Cytochrome P450 2D6 (CYP2D6)
Pharmacogenetic Competency

Updated on 6/2015
What is the activity score for the pharmacogenetic test result of CYP2D6 (*1/*1)2N?

a) 0.5  
b) 1.0  
c) 1.5  
d) 2.0
What is the predicted CYP2D6 phenotype for the test result of \textit{CYP2D6} (*2/*17)2N?

a) Ultra-rapid metabolizer
b) Extensive metabolizer
c) Intermediate metabolizer
d) Poor metabolizer
ZB is experiencing pain following a minor surgical procedure. A clinician wants to prescribe codeine to treat the pain and asks you for the appropriate dose. The patient has a pharmacogenetic test result of *CYP2D6 (*/4/*4) duplication.

Based on the pharmacogenetic test result, what recommendation would you give to the clinician?

a) Use label recommended dosing
b) Reduce the initial starting codeine dose by 50%
c) Avoid codeine due an increased risk of adverse events
d) Avoid codeine due to a lack of analgesic effects
MJ is about to be prescribed amitriptyline for treatment of depression. The patient has a reported pharmacogenetic test result of CYP2D6 (*1/*4)2N. Based on the pharmacogenetic test result, which of the following statements is correct?

a) The patient should not receive amitriptyline due to decreased plasma concentrations of the drug and likely therapeutic failure

b) The patient should not receive amitriptyline due to increased plasma concentrations of the drug and likely development of side effects

c) There is no reason to adjust the dose of amitriptyline based on the CYP2D6 genotype test result

d) The patient’s initial dose should be increased by 25%
Objectives

• Upon completion of this competency, participants will be able to:
  – Recognize the different *CYP2D6* allele variants
  – Recognize the different *CYP2D6* phenotypes
  – Calculate a *CYP2D6* activity score
  – Assign the correct phenotype based upon the activity score
  – Make therapeutic recommendations for medications metabolized by *CYP2D6* based on a patient's predicted *CYP2D6* phenotype
Patient Case

• A 14-year old girl received a prescription for a codeine-containing analgesic for hip pain.

• The patient received 15 mg of codeine and the mother noticed that she was having trouble breathing, gasping and opening her mouth widely to search for air.

• She was admitted to the ER and given a dose of naloxone which seemed to relieve the symptoms.

• Genotyping revealed that she a CYP2D6 *4/*5 genotype. The patient was assigned a CYP2D6 poor metabolizer phenotype.

CYP2D6 Pharmacogenetics
CYP2D6 Enzyme

• CYP2D6 is an enzyme that metabolizes many commonly prescribed drugs

• Metabolism by CYP2D6 can either activate or inactivate a drug:
  – Codeine is a prodrug that is metabolized to an active form (morphine) by CYP2D6
  – Amitriptyline is metabolized by CYP2D6 to a less active form
CYP2D6

• Genetic variations in the *CYP2D6* gene may lead to changes in metabolic activity of the CYP2D6 enzyme (increased or reduced activity)

• For certain medications, such as codeine, dose adjustments or an alternative therapy may be necessary in instances where metabolic activity is altered
Certain \textit{CYP2D6} alleles are characterized as wild-type (normal function) alleles

- These alleles will encode for CYP2D6 enzymes that will have normal (extensive) metabolic activity

\textbf{CYP2D6} wild-type (normal) function alleles include:

- *1, *2, and *2A
Certain *CYP2D6* alleles are characterized as reduced function alleles – These alleles will encode for *CYP2D6* enzymes that have less metabolic activity than wild-type (normal function) alleles

*CYP2D6* reduced function alleles include: – *9, *10, *17, *29, and *41
• Certain **CYP2D6** alleles are characterized as non-functional alleles
  – These alleles will encode for CYP2D6 enzymes that have little or no metabolic activity

• **CYP2D6** non-functional alleles include:
  – Please note that *5 is the nomenclature for a deleted allele

http://www.cypalleles.ki.se/cyp2d6.htm
CYP2D6 Allele Variants

• If no variant alleles are detected, the reference lab (e.g., ARUP) may report the result as “negative”
  – A negative result is the same as **CYP2D6*1**
CYP2D6 Activity Score
Most patients have two copies of the \textit{CYP2D6} gene, one allele inherited from the maternal parent and one allele inherited from the paternal parent.

A small percentage of patients will have multiple copies of a \textit{CYP2D6} gene, the result will display in two different ways in the medical record:

- Some reference laboratories will give an exact copy number \((xN)\)
  - The result of \(xN\) does NOT indicate which allele is duplicated

- Some reference laboratories display the result as “duplication”
  - The result of “duplication” does NOT indicate the exact number of alleles present or which allele is duplicated
A small percentage of patients will have one or both *CYP2D6* genes deleted, indicated by the *5* allele. For example:

- *1/*5 patients will have one copy of a functional (*1) allele and one deleted allele (*5)
- *5/*5 patients will have both *CYP2D6* alleles deleted
Each allele is assigned an activity value as shown below:

<table>
<thead>
<tr>
<th>Activity value</th>
<th>Alleles</th>
<th>Type of Allele</th>
</tr>
</thead>
</table>

