Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for *UGT1A1* and Atazanavir Prescribing

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Literature Review

We searched the PubMed database (1966 to December 2015) for keywords (UGT1A1 or UGT1A* or Gilbert or hyperbilirubinemia or jaundice or UGT1A1 and discontinuation) AND (atazanavir).Using these search terms, 212 publications were identified. In addition, studies annotated in PharmGKB (http://www.pharmgkb.org) were identified. Study inclusion criteria included publications that included analyses of the effect of *UGT1A1* on clinical outcomes of atazanavir use (hyperbilirubinemia, jaundice, or drug discontinuation). Non-English manuscripts were excluded. Following application of these inclusion criteria, 24 publications were reviewed and included in the evidence table (**Supplemental Table S4**).

Gene: *UGT1A1*

Genetic Test Interpretation

The haplotype, or star (*) allele name, is determined by a specific SNP or a combination of SNPs that are interrogated in the genotyping analysis. The genotypes that constitute the haplotype, or star (*) alleles for *UGT1A1*, and the rs# for each of the specific genomic nucleotide alterations that define the alleles, are described in **Supplemental Table S1**.

The genotype results are generally reported as a diplotype, which includes one maternal and one paternal star allele (e.g., **1/*28*). The UGT1A1 function associated with each of the common * alleles is summarized in **Supplemental Table S2**.

Available Genetic Test Options

Commercially available genetic testing options change over time. The Genetic Testing Registry (GTR) provides a central location for voluntary submission of genetic test information by providers and is available at http://www.ncbi.nlm.nih.gov/gtr/.

Panel and molecular based sequencing tests for *UGT1A1* are available (see www.genetests.org). Many commercial laboratories test and report only the **1* and **28* alleles. However, the INFINITI *UGT1A1* Assay® (http://www.autogenomics.com) is an *in vitro* diagnostic test for research use only that detects and genotypes the **1*, **28*, **36*, and **37* alleles of the *UGT1A1* gene.

Levels of Evidence

The evidence summarized in **Supplemental Table 5** is graded using a scale modified slightly from Valdes *et al*. (1)

High: Evidence includes consistent results from well-designed, well-conducted studies.

Moderate: Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence.

Weak: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.

Strength of Recommendations

CPIC's dosing recommendations are based weighting the evidence from a combination of preclinical, functional, and clinical data, as well as on some existing disease-specific consensus guidelines (2). Some of the factors that have been taken into account for this guideline include *in vivo* clinical outcome for atazanavir/r and *in vivo* PK/PD for atazanavir/r.

Overall, the dosing recommendations are simplified to allow rapid interpretation by clinicians. We chose to use a slight modification of a transparent and simple system for just three categories of recommendations adopted from the rating scale for evidence-based recommendations on the use of antiretroviral agents (http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf): strong, where "the evidence is high quality and the desirable effects clearly outweigh the undesirable effects"; moderate, in which "there is a close or uncertain balance" as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects; and optional, in which the desirable effects are closely balanced with undesirable effects and there is room for differences in opinion as to the need for the recommended course of action.

Strong recommendation for the statement

Moderate recommendation for the statement

Optional recommendation for the statement

Resources to Incorporate Pharmacogenetics into an EHR with CDS

Use of clinical decision support (CDS) tools within electronic health records (EHRs) can assist clinicians to use genetic information to optimize drug therapy (3-7). Supplementary material provides resources from CPIC to support the adoption of CPIC guidelines within an EHR (8). Based on the capabilities of various EHRs and local preferences, we recognize approaches may vary across organizations. Our intent is to synthesize foundational knowledge that provides a common starting point for incorporating the use of *UGT1A1* genotype results to guide the use of atazanavir in any EHR.

Effectively incorporating pharmacogenetic information into an EHR to optimize drug therapy should have some key attributes. First, pharmacogenetic results, an interpreted phenotype, and a concise interpretation or summary of the result must be documented in the EHR (9). Because clinicians must be able to easily find the information, the interpreted phenotype may be documented as a problem list entry or in a patient summary section; these phenotypes are best stored in the EHR at the "person level" rather than at the date-centric "encounter level." Second, results should be entered as standardized and discrete terms to facilitate using them to provide point of care CDS (10, 11). Because pharmacogenetic results have lifetime implications and clinical significance, results should be placed into a section of the EHR that is accessible independent of the test result date to allow clinicians to quickly find the result at any time after it is initially placed in the EHR. Point-of-care CDS should be designed to effectively remind clinicians of prescribing implications at any time after the test result is entered into the EHR. Guidance to achieve these objectives is provided in diagrams that illustrate how *UGT1A1* pharmacogenetic test results could be entered into an EHR (**Supplemental Figure S1**) and be used for point-of-care CDS (**Supplemental Figure S2**). **Supplemental Tables S5** and **S6** provide a cross-reference to widely used nomenclature systems for the drug and the gene, respectively.

To incorporate a phenotype in the EHR in a standardized manner, genotype test results provided by the laboratory must be consistently translated into an interpreted phenotype (**Table 1, main manuscript**). **Supplemental Table S7** further translates results into a coded diplotype/phenotype summary, priority result notification, and sample interpretative result text.

The result tables provide summary genotype/phenotype terms, example text for documentation in the EHR and point-of-care alerts. Finally, sample point-of-care alert text that corresponds to the workflow described in **Supplemental Figure S2** is provided in **Supplemental Table S8**.

