Uridine Diphosphate Glucuronosyltransferase 1A1 (*UGT1A1*) Pharmacogenetic Competency

Updated on 7/2015

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Pre-test Question #1

The UGT1A1 enzyme is responsible for the _____ of bilirubin.

A. glucuronidation
B. sulfation
C. methylation
D. acetylation

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Pre-test Question #2

Bilirubin is formed when _____ break down.

A. White blood cells
B. Red blood cells
C. Neutrophils
D. Platelets

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Pre-test Question #3

Patients with low UGT1A1 function are at increased risk of which of the following if they are also taking atazanavir?

A. Hepatotoxicity
B. Jaundice
C. Headache
D. Weight gain

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Pre-test Question #4

Which of the following statements best describes the relationship between atazanavir and UGT1A1?

A. Atazanavir is metabolized by UGT1A1
B. UGT1A1 prevents atazanavir from being inactivated
C. Atazanavir inhibits UGT1A1
D. UGT1A1 inhibits atazanavir

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Pre-test Question #5

Which *UGT1A1* genotype is associated with a UGT1A1 LOW FUNCTION phenotype?

A. *1/*1
B. *1/*28
C. *1/*6
D. *28/*28

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Pre-test Question #6

A clinician should consider avoiding atazanavir in a patient with low UGT1A1 function, particularly if jaundice would be of concern to the patient.

A. TRUE
B. FALSE

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Pre-test Question #7

UGT1A1 genotype should be used to guide irinotecan therapy at St. Jude.

A. TRUE
B. FALSE

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Pre-test Question #8

A *28+60+93 allele is equivalent in function to a *28 allele.

A. TRUE
B. FALSE

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Pre-test Question #9

Which of the following is TRUE regarding the severe hyperbilirubinemia and jaundice that may occur when patients who have low UGT1A1 function take atazanavir?

A. The severe hyperbilirubinemia/jaundice will likely lead to serious liver damage
B. The severe hyperbilirubinemia/jaundice is irreversible
C. The severe hyperbilirubinemia/jaundice may lead to premature discontinuation of atazanavir
D. The severe hyperbilirubinemia/jaundice is caused by the accumulation of conjugated bilirubin in the blood

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Pre-test Question #10

What is the name of the condition that describes a patient who has the *UGT1A1**28/*28 genotype and has evidence of hyperbilirubinemia?

A. Gilbert syndrome
B. Atazanavir syndrome
C. UGT1A1 syndrome
D. Bilirubin syndrome

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UGT1A1 Pharmacogenetic Competency

- **The target audience for this *UGT1A1* pharmacogenetic competency is pharmacists or other general practitioners.**
- **Please refer to the INTRODUCTION TO PHARMACOGENETICS competency for explanation of terminology.**

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Objectives

- **Upon completion this competency, participants will be able to:**
  - **Recognize the different *UGT1A1* allele variants**
  - **Recognize the different UGT1A1 phenotypes**
  - **Make therapeutic recommendations for atazanavir based on a patient's *UGT1A1* genotype**

UGT1A1 Advanced Pharmacogenetics

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UGT1A1

- **UGT1A1 is an enzyme that adds a glucuronide group to bilirubin, a byproduct of heme catabolism.**
- **This process is called conjugation, and it facilitates bilirubin elimination in the bile.**

