Patient ID	Patient Name		Birth Date	Sex	Age
321	TESTRNV, TESTING ATLAS		1968-02-19	M	55
Order Number	**Client Order Number**	**Ordering Physician**	**Report Notes**		
X100427947	X100427947	Test,Atlas			
Account Information		**Collected**			
C7028846 DLMP Rochester		30 Aug 2023 06:33			

UGT1A1 Full Gene Sequencing, V

Result Summary

MCR

VARIANT(S) DETECTED

TA Repeat Result

MCR

TA6/TA7 (Heterozygous *28)

Full Gene Sequence Result

MCR

The following additional UGT1A1 variant(s) were detected by sequencing:
Variant name: *6
gDNA change: Chr2(GRCh37):g.234669144
cDNA change: c.211G>A
Amino Acid change: p.Gly71Arg
Zygosity: Heterozygous
Classification: Pathogenic

No additional reportable sequence variants were detected in the UGT1A1 gene.

Interpretation

MCR

This result has implications for bilirubin metabolism and drug metabolism.

This individual is heterozygous for the TA7 promoter variant (also known as *28) and heterozygous for the c.211G>A (p.Gly71Arg) variant (also known as *6). Both variants reduce UGT1A1 enzyme activity (1–3).

BILIRUBIN METABOLISM:

This result indicates this individual may be at increased risk for UGT1A1-associated hyperbilirubinemia.

The method used here cannot confirm if the detected variants are in cis (i.e., on the same chromosome) or in trans (i.e., on opposite chromosomes).

In most cases, the *28 and *6 variants occur in trans. If these variants occur in trans in the individual tested here, this result is consistent with autosomal recessive Gilbert syndrome, which is associated with an increased risk for hyperbilirubinemia (1–3).

However, if these variants are in cis, this result is consistent with carrier status of an autosomal recessive UGT1A1-associated condition ranging in clinical severity from Gilbert syndrome to Crigler-Najjar syndrome. Carrier status is not associated with hyperbilirubinemia in healthy individuals.

Clinical correlation is recommended.

DRUG METABOLISM:

This result indicates that this individual is at an increased risk for toxicity with irinotecan and hyperbilirubinemia with nilotinib. For other drugs, the risk depends on the cis/trans status of the identified variants. If the variants are in trans, this individual may also be at risk for increased drug levels, toxicity, and/or hyperbilirubinemia with atazanavir, belinostat, dolutegravir, pazopanib, raltegravir, sacituzumab govitecan-hziy, or other medications metabolized by UGT1A1. The medication label should be consulted for dosing recommendations.

Additional information regarding other drugs metabolized by UGT1A1 can be found in the Pharmacogenomic Associations Tables at www.mayocliniclabs.com and see the link to the FDA Table of Pharmacogenetic Associations in Appendix 1.

The risk assessment for drug toxicity is specific for the UGT1A1 genotype. Adverse drug reactions may still result due to other causes.

This result should be interpreted in the context of clinical findings, family history, and other laboratory testing. A genetic consultation may be of benefit for interpretation of this result.

References:
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. (PMID 26417955)

2) Bosma PJ, Chowdhury JR, Bakker C, et al. The genetic basis of the reduced expression of bilirubin UDP-glucuronosyltransferase 1 in Gilbert's syndrome. N Engl J Med.

Performing Site Legend

Code	Laboratory	Address	Lab Director	CLIA Certificate
MCR	Mayo Clinic Laboratories - Rochester Main Campus	200 First Street SW, Rochester, MN 55905	William G. Morice M.D. Ph.D	24D0404292

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1995;333(18):1171–1175. (PMID 7565971)

3) Yu Z, Zhu K, Wang L, Liu Y, Sun J. Association of Neonatal Hyperbilirubinemia with UGT1A1 Gene Polymorphisms: A Meta-Analysis. Med Sci Monit. 2015;21:3104–3114. Published 2015 Oct 15. (PMID 26467199)

Method

MCR

Bidirectional sequence analysis was used to test for the presence of variants in TA repeat region of the promoter, all coding regions, and intron/exon boundaries of the UGT1A1 gene (GenBank accession number NM_000436.2; build GRCh37 (hg19)).

Human Genome Variation Society (HGVS) nomenclature for the various TA repeat alleles detected by this assay, based on UGT1A1 transcript NM_000436.2, human genome build 19 (GRCh37), is as follows: TA5 or *36: c.–41_-40delTA (g.234668893_234668894) TA7 or *28: c.–41_-40dupTA (g.234668893_234668894) TA8 or *37: c.–43_-40dupTATA (g.234668891_234668894)

Disclaimer

1 MCR

Some individuals who have a diagnosis of unconjugated hyperbilirubinemia (i.e., Gilbert syndrome, Crigler-Najjar syndrome) may have a pathogenic variant(s) that is not detected by the method described above. The presence of a UGT1A1 variant(s) does not necessarily confirm a diagnosis of unconjugated hyperbilirubinemia. In addition, some individuals who experience an adverse outcome with a drug metabolized by UGT1A1 may have a variant that is not detected by the method described above.

Irinotecan, atazanavir, belinostat, nilotinib and pazopanib undergo metabolism by CYP3A4 in addition to UGT1A1. Concomitant use of these drugs with strong CYP3A4 inhibitors or inducers may significantly increase or decrease drug concentrations, respectively. See applicable drug labels for drug-drug interactions, CYP3A4 inhibitors and inducers, and dosing recommendations.

Some detected variants may not have been studied in the context of drug metabolism. Evaluation and categorization of variants is performed using available literature and variant classification guidelines. At this time, it is not standard practice for the laboratory to systematically re-review likely pathogenic variants or variants of uncertain significance that are detected and reported. The laboratory encourages health care providers to contact the laboratory at any time to learn how the status of a particular variant may have changed over time. Consultation with genetics professional should be considered for interpretation of this result.

Homozygous variants cannot always be distinguished from hemizygous variants as this assay does not detect large deletions in UGT1A1.

Multiple in silico evaluation tools may be used to assist in the interpretation of these results and predictions made by these tools may change over time.

A list of common, benign variants detected in this patient is available from the laboratory upon request (if applicable).

For additional information regarding pharmacogenomic genes and their associated drugs, please see the Pharmacogenomic Associations Tables on the Mayo Clinic Laboratories webpage, www.mayocliniclabs.com and see the link to the FDA Table of Pharmacogenetic Associations in Appendix 1. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices. Please note that the information at this link is educational material intended for health care professionals and may not be comprehensive. This educational material is not intended to supersede the care provider's experience and knowledge of their patient to establish a diagnosis or a treatment plan. All medications require careful clinical monitoring.

CAUTIONS:

Rare variants may be present that could impact results. This assay may not detect large deletions or rearrangements that may affect UGT1A1 protein expression.

If more than one heterozygous variant is detected, the cis/trans relationship (i.e. whether the variants are inherited on the same or opposite alleles) of these variants cannot be definitively determined with the methods used by this assay. Therefore, test

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results should be interpreted in the context of clinical findings, family history, and other laboratory data.

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

Samples may contain donor DNA if obtained from patients who received non-leukocyte reduced 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.

Reviewed By MCR

Ann Marie Moyer, M.D., Ph.D.

Received: 30 Aug 2023 13:20 **Reported:** 07 Sep 2023 16:57

Laboratory Notes

1 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.

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