Supplemental Table S1. Commonly tested[a] genotypes[b] that constitute the * alleles for *UGT1A1*

Allele	Constituted by genotypes at:
**1*	Wild-type
**6*	rs4148323 (NM_000463.2 c.211G>A; G71R)
**27*	rs35350960 (NM_000463.2 c.686C>A; P229Q)
**28*	rs8175347 (NM_000463.2 c.-53-52TA[6]>TA[7])
**36*	rs8175347 (NM_000463.2 c.-53-52TA[6]>TA[5])
**37*	rs8175347 (NM_000463.2 c.-53-52TA[6]>TA[8])
**60*	rs4124874 (NM_001072.3 c.862-10021T>G)
**80*	rs887829 (NM_000463.2 c.-364C>T)

[a]To see a full list of known *UGT1A1* alleles see http://www.pharmacogenomics.pha.ulaval.ca/files/content/sites/pharmacogenomics/files/Nomenclature/UGT1A/UGT1A1.htm.
[b]Bases reported on the positive chromosomal strand from dbSNP (http://www.ncbi.nlm.nih.gov/SNP/). Alleles are derived from the UDP-Glucoronosyltransferase (UGT) Alleles Nomenclature page (http://www.pharmacogenomics.pha.ulaval.ca/cms/site/pharmacogenomics/ugt_alleles). See https://www.pharmgkb.org/gene/PA420 for updates on *UGT1A1* gene alleles and nomenclature.

Supplemental Table S2. Association between allelic variants and UGT1A1 function for commonly tested alleles[a]

Functional Status	Alleles	References
Normal function[b]	**1*	Bosma, *et al*. (1995)(12)
Increased function	**36*	Beautler, *et al.* (1998) (13)
Decreased function	**6, *27, *28, *37, *80*	Aono, *et al. (*1995) (14) Aono, *et al*. (1993) (15) Beutler, *et al* (1998) (13) Bosma, *et al.* (1995) (12) Sai K, *et al.* (2004) (16)
Unknown/Unclear/Conflicting data (these alleles have been well described but their functions are unknown (i.e. very little testing has been done) or it is unclear/controversial (conflicting data on function or unclear data on function).	**60*[c]	Sugatani, *et al.* (2002) (17)

[a]To see a full list of known *UGT1A1* alleles and function see http://www.pharmacogenomics.pha.ulaval.ca/files/content/sites/pharmacogenomics/files/Nomenclature/UGT1A/UGT1A1.htm.

[b]An important caveat for all genotyping tests is that the decision to assign an allele a "wild-type" status is based upon a genotyping test that interrogates only the most common and already-proven sites of functional variation. In human DNA, it is always possible that a new, previously undiscovered (and therefore un-interrogated) site of variation may confer loss-of-function in an individual, and thus lead to the rare possibility of a non-functional allele being erroneously called as "wild-type".

[c]*UGT1A1*60* is in incomplete linkage disequilibrium with *28 and to date, there are no data to suggest that **60* by itself results in decreased UGT1A1 function.

Supplemental Table S3a. Frequencies (%) of rs8175347 alleles[a,b] in major race/ethnic groups[3]

Allele	Caucasian	African or African-American	Hispanic	Native Hawaiian or Other Pacific Islander	East and Southeast Asian	South Asian	Middle Eastern
**1*	68.2	50.0	60.0	95.7	85.2	58.6	69.6
**28*	31.6	39.1	40.0	4.3	14.8	41.4	29.5
**36*	0	6.6	0.0	0.0	0.0	0.0	0.6
**37*	0.1	3.6	0.0	0.0	0.0	0.0	0.3

[a] Here the *1 allele refers to the rs8175347 TA_6 allele
[b] Average allele frequencies are reported, based on the actual numbers of subjects with each allele reported in multiple studies and then grouped according to [3] major race/ethnic groups for studies as defined in Supplemental Table S4 (details and references)

For full details and references please see
https://preview.pharmgkb.org/download.do?objCls=Attachment&objId=CPIC_atazanavir_UGT1A1_allele_frequency.xlsx

Supplemental Table S3b. Frequencies (%) of rs4148323 alleles[a] in major race/ethnic groups[b]

Allele	Caucasian	African or African-American	Hispanic	Native Hawaiian or Other Pacific Islander	East and Southeast Asian	South Asian	Middle Eastern
rs4148323 G	99.0	99.9	99.0	NA	85.4	95.7	100.0
*rs4148323 A (*6)*	1.0	0.1	1.0	NA	14.6	4.3	0.0
[a]Average allele frequencies are reported, based on the actual numbers of subjects with each allele reported in multiple studies and then grouped according to [b] major race/ethnic groups for studies as defined in Supplemental Table S4 (details and references)							

For full details and references please see
https://preview.pharmgkb.org/download.do?objCls=Attachment&objId=CPIC_atazanavir_UGT1A1_allele_frequency.xlsx

Supplemental Table S3c. Frequencies (%) of rs887827 alleles[a] in major race/ethnic groups[b]