Heme from red blood cells

→ *unconjugated (indirect)* bilirubin

UGT1A1

→ *conjugated (direct)* bilirubin

↓ excreted in the bile

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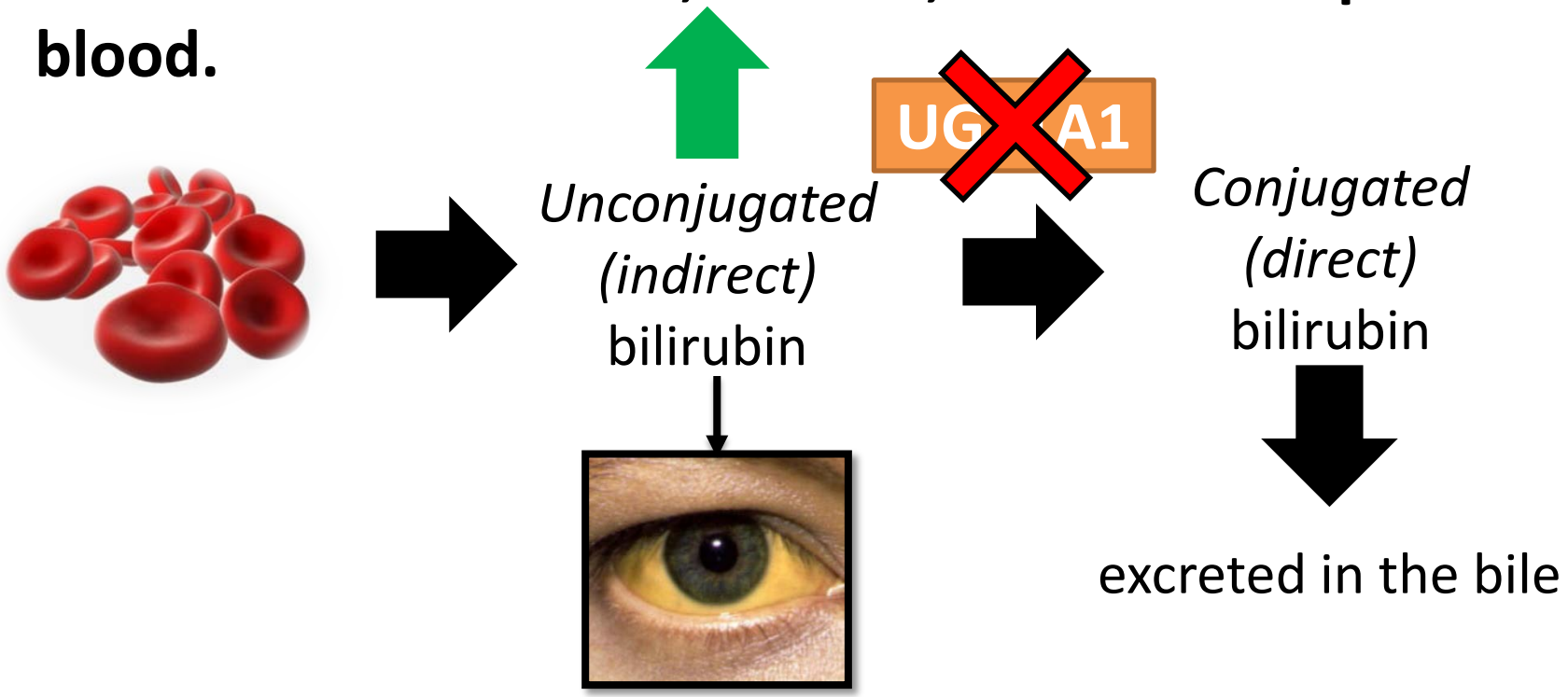
UGT1A1

- **If UGT1A1 function is reduced or inhibited, hyperbilirubinemia and/or jaundice may occur. This is because unconjugated bilirubin cannot be eliminated via the bile; instead, it will build up in the blood.**



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UGT1A1 Allele Variants

- **Genetic variations in the *UGT1A1* gene may lead to decreased UGT1A1 function.**
- **Decreased UGT1A1 function may put patients at increased risk for severe hyperbilirubinemia and jaundice if they are also taking a medication that inhibits the UGT1A1 enzyme (e.g., atazanavir).**

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UGT1A1 Allele Variants

- ***UGT1A1* alleles are characterized into different groups:**
  - **Wild-type (normal function) alleles**
  - **Reduced function alleles**
  - **Non-functional alleles (rare)**

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UGT1A1 Allele Variants

There are >100 known variants of *UGT1A1*. Some examples of alleles that our current DMET assay tests for include:

Allele Function	*UGT1A1* Haplotypes
Wild-type Function	*1
Reduced Function	*6, *27, *28, *80
Non-functional	*8, *14, *15, *45

http://www.pharmacogenomics.pha.ulaval.ca/cms/ugt_alleles/

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UGT1A1 Allele Variants

- Note that most of the *28 alleles will be reported with other variants as follows:
  - *27+28+60+93
  - *27+28+60
  - *28+60
  - *28+60+93
- These alleles are considered to be equivalent in function as *28 (reduced function).