CYP2D6 activity score is calculated by adding up the activity value for each allele as follows:

- Activity score for \( CYP2D6 \ (*1/\ast 2A)2N \) = 1 + 1 = 2
- Activity score for \( CYP2D6 \ (*2/\ast 10)2N \) = 1 + 0.5 = 1.5
- Activity score for \( CYP2D6 \ (*4/\ast 4)2N \) = 0 + 0 = 0
- Activity score for \( CYP2D6 \ (*3/\ast 9)2N \) = 0 + 0.5 = 0.5

CYP2D6 Activity Score

- When duplicated alleles are reported, the reference laboratory may not:
  - Indicate which allele is duplicated
  - Quantify the number of additional CYP2D6 allele copies

- For the purpose of calculating a CYP2D6 activity score when a duplication is reported, assume the patient has 1 additional CYP2D6 allele (a total of 3 copies of the gene)
For a result of *CYP2D6* (*4/*9) duplication:

- The patient may have two *4* alleles and one *9* allele (for a total of 3 alleles)

  OR

- The patient may have one *4* allele and two *9* alleles (for a total of 3 alleles)
What is the CYP2D6 activity score for the result of \( \text{CYP2D6}^{(*)4/9} \) duplication?

1. First, we assume 3 alleles are present but do not know which allele is duplicated.
2. What are the possibilities?
   - \( *4 + *4 + *9 \) (3 alleles total)
   - OR
   - \( *4 + *9 + *9 \) (3 alleles total)

<table>
<thead>
<tr>
<th>Activity value</th>
<th>Alleles</th>
<th>Type of Allele</th>
</tr>
</thead>
</table>

**CYP2D6 Activity Score Calculation**

<table>
<thead>
<tr>
<th>Activity value</th>
<th>Alleles</th>
<th>Type of Allele</th>
</tr>
</thead>
</table>

3. **Calculate the different possibilities**

   **If *4 is duplicated:**
   
   \[ *4 + *4 + *9 = 0 + 0 + 0.5 = 0.5 \]

   **If *9 is duplicated:**
   
   \[ *4 + *9 + *9 = 0 + 0.5 + 0.5 = 1.0 \]

What is the CYP2D6 activity score for a diplotype result of *4/*9 with a duplication?

The activity score will range from 0.5-1.0
CYP2D6 Activity Score

• A reference laboratory may report the exact allele copy number but may NOT indicate which allele is duplicated
  – For the result of (*2A/*10)3N

• We already know that the patient has at least one *2A allele and at least one *10 allele. Because there are three alleles present, indicated by 3N, there will be an additional copy of either *2A or *10
## CYP2D6 Activity Score Calculation

### Activity value | Alleles | Type of Allele
--- | --- | ---

What is the activity score for a CYP2D6 diplotype result of (*2A/*10)3N?

1. **First, we do not know which allele is duplicated**
2. **What are the possibilities?**
   - *2A + *2A + *10 (3 total)  
   - OR  
   - *2A + *10 + *10 (3 total)

3. Calculate the different possibilities

If *10 is duplicated:

\[ *2A + *10 + *10 = 1 + 0.5 + 0.5 = 2.0 \]

If *2A is duplicated:

\[ *2A + *2A + *10 = 1 + 1 + 0.5 = 2.5 \]
What is the CYP2D6 activity score for a diplotype result of *2A/*17 duplicated?

The activity score will range from 2.0-2.5
Assigning a CYP2D6 Phenotype
CYP2D6 Phenotypes

- There are four CYP2D6 phenotypes
  - Ultra-rapid metabolizer (UM)
  - Extensive metabolizer (EM)
  - Intermediate metabolizer (IM)
  - Poor metabolizer (PM)

- In some cases the CYP2D6 genotype result may be ambiguous and additional phenotype terminology is needed including
  - Possible ultra-rapid metabolizer
  - Possible intermediate metabolizer
  - Possible poor metabolizer
Percentage of CYP2D6 Phenotypes in the Population

- 2% Ultra-rapid Metabolizer - very high activity
- 78% Extensive Metabolizer - normal activity
- 10% Intermediate Metabolizer - lower activity
- 10% Poor Metabolizer - low or no activity

* The exact percent of each phenotype group varies by ethnicity
### CYP2D6 Phenotype Assignment

<table>
<thead>
<tr>
<th>CYP2D6 activity score</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;2</td>
<td>Ultra-rapid metabolizer</td>
</tr>
<tr>
<td>1-2</td>
<td>Extensive metabolizer</td>
</tr>
<tr>
<td>0.5</td>
<td>Intermediate metabolizer</td>
</tr>
<tr>
<td>0</td>
<td>Poor metabolizer</td>
</tr>
</tbody>
</table>

- Please note that reference laboratories or other institutions may have different guidelines for assigning a CYP2D6 phenotype.
- In particular, some reference laboratories and institutions may classify a patient with a CYP2D6 activity score of 1.0 as an intermediate metabolizer.