Allele	Caucasian	African or African-American	Hispanic	Native Hawaiian or Other Pacific Islander	East and Southeast Asian	South Asian	Middle Eastern
rs887827 C	68.0	55.0	62.0	NA	NA	NA	NA
*rs887827 T (*80)*	32.0	45.0	38.0	NA	NA	NA	NA
[a]Average allele frequencies are reported, based on the actual numbers of subjects with each allele reported in multiple studies and then grouped according to [b] major race/ethnic groups for studies as defined in Supplemental Table S4 (details and references)							

For full details and references please see
https://preview.pharmgkb.org/download.do?objCls=Attachment&objId=CPIC_atazanavir_UGT1A1_allele_frequency.xlsx

Supplemental Table S4. Evidence linking genotype to phenotype

Type of experimental model (in vitro, in vivo preclinical, or clinical)	Major Finding	References (PMID)	Level of Evidence[a]
Clinical	*UGT1A1*28* is associated with increased risk of hyperbilirubinemia or jaundice among patients taking atazanavir as compared to *UGT1A1*1*.	Panagopoulos, *et al.* (2014) (18) Eley, *et al.* (2013) (19) Culley, *et al.* (2013) (20) Ribaudo, *et al.* (2013) (21) Turatti, *et al.* (2012) (22) Javelle, *et al.* (2012) (23) Ferraris, *et al.* (2012) (24) Cicconi, *et al.* (2011) (25) Morello, *et al.* (2011) (26) Park, *et al.* (2010) (27) Anderson, *et al.* (2009) (28) Rodriguez-Novoa, *et al.* (2007) (29) Lankisch, *et al.* (2006) (30) Rotger, *et al.* (2005) (31)	High
Clinical	*UGT1A1*28* is not associated with increased risk of hyperbilirubinemia or jaundice among patients taking atazanavir as compared to *UGT1A1*1*.	Rodriguez-Novoa, *et al.* (2008) (32)	Weak
Clinical	*UGT1A1*28* is not associated with increased risk of hyperbilirubinemia among neonates whose mothers are taking atazanavir as compared to *UGT1A1*1*.	Eley, *et al.* (2013) (19)	Moderate
Clinical	*UGT1A1*6* is not associated with increased risk of hyperbilirubinemia or jaundice among patients taking atazanavir as compared to *UGT1A1*1*.	Park, *et al.* (2010) (27)	Moderate
Clinical	*UGT1A1*36* is associated with decreased severity of hyperbilirubinemia or jaundice among pregnant women taking atazanavir as compared to *UGT1A1*1, *28*, or **37*, but is not associated with severity of hyperbilirubinemia or jaundice in their neonates.	Eley, et al. (2013) (33)	Weak

Clinical	*UGT1A1* genotype does not predict atazanavir plasma concentrations.	Rodriguez-Novoa, *et al.* (2007) (29)	Moderate
Clinical	*UGT1A1* genotype may predict atazanavir discontinuation.	Vardhanabhuti, et al. (2015) (34) Ribaudo, *et al.* (2013) (35) Lubomirov, *et al.* (2011) (36)	High
Clinical	*UGT1A1*28* is not associated with increased risk of nephrolithiasis among patients taking atazanavir as compared to *UGT1A1*1*.	Nishijima, *et al.* (2014) (37)	Weak
Clinical	rs8330 G/G or G/C genotype versus C/C genotype is associated with an increased risk of nephrolithiasis among patients taking atazanavir (Adj OR 5.8; 95% CI 1.56-21.3 P=0.009).	Nishijima, *et al.* (2014) (37)	Moderate
Clinical	rs887829 TT genotype is associated with increased risk of hyperbilirubinemia among patients taking atazanavir as compared to rs887889 CT or CC genotype.	Johnson, *et al.* (2014) (38)	Moderate

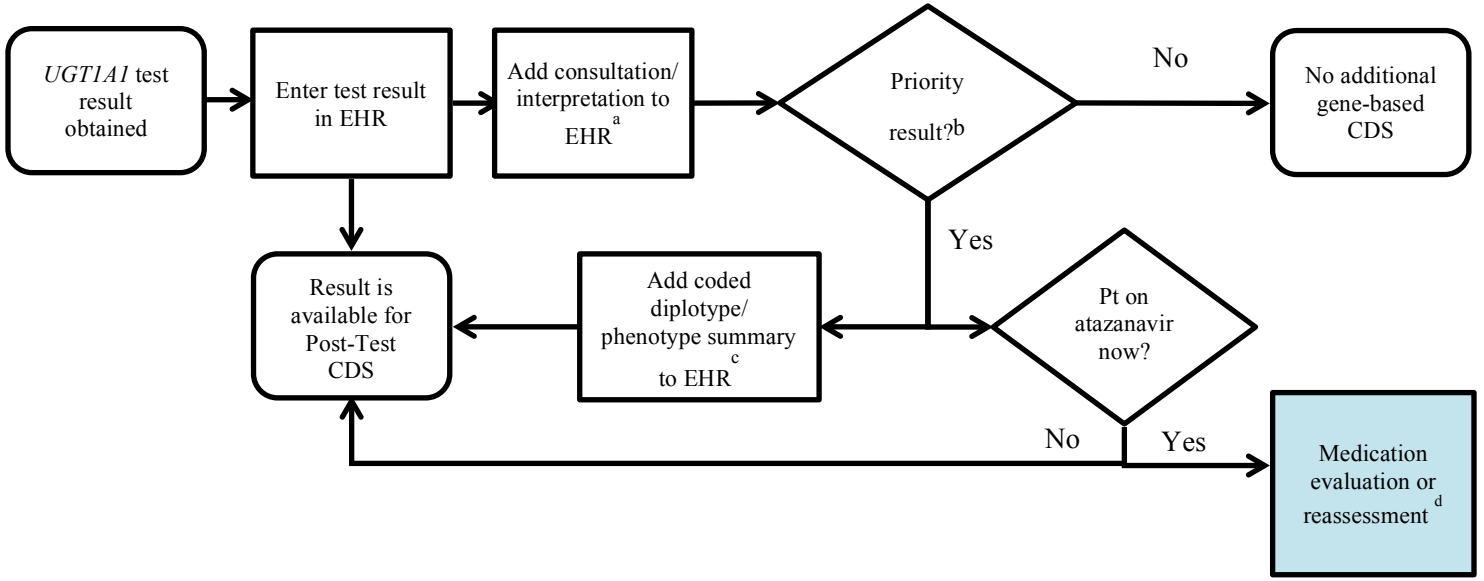
[a]High: Evidence includes consistent results from well-designed, well-conducted studies.
Moderate: Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence.
Weak: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information