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UGT1A1 Allele Variants

- The most clinically significant *UGT1A1* allele variant is *UGT1A1*28*.
- Patients who have inherited the *UGT1A1*28/*28* genotype have about 30% of normal UGT1A1 function.
- When patients with the *UGT1A1*28/*28* genotype also have clinical signs of jaundice or hyperbilirubinemia, they may have a benign condition called Gilbert syndrome.
- *UGT1A1*6* also has 30% of normal UGT1A1 function. It is more common in Asian populations, and is also associated with Gilbert syndrome.

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UGT1A1 Phenotypes

- **The assignment of UGT1A1 phenotype is based on genotype.**
- **There are 3 UGT1A1 phenotypes**
  - **Normal Function**
    - **2 wild-type alleles (e.g. *1/*1)**
  - **Intermediate Function**
    - **1 wild-type allele + 1 reduced function allele (e.g. *1/*28)**
  - **Low Function**
    - **2 reduced function alleles (e.g. *28/*28)**
- **If a patient has at least one allele with indeterminate function, their UGT1A1 phenotype is considered indeterminate.**

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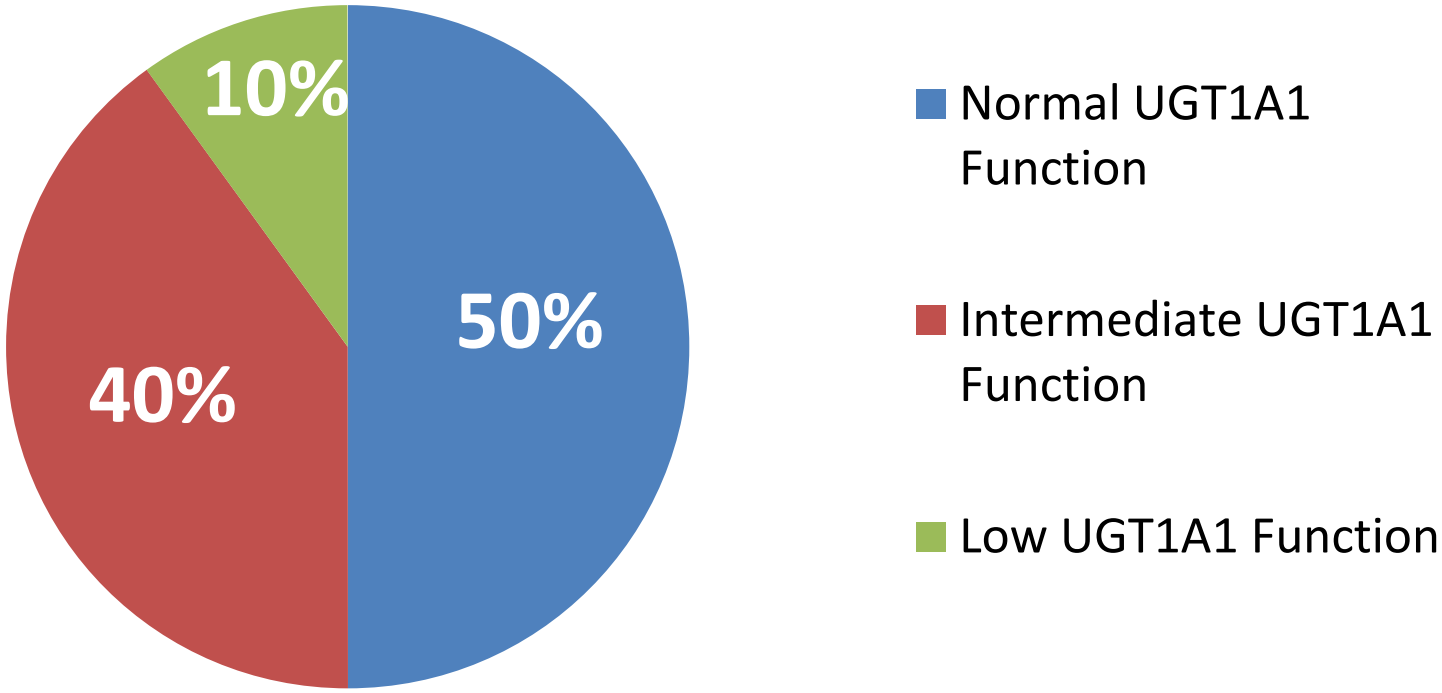
UGT1A1 Phenotypes in the PG4KDS Population



