MAYO CLINIC LABORATORIES

Test Definition: U1A1Q

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 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

Identifying individuals who are carriers of Gilbert syndrome due to the presence of heterozygous 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*. 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 UGT1A1, especially atazanavir, irinotecan, nilotinib, pazopanib, and belinostat. Homozygosity for TA7, TA8, or compound heterozygosity for TA7/TA8 is also consistent with a diagnosis of Gilbert syndrome. Heterozygosity for TA7 or TA8 is consistent with carrier status for Gilbert syndrome. Note that this testing uses a tagging single nucleotide variant (SNV) 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. In addition, this test evaluates the *UGT1A1*6* (c.211G>A) allele.

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 UGTFG / UDP-Glucuronosyltransferase 1A1 (*UGT1A1*), Full Gene Sequencing, Varies.

If Crigler-Najjar syndrome testing is requested, order UGTFG / 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.

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.**
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)
Specimen Volume: 1 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 mcL (microliters)
Collection Instructions:
1. The preferred volume is 100 mcL at a concentration of 50 ng/mcL.
2. Provide concentration of DNA 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:
-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

Blood: 0.4 mL
Saliva, extracted DNA: 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 *UGT1A* 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 *UGT1A1* expression. Individuals with TA7 repeat (*28: c.-41_-40dupTA) or the rare TA8 repeat (TA8 or *37: c.-43_-40dupTATA, 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).

UGT1A1 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 the combination of neutropenia with diarrhea 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 treated with irinotecan are heterozygous for the TA7 repeat allele (ie, TA6/TA7 or heterozygous *28). These 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 FDA 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 a diagnosis of Gilbert syndrome. Heterozygosity for *6, TA7 or TA8 is consistent with carrier status for Gilbert syndrome.

Reference Values

An interpretive report will be provided.

Interpretation

An interpretive report will be provided.

Drug-drug interactions must be considered when predicting the *UGT1A1* phenotype, especially in individuals heterozygous for the TA7 polymorphism. 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

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 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 renal 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. 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
3. 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:1 0.1007/s10147-013-0562-5
4. U.S. Food and Drug Administration: Pharmacogenomic Biomarkers in Drug Labeling. FDA;. Accessed October 14, 2020. Available at www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm
5. UGT Nomenclature Committee: UGT1A and UGT2B haplotypes and SNPs tables. Canada Research Chair in Pharmacogenomics. June 2005. Accessed October 14, 2020. 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

Performing Laboratory Location

Rochester

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