Supplemental Table S5. Drug(s) that pertain to this guideline.

Drug or Ingredient	Source	Code Type	Code
Atazanavir	RxNorm	RxCUI	343047
Atazanavir	DrugBank	Accession Number	DB01072
Atazanavir	ATC	ATC Code	J05AR15
Atazanavir	PharmGKB	PharmGKB ID	PA10251

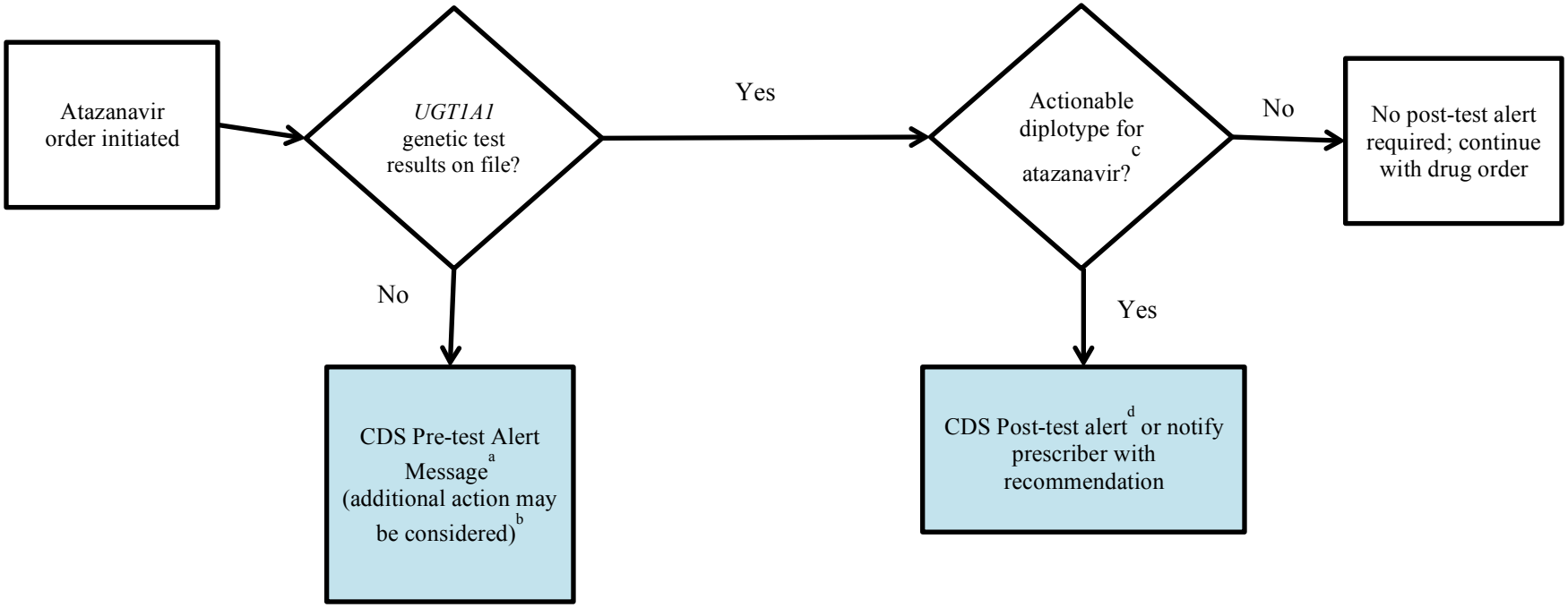
Supplemental Table S6. Gene(s) that pertain to this guideline

Gene Symbol	Source	Code Type	Code
UGT1A1	HGNC	Symbol	UGT1A1
UGT1A1	HGNC	HGNC ID	HGNC:12530
UGT1A1	NCBI	Gene ID	54658
UGT1A1	Ensembl	Ensembl ID	ENSG00000241635
UGT1A1	PharmGKB	PharmGKB ID	PA420



Supplemental Figure S1. *UGT1A1* Pharmacogenetic Test Result: Clinical Implementation Workflow for EHR

[a]See **Supplementary Table S8** for diplotype/phenotype specific examples
[b]Priority result is defined as a genetic test result that necessitates a change in drug, drug dose, or drug monitoring now or potentially in the future.
[c]Documentation in the EHR is institution specific. Optimally, the phenotype and/or genotype are available in the EHR to permanently inform prescribing decisions. See **Supplementary Table S8** for genotype/phenotype-specific summaries.
[d]*UGT1A1* genetic testing is most helpful prior to initiation of the drug. However, in some cases (e.g., patient experiencing side effects, current drug therapy ineffective) *UGT1A1* genetic results might be useful in choosing alternative therapy.