- Percentage of each phenotype in the population
- The exact percent of each phenotype group varies by ethnicity

Gene-Based Dosing Recommendations for Atazanavir

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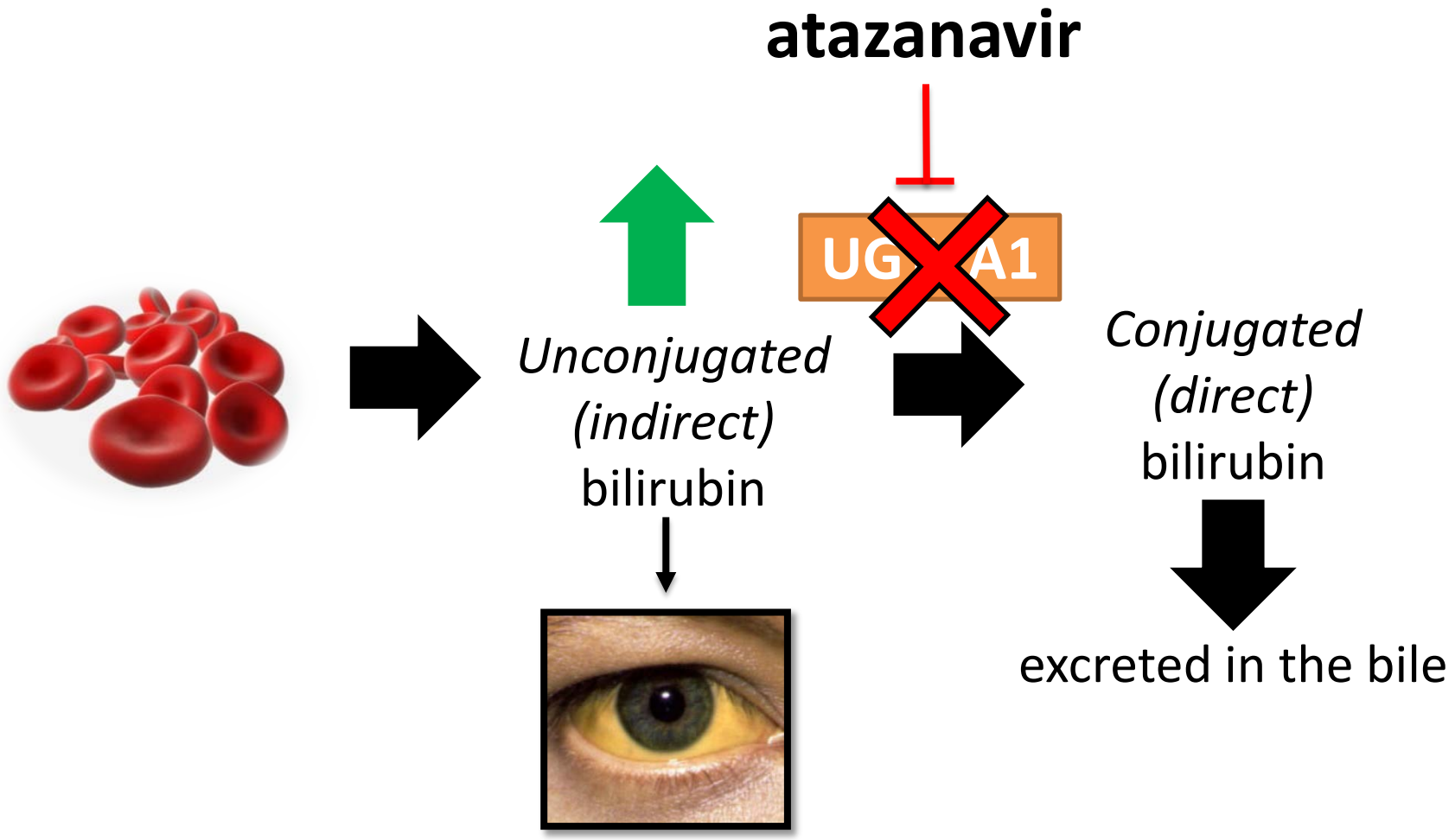
Atazanavir inhibits UGT1A1 activity



