TA7 variant. For additional information regarding pharmacogenomic genes and their associated drugs, see Pharmacogenomic Associations Tables. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

Cautions

This test is a genotyping test that evaluates 3 common variants in the *UGT1A1* gene only. It is important to note that patients with a negative test may have a rare variant resulting in increased risk of irinotecan and other drug toxicity that is not detected by this test. A sequencing assay is available that can detect rare variants located in the exons of *UGT1A1*; however, it will not detect copy number variations; see UGTFZ / UDP-Glucuronosyltransferase 1A1 (UGT1A1), Full Gene Sequencing, Varies. Additionally, *UGT1A1* sequencing with copy number analysis is available through custom gene ordering; see CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies.

Samples may contain donor DNA if obtained from patients who received non-leukoreduced 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 non-leukoreduced blood transfusions, the genotype usually reverts to that of the recipient within 6 weeks. For individuals who have received allogeneic hematopoietic stem cell transplantation, 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.

Liver or kidney dysfunction may result in adverse drug reactions with irinotecan independently of thymine-adenine (TA)-repeat variants.

Clinical Reference

1. Gammal RS, Court MH, Haidar CE, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for UGT1A1 and atazanavir prescribing. Clin Pharmacol Ther. 2016;99(4):363-369. doi:10.1002/cpt.269
2. Clinical Pharmacogenetics Implementation Consortium (CPIC). CPIC Guideline for Atazanavir and UGT1A1. Updated November 2017. Accessed March 27, 2025. Available at https://cpicpgx.org/guidelines/guideline-for-atazanavir-and-ugt1a1/
3. Innocenti F, Grimsley C, Das S, et al. Haplotype structure of the UDP-glucuronosyltransferase 1A1 promoter in different ethnic groups [published correction appears in Pharmacogenetics. 2003 Mar;13(3):183]. Pharmacogenetics. 2002;12(9):725-733. doi:10.1097/00008571-200212000-00006
4. 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(2):391-396. doi:10.1007/s10147-013-0562-5
5. US Food and Drug Administration: Pharmacogenomic Biomarkers in Drug Labeling. FDA; Updated September 23, 2024. Accessed March 28, 2025. Available at www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling
6. UGT Nomenclature Committee: UGT1A and UGT2B haplotypes and SNPs tables. Canada Research Chair in Pharmacogenomics. June 2005. Accessed March 28, 2025. www.pharmacogenomics.pha.ulaval.ca/ugt-alleles-nomenclature/

Performance

Method Description

Genomic DNA is extracted from whole blood or saliva. Genotyping is performed using a polymerase chain reaction (PCR)-based 5'-nuclease assay. Fluorescently labeled detection probes anneal to the target DNA. PCR is used to amplify the section of DNA that contains the variant. If the detection probe is an exact match to the target DNA, the 5'-nuclease polymerase degrades the probe, the reporter dye is released from the effects of the quencher dye, and a fluorescent signal is detected. Genotypes are assigned based on the allele-specific fluorescent signals that are detected.(Unpublished Mayo method)

PDF Report

No

Day(s) Performed

Monday through Friday

Report Available

3 to 6 days

Specimen Retention Time

Whole blood (if available): 28 days; Saliva: 30 days (if available); Extracted DNA: 2 months

Performing Laboratory Location

Mayo Clinic Laboratories - Rochester Main Campus

Fees & 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 account representative. 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. It has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information

81350-*UGT1A1* (UDP glucuronosyltransferase 1 family, polypeptide AI) (eg, irinotecan metabolism), gene analysis, common variants (eg, *28, *36, *37)

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
U1A1Q	UGT1A1 TA Repeat Genotype, V	34509-0

Result ID	Test Result Name	Result LOINC® Value
610168	UGT1A1 Genotype	93845-6
610169	UGT1A1 Phenotype	79718-3
610170	Interpretation	69047-9
610171	Additional Information	48767-8
610172	Method	85069-3
610173	Disclaimer	62364-5
610174	Reviewed by	18771-6