Supplemental Figure S2. *UGT1A1* Genotype and Atazanavir: Point of Care Clinical Decision Support

[a]See **Supplementary Table S9** for diplotype/phenotype specific pre-test alert examples.
[b]In the context of *UGT1A1* and atazanavir, because the side effect of hyperbilirubinemia/jaundice is reversible once the medicine is stopped, pre-test alerts guiding the clinicians to order a *UGT1A1* genotype prior to starting atazanavir should be considered a soft recommendation.
[c]Priority result defined as a genetic test result that necessitates a change in drug, drug dose, or drug monitoring now or potentially in the future.
[d]See **Supplementary Table S9** for diplotype/phenotype specific post-test alert examples.

Supplemental Table S7. Example Implementation of this Guideline for UGT1A1: Pharmacogenetic Diplotype/Phenotype Summary Entries[a]

Diplotype Test Result for *UGT1A1*	Coded Diplotype/Phenotype Summary[b]	EHR Priority Result Notation[c]	Consultation (Interpretation) Text Provided with Test Result[e]
**1/*1*	None	Normal/Routine/ Low Risk	This result signifies that the patient has two copies of a normal function allele (*1). Based on the genotype result this patient is predicted to be an extensive (normal) metabolizer of UGT1A1 substrates. There is no reason to selectively adjust the dose of most medications that inhibit or are inactivated by UGT1A1. Please consult a clinical pharmacist for more information about how UGT1A1 metabolic status influences drug selection and dosing.
**1/*6*	UGT1A1 Intermediate Metabolizer	Normal/Routine/ Low Risk	This result signifies that the patient has one copy of a normal function allele (*1) and one copy of a decreased function allele (*6). Based on the genotype result this patient is predicted to be an intermediate metabolizer of UGT1A1 substrates. There is no reason to selectively adjust the dose of most medications that inhibit or are inactivated by UGT1A1. Please consult a clinical pharmacist for more information about how UGT1A1 metabolic status influences drug selection and dosing.
**1/*27*	UGT1A1 Intermediate Metabolizer	Normal/Routine/ Low Risk	This result signifies that the patient has one copy of a normal function allele (*1) and one copy of a decreased function allele (*27). Based on the genotype result this patient is predicted to be an intermediate metabolizer of UGT1A1 substrates. There is no reason to selectively adjust the dose of most medications that inhibit or are inactivated by UGT1A1. Please consult a clinical pharmacist for more information about how UGT1A1 metabolic status influences drug selection and dosing.

**1/*28*	UGT1A1 Intermediate Metabolizer	Normal/Routine/ Low Risk	This result signifies that the patient has one copy of a normal function allele (*1) and one copy of a decreased function allele (*28). Based on the genotype result this patient is predicted to be an intermediate metabolizer of UGT1A1 substrates. There is no reason to selectively adjust the dose of most medications that inhibit or are inactivated by UGT1A1. Please consult a clinical pharmacist for more information about how UGT1A1 metabolic status influences drug selection and dosing.
**1/*36*	None	Normal/Routine/ Low Risk	This result signifies that the patient has one copy of a normal function allele (*1) and one copy of an increased function allele (*36). Based on the genotype result this patient is predicted to be an extensive (normal) metabolizer of UGT1A1 substrates. There is no reason to selectively adjust the dose of most medications that inhibit or are inactivated by UGT1A1. Please consult a clinical pharmacist for more information about how UGT1A1 metabolic status influences drug selection and dosing.
**1/*37*	UGT1A1 Intermediate Metabolizer	Normal/Routine/ Low Risk	This result signifies that the patient has one copy of a normal function allele (*1) and one copy of a decreased function allele (*37). Based on the genotype result this patient is predicted to be an intermediate metabolizer of UGT1A1 substrates. There is no reason to selectively adjust the dose of most medications that inhibit or are inactivated by UGT1A1. Please consult a clinical pharmacist for more information about how UGT1A1 metabolic status influences drug selection and dosing.
**1/*80*	UGT1A1 Intermediate Metabolizer	Normal/Routine/ Low Risk	This result signifies that the patient has one copy of a normal function allele (*1) and one copy of a decreased function allele (*60). Based on the genotype result this patient is predicted to be an intermediate metabolizer of UGT1A1 substrates. There is no reason to selectively adjust the dose of most medications that inhibit or are inactivated