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Atazanavir and *UGT1A1*

- **Patients who have inherited the *UGT1A1**28/*28 or *UGT1A1**6/*6 genotype (low UGT1A1 function) may be at increased risk of severe hyperbilirubinemia and jaundice if they are prescribed atazanavir.**
- **As a result of these side effects, the patients may also be at risk for discontinuing treatment.**

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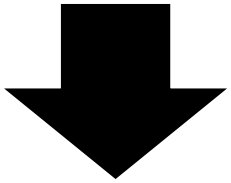
Atazanavir Therapy Recommendation

IF** UGT1A1 genotype is known **AND

***UGT1A1*28/*28**
OR
UGT1A1 *6/*6



Consider avoiding atazanavir

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Atazanavir Therapy Recommendation

- **Clinicians should use the *UGT1A1**28/*28 or *UGT1A1**6/*6 genotype to guide their patient discussion and consider if using an alternative antiretroviral agent is warranted for that particular patient.**
- **The recommendation is framed in this manner because severe hyperbilirubinemia and jaundice is a benign adverse effect that is reversible upon drug discontinuation. In addition, it can be clinically monitored by obtaining serum bilirubin levels.**

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UGT1A1 and Irinotecan

- **UGT1A1 is responsible for inactivating SN-38, the active metabolite of irinotecan.**
- **HOWEVER, *UGT1A1* genotype should NOT be used to guide irinotecan therapy at St. Jude, because it is not clinically significant with our current dosing regimens.**
- ***UGT1A1* genotype is only relevant for irinotecan doses > 250 mg/m^2.**
- **For more information:**

Stewart CF, et al. UGT1A1 promoter genotype correlates with SN-38 pharmacokinetics, but not severe toxicity in patients receiving low-dose irinotecan. *J Clin Oncol*. 2007; 25(18): 2594-600.

Pharmacogenetic Results in Milli

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Pharmacogenetics tab in Milli

- **Three types of gene-specific PG4KDS entries**
  - **Genotype**
    - **Provides genotype results (* alleles)**
  - **Consult**
    - **Provides interpretation of genotype results**
  - **Letter**
    - **Individualized letter sent to patient**

Pharmacogenetics	4/9/2014 09:04
Pharmacogenetics	
CYP2C19 PG4KDS Genotype	f *1/*1
CYP2C19 PG4KDS Consult	f Routine
CYP2C19 PG4KDS Letter	CYP2C19 PG4KDS Letter
CYP2D6 PG4KDS Genotype	f (*1/*41)2N
CYP2D6 PG4KDS Consult	f Routine
CYP2D6 PG4KDS Letter	CYP2D6 PG4KDS Letter
DPYD PG4KDS Genotype	f *1/*1
DPYD PG4KDS Consult	f Routine
DPYD PG4KDS Letter	DPYD PG4KDS Letter
SLCO1B1 PG4KDS Genotype	f Abn *1a/*14,*1b/*4
SLCO1B1 PG4KDS Consult	f Abn Indeterminate
TPMT PG4KDS Genotype	f *1/*1
TPMT PG4KDS Consult	f Routine
TPMT PG4KDS Letter	TPMT PG4KDS Letter
UGT1A1 PG4KDS Genotype	f *1/*1
UGT1A1 PG4KDS Consult	f Routine

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"See Consult" Entries

Pharmacogenetics	9/21/2011 09:51
Pharmacogenetics	
CYP2C19 PG4KDS Genotype	f *1/*1
CYP2C19 PG4KDS Consult	f Routine
CYP2C19 PG4KDS Letter	PG4KDS CYP2C19 Letter
CYP2D6 PG4KDS Genotype	f (*1/*4)2N
CYP2D6 PG4KDS Consult	f Routine
CYP2D6 PG4KDS Letter	PG4KDS CYP2D6 LETTER
DPYD PG4KDS Genotype	f *1/*1
DPYD PG4KDS Consult	f Routine
DPYD PG4KDS Letter	DPYD PG4KDS Letter
SLCO1B1 PG4KDS Genotype	f Abn *15/*15
SLCO1B1 PG4KDS Consult	f Abn Priority
SLCO1B1 PG4KDS Letter	PG4KDS SLCO1B1 Letter
TPMT PG4KDS Genotype	f *1/*1
TPMT PG4KDS Consult	f Routine
TPMT PG4KDS Letter	PG4KDS TPMT Letter
UGT1A1 PG4KDS Genotype	f Abn See Consult
UGT1A1 PG4KDS Consult	f Abn Priority

- Some UGT1A1 results will say "see consult," and the genotype result may only be viewed in the consultation note.
- This is because some of the *28 results will look like *27+28+60+93, or another variation of this, and it cannot fit in the main result box.

