Uridine Diphosphate Glucuronosyltransferase 1A1 (UGT1A1) Pharmacogenetic Competency
General Tips for Viewing Material

• Upon completion of the educational material, close out the presentation screen to return to the learn center page and complete the exam.
Pre-test Question #1

The UGT1A1 enzyme is responsible for the __________________ of bilirubin.

A. glucuronidation
B. sulfation
C. methylation
D. acetylation
Pre-test Question #2

Bilirubin is formed when ____________ break down.

A. White blood cells
B. Red blood cells
C. Neutrophils
D. Platelets
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
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
Which *UGT1A1* genotype is associated with a *UGT1A1 LOW FUNCTION* phenotype?

A. *1/*1  
B. *1/*28  
C. *1/*6  
D. *28/*28
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
UGT1A1 genotype should be used to guide irinotecan therapy at St. Jude.

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

A. TRUE
B. FALSE
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
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
• 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.
Upon completion this competency, participants will be able to:

- Recognize the different \textit{UGT1A1} allele variants
- Recognize the different \textit{UGT1A1} phenotypes
- Make therapeutic recommendations for atazanavir based on a patient's \textit{UGT1A1} genotype
UGT1A1 Advanced Pharmacogenetics
• 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 $\xrightarrow{UGT1A1} \text{unconjugated (indirect) bilirubin} \xrightarrow{\text{conjugated (direct) bilirubin}} \text{excreted in the bile}$
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.

**Unconjugated (indirect) bilirubin**

**Conjugated (direct) bilirubin**

excreted in the bile
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).
• *UGT1A1* alleles are characterized into different groups:
  – Wild-type (normal function) alleles
  – Reduced function alleles
  – Non-functional alleles (rare)
There are >100 known variants of *UGT1A1*. Some examples of alleles that our current DMET assay tests for include:

<table>
<thead>
<tr>
<th>Allele Function</th>
<th><em>UGT1A1</em> Haplotype(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild-type Function</td>
<td>*1</td>
</tr>
</tbody>
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http://www.pharmacogenomics.pha.ulaval.ca/cms/ugt_alleles/
• 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).
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.
• 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.
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
Atazanavir inhibits UGT1A1 activity

Unconjugated (indirect) bilirubin

Conjugated (direct) bilirubin excreted in the bile
Atazanavir and \textit{UGT1A1}

- Patients who have inherited the \textit{UGT1A1}*28/*28 or \textit{UGT1A1}*6/*6 genotype (low \textit{UGT1A1} function) may be at increased risk of \textit{severe hyperbilirubinemia} and \textit{jaundice} if they are prescribed atazanavir.

- As a result of these side effects, the patients may also be at risk for \textit{discontinuing treatment}.
**Atazanavir Therapy Recommendation**

**IF** UGT1A1 genotype is known **AND**

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

**Consider avoiding atazanavir**
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.
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/m².
- For more information:

Pharmacogenetic Results in Milli
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
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.
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.
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.
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.
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.

Based on the genotype result, this patient is predicted to have low UGT1A1 function. If atazanavir is prescribed to a patient with low UGT1A1 function, severe hyperbilirubinemia and jaundice are likely. Consider using an alternative antiretroviral regimen that does not include atazanavir.
• 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.
Patient Letters

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

<table>
<thead>
<tr>
<th>Pharmacogenetics</th>
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<tbody>
<tr>
<td>PG4KDS UGT1A1 Genotype</td>
<td>f (*1/*1)</td>
</tr>
<tr>
<td>PG4KDS UGT1A1 Consult</td>
<td>f Routine</td>
</tr>
<tr>
<td>PG4KDS UGT1A1 Letter</td>
<td>PG4KDS UGT1A1 LETTER</td>
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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](http://www.stjude.org/pg4kds) is a website that explains the PG4KDS protocol and the gene-drug pairs we have implemented
Questions

• For questions about *UGT1A1* pharmacogenetics see:
  – Mary Relling
  – Cyrine Haidar
  – Kristine Crews
  – Clinical Pharmacogenetics Resident
• Congratulations, you have completed the review of material for this competency!

• Please close out this window to return to the Learn Center for the exam.
  – Please note, you will not receive credit for completion of this competency until you have completed the exam and received a passing score.