			by UGT1A1. Please consult a clinical pharmacist for more information about how UGT1A1 metabolic status influences drug selection and dosing.
**6/*6*[f]	UGT1A1 Poor Metabolizer	Abnormal/Priority/High Risk	This result signifies that the patient has two copies of a decreased function allele (*6). Based on the genotype result this patient is predicted to be a poor metabolizer of UGT1A1 substrates. This patient may be at risk for an adverse or poor response to medications that inhibit or are inactivated by UGT1A1. Based on the genotype result, this patient is predicted to have low UGT1A1 function, which is generally indicative of Gilbert syndrome. This patient may be at high risk for toxicity from select medications that inhibit or are inactivated by UGT1A1. Please consult a clinical pharmacist for more information about how UGT1A1 metabolic status influences drug selection and dosing.
**6/*27*	UGT1A1 Poor Metabolizer	Abnormal/Priority/High Risk	This result signifies that the patient has two copies of a decreased function allele (*6 and *27). Based on the genotype result this patient is predicted to be a poor metabolizer of UGT1A1 substrates. This patient may be at risk for an adverse or poor response to medications that inhibit or are inactivated by UGT1A1. Based on the genotype result, this patient is predicted to have low UGT1A1 function, which is generally indicative of Gilbert syndrome. This patient may be at high risk for toxicity from select medications that inhibit or are inactivated by UGT1A1. Please consult a clinical pharmacist for more information about how UGT1A1 metabolic status influences drug selection and dosing.
**6/*28*	UGT1A1 Poor Metabolizer	Abnormal/Priority/High Risk	This result signifies that the patient has two copies of a decreased function allele (*6 and *28). Based on the genotype result this patient is predicted to be a poor metabolizer of UGT1A1 substrates. This patient may be at

			risk for an adverse or poor response to medications that inhibit or are inactivated by UGT1A1. Based on the genotype result, this patient is predicted to have low UGT1A1 function, which is generally indicative of Gilbert syndrome. This patient may be at high risk for toxicity from select medications that inhibit or are inactivated by UGT1A1. Please consult a clinical pharmacist for more information about how UGT1A1 metabolic status influences drug selection and dosing.
**6/*36*	UGT1A1 Intermediate Metabolizer	Normal/Routine/ Low Risk	This result signifies that the patient has one copy of a decreased function allele (*6) and one copy of an increased function allele (*36). Based on the genotype result this patient is predicted to be an intermediate metabolizer of UGT1A1 substrates. There is no reason to selectively adjust the dose of most medications that inhibit or are inactivated by UGT1A1. Please consult a clinical pharmacist for more information about how UGT1A1 metabolic status influences drug selection and dosing.
**6/*37*	UGT1A1 Poor Metabolizer	Abnormal/Priority/High Risk	This result signifies that the patient has two copies of a decreased function allele (*6 and *37). Based on the genotype result this patient is predicted to be a poor metabolizer of UGT1A1 substrates. This patient may be at risk for an adverse or poor response to medications that inhibit or are inactivated by UGT1A1. Based on the genotype result, this patient is predicted to have low UGT1A1 function, which is generally indicative of Gilbert syndrome. This patient may be at high risk for toxicity from select medications that inhibit or are inactivated by UGT1A1. Please consult a clinical pharmacist for more information about how UGT1A1 metabolic status influences drug selection and dosing.
**6/*80*	UGT1A1 Poor Metabolizer	Abnormal/Priority/High Risk	This result signifies that the patient has two copies of a decreased function allele (*6 and *80). Based on the

			genotype result this patient is predicted to be a poor metabolizer of UGT1A1 substrates. This patient may be at risk for an adverse or poor response to medications that inhibit or are inactivated by UGT1A1. Based on the genotype result, this patient is predicted to have low UGT1A1 function, which is generally indicative of Gilbert syndrome. This patient may be at high risk for toxicity from select medications that inhibit or are inactivated by UGT1A1. Please consult a clinical pharmacist for more information about how UGT1A1 metabolic status influences drug selection and dosing.
**27/*27*[f]	UGT1A1 Poor Metabolizer	Abnormal/Priority/High Risk	This result signifies that the patient has two copies of a decreased function allele (*27). Based on the genotype result this patient is predicted to be a poor metabolizer of UGT1A1 substrates. This patient may be at risk for an adverse or poor response to medications that inhibit or are inactivated by UGT1A1. Based on the genotype result, this patient is predicted to have low UGT1A1 function, which is generally indicative of Gilbert syndrome. This patient may be at high risk for toxicity from select medications that inhibit or are inactivated by UGT1A1. Please consult a clinical pharmacist for more information about how UGT1A1 metabolic status influences drug selection and dosing.
**27/*28*	UGT1A1 Poor Metabolizer	Abnormal/Priority/High Risk	This result signifies that the patient has two copies of a decreased function allele (*27 and *28). Based on the genotype result this patient is predicted to be a poor metabolizer of UGT1A1 substrates. This patient may be at risk for an adverse or poor response to medications that inhibit or are inactivated by UGT1A1. Based on the genotype result, this patient is predicted to have low UGT1A1 function, which is generally indicative of Gilbert syndrome. This patient may be at high risk for toxicity from