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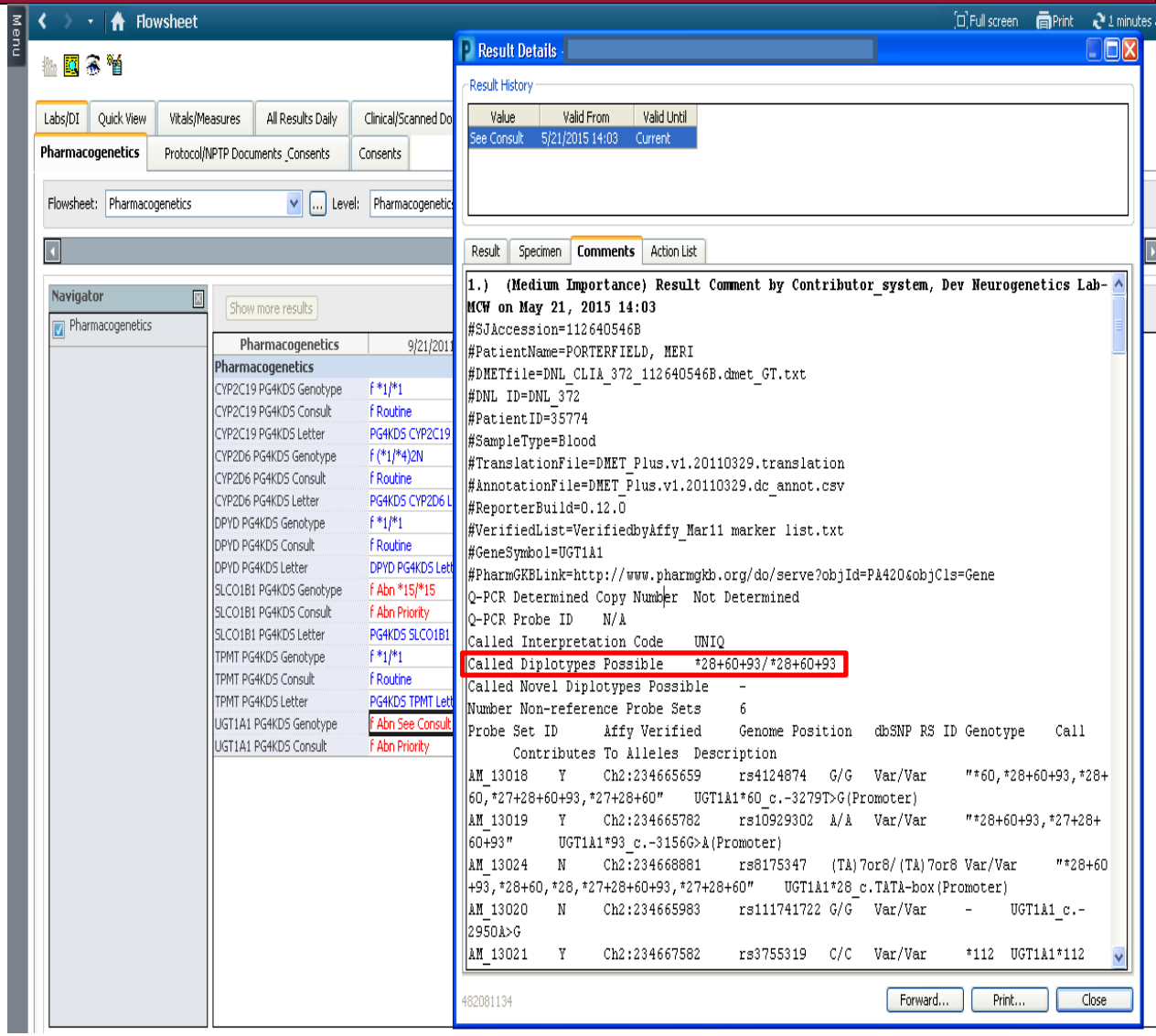
PG4KDS Genotype