			select medications that inhibit or are inactivated by UGT1A1. Please consult a clinical pharmacist for more information about how UGT1A1 metabolic status influences drug selection and dosing.
**27/*36*	UGT1A1 Intermediate Metabolizer	Normal/Routine/ Low Risk	This result signifies that the patient has one copy of a decreased function allele (*27) and one copy of an increased function allele (*36). Based on the genotype result this patient is predicted to be an intermediate metabolizer of UGT1A1 substrates. There is no reason to selectively adjust the dose of most medications that inhibit or are inactivated by UGT1A1. Please consult a clinical pharmacist for more information about how UGT1A1 metabolic status influences drug selection and dosing.
**27/*37*	UGT1A1 Poor Metabolizer	Abnormal/Priority/High Risk	This result signifies that the patient has two copies of a decreased function allele (*27 and *37). Based on the genotype result this patient is predicted to be a poor metabolizer of UGT1A1 substrates. This patient may be at risk for an adverse or poor response to medications that inhibit or are inactivated by UGT1A1. Based on the genotype result, this patient is predicted to have low UGT1A1 function, which is generally indicative of Gilbert syndrome. This patient may be at high risk for toxicity from select medications that inhibit or are inactivated by UGT1A1. Please consult a clinical pharmacist for more information about how UGT1A1 metabolic status influences drug selection and dosing.
**27/*80*	UGT1A1 Poor Metabolizer	Abnormal/Priority/High Risk	This result signifies that the patient has two copies of a decreased function allele (*27 and *80). Based on the genotype result this patient is predicted to be a poor metabolizer of UGT1A1 substrates. This patient may be at risk for an adverse or poor response to medications that inhibit or are inactivated by UGT1A1. Based on the genotype result, this patient is predicted to have low

			UGT1A1 function, which is generally indicative of Gilbert syndrome. This patient may be at high risk for toxicity from select medications that inhibit or are inactivated by UGT1A1. Please consult a clinical pharmacist for more information about how UGT1A1 metabolic status influences drug selection and dosing.
**28/*28*	UGT1A1 Poor Metabolizer	Abnormal/Priority/High Risk	This result signifies that the patient has two copies of a decreased function allele (*28). Based on the genotype result this patient is predicted to be a poor metabolizer of UGT1A1 substrates. This patient may be at risk for an adverse or poor response to medications that inhibit or are inactivated by UGT1A1. Based on the genotype result, this patient is predicted to have low UGT1A1 function, which is generally indicative of Gilbert syndrome. This patient may be at high risk for toxicity from select medications that inhibit or are inactivated by UGT1A1. Please consult a clinical pharmacist for more information about how UGT1A1 metabolic status influences drug selection and dosing.
**28/*36*	UGT1A1 Intermediate Metabolizer	Normal/Routine/ Low Risk	This result signifies that the patient has one copy of a decreased function allele (*28) and one copy of an increased function allele (*36). Based on the genotype result this patient is predicted to be an intermediate metabolizer of UGT1A1 substrates. There is no reason to selectively adjust the dose of most medications that inhibit or are inactivated by UGT1A1. Please consult a clinical pharmacist for more information about how UGT1A1 metabolic status influences drug selection and dosing.
**28/*37*	UGT1A1 Poor Metabolizer	Abnormal/Priority/High Risk	This result signifies that the patient has two copies of a decreased function allele (*28 and *37). Based on the genotype result this patient is predicted to be a poor metabolizer of UGT1A1 substrates. This patient may be at risk for an adverse or poor response to medications that

			inhibit or are inactivated by UGT1A1. Based on the genotype result, this patient is predicted to have low UGT1A1 function, which is generally indicative of Gilbert syndrome. This patient may be at high risk for toxicity from select medications that inhibit or are inactivated by UGT1A1. Please consult a clinical pharmacist for more information about how UGT1A1 metabolic status influences drug selection and dosing.
**28/*80*	UGT1A1 Poor Metabolizer	Abnormal/Priority/High Risk	This result signifies that the patient has two copies of a decreased function allele (*28 and *37). Based on the genotype result this patient is predicted to be a poor metabolizer of UGT1A1 substrates. This patient may be at risk for an adverse or poor response to medications that inhibit or are inactivated by UGT1A1. Based on the genotype result, this patient is predicted to have low UGT1A1 function, which is generally indicative of Gilbert syndrome. This patient may be at high risk for toxicity from select medications that inhibit or are inactivated by UGT1A1. Please consult a clinical pharmacist for more information about how UGT1A1 metabolic status influences drug selection and dosing.
**36/*36*	None	Normal/Routine/ Low Risk	This result signifies that the patient has two copies of an increased function allele (*36). Based on the genotype result this patient is predicted to be an extensive (normal) metabolizer of UGT1A1 substrates. There is no reason to selectively adjust the dose of most medications that inhibit or are inactivated by UGT1A1. Please consult a clinical pharmacist for more information about how UGT1A1 metabolic status influences drug selection and dosing.
**36/*37*	UGT1A1 Intermediate Metabolizer	Normal/Routine/ Low Risk	This result signifies that the patient has one copy of a decreased function allele (*37) and one copy of an increased function allele (*36). Based on the genotype result this patient is predicted to be an intermediate

			metabolizer of UGT1A1 substrates. There is no reason to selectively adjust the dose of most medications that inhibit or are inactivated by UGT1A1. Please consult a clinical pharmacist for more information about how UGT1A1 metabolic status influences drug selection and dosing.
**36/*80*	UGT1A1 Intermediate Metabolizer	Normal/Routine/ Low Risk	This result signifies that the patient has one copy of a decreased function allele (*80) and one copy of an increased function allele (*36). Based on the genotype result this patient is predicted to be an intermediate metabolizer of UGT1A1 substrates. There is no reason to selectively adjust the dose of most medications that inhibit or are inactivated by UGT1A1. Please consult a clinical pharmacist for more information about how UGT1A1 metabolic status influences drug selection and dosing.
**37/*37*	UGT1A1 Poor Metabolizer	Abnormal/Priority/High Risk	This result signifies that the patient has two copies of a decreased function allele (*37). Based on the genotype result this patient is predicted to be a poor metabolizer of UGT1A1 substrates. This patient may be at risk for an adverse or poor response to medications that inhibit or are inactivated by UGT1A1. Based on the genotype result, this patient is predicted to have low UGT1A1 function, which is generally indicative of Gilbert syndrome. This patient may be at high risk for toxicity from select medications that inhibit or are inactivated by UGT1A1. Please consult a clinical pharmacist for more information about how UGT1A1 metabolic status influences drug selection and dosing.
**37/*80*	UGT1A1 Poor Metabolizer	Abnormal/Priority/High Risk	This result signifies that the patient has two copies of a decreased function allele (*37 and *80). Based on the genotype result this patient is predicted to be a poor metabolizer of UGT1A1 substrates. This patient may be at risk for an adverse or poor response to medications that inhibit or are inactivated by UGT1A1. Based on the

			genotype result, this patient is predicted to have low UGT1A1 function, which is generally indicative of Gilbert syndrome. This patient may be at high risk for toxicity from select medications that inhibit or are inactivated by UGT1A1. Please consult a clinical pharmacist for more information about how UGT1A1 metabolic status influences drug selection and dosing.
**80/80*	UGT1A1 Poor Metabolizer	Abnormal/Priority/High Risk	This result signifies that the patient has two copies of a decreased function allele (*80). Based on the genotype result this patient is predicted to be a poor metabolizer of UGT1A1 substrates. This patient may be at risk for an adverse or poor response to medications that inhibit or are inactivated by UGT1A1. Based on the genotype result, this patient is predicted to have low UGT1A1 function, which is generally indicative of Gilbert syndrome. This patient may be at high risk for toxicity from select medications that inhibit or are inactivated by UGT1A1. Please consult a clinical pharmacist for more information about how UGT1A1 metabolic status influences drug selection and dosing.

This table is provided to show examples of how a test result could be translated into discrete fields within an EHR, including a brief interpretation that summarizes the result. The information presented here is consistent with the guideline but may need to be adapted to a given EHR's design and capabilities. It is up to date as of the publication date of this guideline. Because various EHRs or organizations may require different terms different options are provided.

[a]A more comprehensive table of genotype/phenotype EHR entries for possible diplotype combinations of all variants listed in Supplemental Table S2 is available at PharmGKB (https://www.pharmgkb.org/drug/PA10251).

[b]The coded diplotype/phenotype summary is used to store an interpretation of the test result. This is a design decision that may differ among sites. Assignment of all Genotype/Phenotype Summaries based on diplotype is available at (https://www.pharmgkb.org/drug/PA10251).

[c]For this example, a priority result is defined as a genetic test result that results in a change in drug, drug dose, or drug monitoring.

[d]The UGT1A1 phenotype (e.g., poor metabolizer) or the coded phenotype summary might be considered a "priority result" for other drugs and should be noted in the chart.

[e]The specific wording of the interpretive text may differ among sites.

[f] The *UGT1A1 *6/*6* diplotype is associated with low UGT1A1 function and is generally indicative of Gilbert syndrome. In the case of atazanavir, it is unclear at the time of publication whether the *UGT1A1*6/*6* or **27/*27* genotypes confer increased risk of severe atazanavir-associated hyperbilirubinemia.

Supplemental Table S8. Example Implementation of this Guideline: Point of Care Clinical Decision Support

CDS Alert trigger Condition	CDS Context, Relative to Genetic Testing	CDS Alert Text[a]
No *UGT1A1* test on file and atazanavir ordered[b]	Pre-Test	*UGT1A1* genetic status may be predictive of cosmetic jaundice with this medication. A *UGT1A1* genotype does not appear to have been ordered for this patient. Please consult a clinical pharmacist[c] for more information.
UGT1A1 Extensive Metabolizer or Intermediate Metabolizer and atazanavir ordered	Post-Test	No CDS
UGT1A1 Poor Metabolizer and atazanavir ordered (see footnote below for **6* and **27*)[d]	Post-Test	This patient is predicted to be a UGT1A1 poor metabolizer and may be at an increased risk of developing jaundice with atazanavir use. Consider an alternative agent particularly if jaundice would be of concern to the patient. Please consult a clinical pharmacist for more information.

[a]The specific wording of the alert text may differ among sites.

[b]In the context of *UGT1A1* and atazanavir, because the side effect of hyperbilirubinemia/jaundice is reversible once the medicine is stopped, pre-test alerts guiding the clinicians to order a *UGT1A1* genotype prior to starting atazanavir should be considered a soft recommendation.

[c]Pharmacist, pharmacologist, or a clinician with pharmacogenetic expertise/training.

[d]The *UGT1A1 *6/*6* diplotype is associated with low UGT1A1 function and is generally indicative of Gilbert syndrome. In the case of atazanavir, it is unclear at the time of publication whether the *UGT1A1*6/*6* or **27/*27* genotypes confer increased risk of severe atazanavir-associated hyperbilirubinemia.

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