- Under Comments you can find the detailed technical report and CLIA report regarding all testing performed (including the detailed *UGT1A1* result and a description of all tests included in the array). These reports are included to comply with regulations and are generally not clinically relevant



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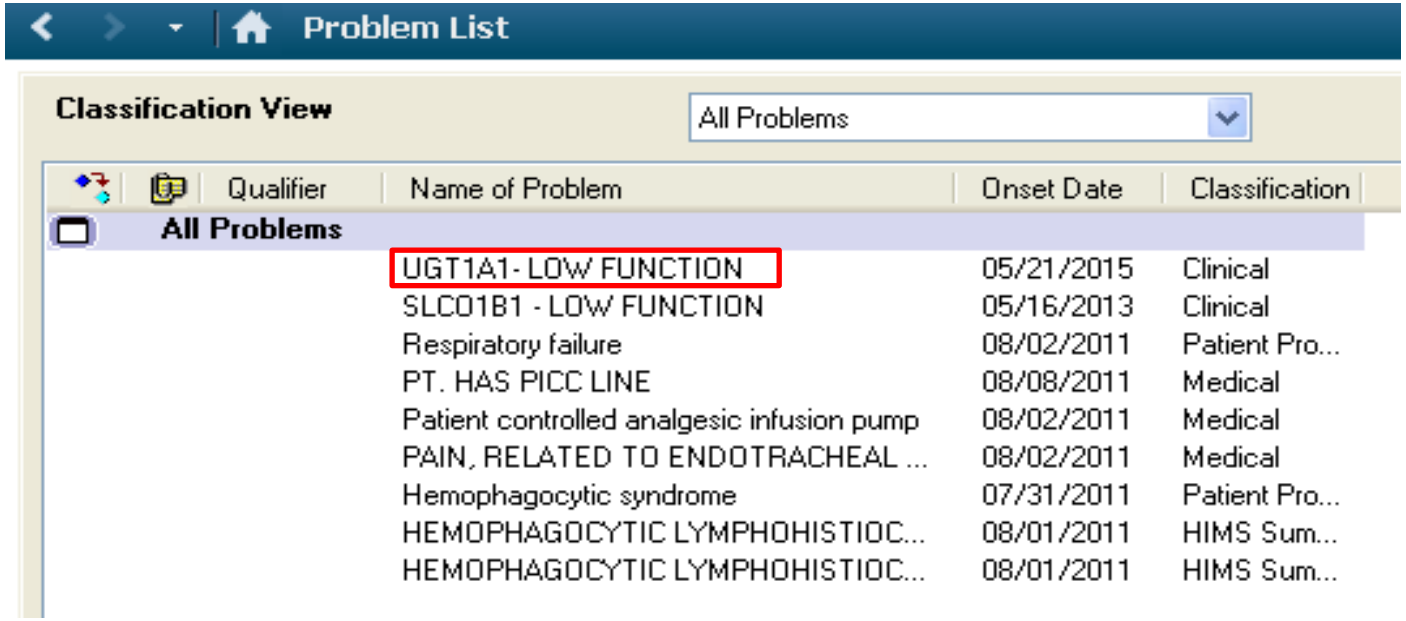
Problem List Entry



- If the interpreted phenotype is considered high-risk, a problem list entry is entered into the health record
- These entries are used to fire active CDS alerts when high-risk drugs are ordered for patients with high-risk phenotypes

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Clinical Decision Support for *UGT1A1*/atazanavir

- **There will be no pre-test alerts for *UGT1A1*/atazanavir.**
- **There will be post-test alerts for the patients with a low UGT1A1 function genotype only.**

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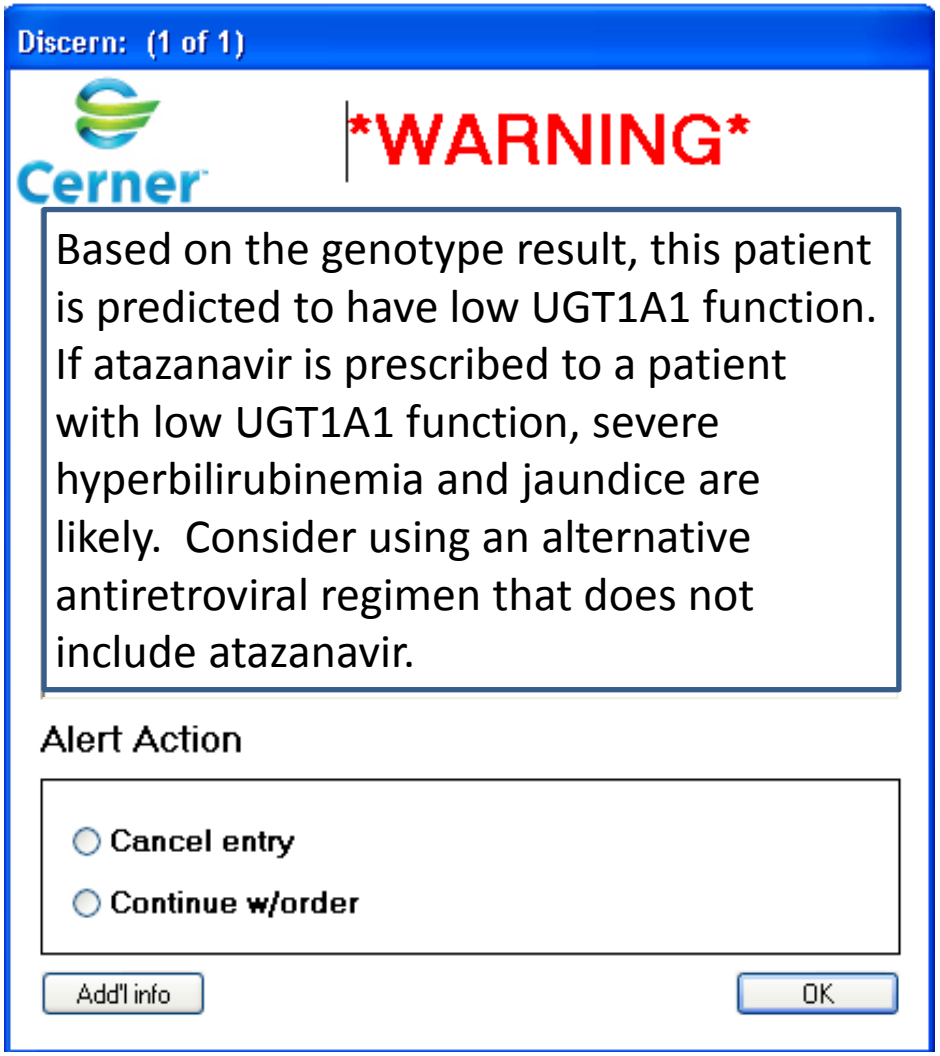
Active CDS Alerts

- **When a prescriber orders atazanavir on a patient who has low UGT1A1 function an active CDS alert like this will appear.**

- **The same alert appears when a pharmacist verifies the order.**



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Patient Letters

- **For patients with a PG4KDS *UGT1A1* genotype result who have requested to be informed of their genotype test results, letters will be sent out to their mailing address on file informing them about their UGT1A1 phenotype.**
- **Patients might ask you about the meaning of these letters once they receive them.**
- **All communications mailed to the patients will be available for review in their medical record.**

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Patient Letters

- The *UGT1A1* letter is obtained by double clicking on the letter box

Pharmacogenetics	6/12/2012 14:13
Pharmacogenetics	
PG4KDS UGT1A1 Genotype	f (*1/*1)
PG4KDS UGT1A1 Consult	f Routine
PG4KDS UGT1A1 Letter	PG4KDS UGT1A1 LETTER

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UGT1A1 Pharmacogenetics

- **For more information about *UGT1A1* pharmacogenetics and dose adjustment of medications, the following resources are available to you:**
  - **Do you know…. Uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) and medicines**
  - **St Jude formulary: Type in pharmacogenetics and you will be directed to a page that contains information about adjusting the doses of medicines based on the patient's pharmacogenetic status**
  - **www.stjude.org/pg4kds is a website that explains the PG4KDS protocol and the gene-drug pairs we have implemented**

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Questions

- **For questions about *UGT1A1* pharmacogenetics see:**
  - **Mary Relling**
  - **Cyrine Haidar**
  - **Kristine Crews**
  - **Clinical Pharmacogenetics Resident**

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