**CYP2D6 Phenotype Assignment**

<table>
<thead>
<tr>
<th>CYP2D6 activity score</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;2</td>
<td>Ultra-rapid metabolizer</td>
</tr>
<tr>
<td>1-2</td>
<td>Extensive metabolizer</td>
</tr>
<tr>
<td>0.5</td>
<td>Intermediate metabolizer</td>
</tr>
<tr>
<td>0</td>
<td>Poor metabolizer</td>
</tr>
</tbody>
</table>

- If an activity score (e.g. 2.0-2.5) indicates the patient MAY be an ultra-rapid metabolizer, the phenotype assigned will be: CYP2D6 possible ultra-rapid metabolizer
- If an activity score (e.g. 0-0.5) indicates the patient MAY be a poor metabolizer, the phenotype assigned will be: CYP2D6 possible poor metabolizer
CYP2D6 is highly polymorphic, with over 100 known allele variants

- The majority of these allele variants are very rare and not routinely tested for

Note that a patient may have an allele variant that is not tested for

- If variants are not tested for, the patient is assumed to have wild-type alleles (CYP2D6*1)

- Therefore, a small chance exists that the assigned phenotype (based on the genotype test) may be wild-type but the patient may actually have a rare inactivating variant that makes the actual phenotype poor or intermediate metabolizer

This is a rare risk for any genetic test

http://www.cypalleles.ki.se/cyp2d6.htm
Gene-Based Dosing Recommendations
Codeine
CYP2D6 metabolizes codeine to the active metabolite morphine.

Codeine analgesia is closely related to CYP2D6 metabolism

- Ultra-rapid metabolizers
  - Convert codeine to morphine at a greater extent than normal leading to an increased risk of toxic side effects, such as over sedation or respiratory depression
  - Because infants may be more susceptible to adverse effects from morphine, breastfeeding mothers who are ultra-rapid metabolizers should NOT take codeine

- CYP2D6 ultra-rapid metabolizers should NOT receive codeine

• Codeine analgesia is closely related to CYP2D6 metabolism
  – Poor metabolizers
    • Cannot activate the prodrug codeine to morphine and will have no analgesic benefit
• CYP2D6 poor metabolizers should NOT receive codeine
• Oxycodone and tramadol are not a good choice in CYP2D6 ultra-rapid and poor metabolizers because they are also affected by CYP2D6 (hydrocodone is affected by CYP2D6 but to a much lesser extent)
Tramadol

CYP2D6 metabolizes tramadol to a more active metabolite O-desmethyltramadol.

Tramadol analgesia is related to CYP2D6 metabolism

– Ultra-rapid metabolizers
  • Convert tramadol to O-desmethyltramadol at a greater extent than normal leading to an increased risk of side effects

– Poor metabolizers
  • Cannot metabolize tramadol to the more active form O-desmethyltramadol, therefore resulting in little to no analgesic benefit
• CYP2D6 extensive and intermediate metabolizers may receive the usual dose of tramadol
  – Monitor intermediate metabolizers for analgesic response

• Similar to codeine, CYP2D6 ultra-rapid and poor metabolizers should NOT receive tramadol
Oxycodone
Oxycodone

- CYP2D6 metabolizes oxycodone to the active metabolite oxymorphone.
- Oxymorphone is a potent opioid that has a 3 to 5 times higher \( \mu \)-opioid receptor affinity than morphine.
- When compared to morphine, oxymorphone has a higher affinity for the \( \mu \)-opioid receptor than the parent compound oxycodone.

http://www.chem.agilent.com/Library/applications/5990-3815EN.pdf
• Oxycodone analgesia is related to CYP2D6 metabolism

  – Ultra-rapid metabolizers

    • Convert oxycodone to oxymorphone at a greater extent than normal leading to an increased risk of toxic side effects, such as over sedation or respiratory depression

    • Other pain medications such as morphine, HYDROMorphone (e.g.: Dilaudid®), or acetaminophen/hydroCODONE (e.g. Lortab®, Vicodin®) should be considered
• Oxycodone analgesia is related to CYP2D6 metabolism
  – Extensive/Intermediate metabolizers
    • No dosage change
  – Poor metabolizers
    • Other pain medications such as morphine, HYDROMorphone (e.g.: Dilaudid®), or acetaminophen/hydroCODONE (e.g.: Lortab®, Vicodin®) should be considered
Ondansetron
CYP2D6 (along with other CYP450 enzymes) metabolizes ondansetron to major inactive metabolites 7- and 8-hydroxy ondansetron and minor inactive metabolites 6- hydroxy and N-desmethyl ondansetron.

— CYP2D6 ultra-rapid metabolizers have increased metabolism and therapeutic failure is possible. Consider another drug not metabolized by CYP2D6 such as granisetron.

— Data are not convincing that CYP2D6 poor metabolizers have more adverse effects to ondansetron.
Amitriptyline
Amitriptyline

- CYP2C19 metabolizes amitriptyline to an active metabolite: nortriptyline
- CYP2D6 metabolizes amitriptyline and nortriptyline to less active hydroxy-metabolites

• Amitriptyline has a wide range of dosing recommendations depending on the indication
• For treatment of conditions such as depression, patients usually receive a higher dose
• For treatment of conditions such as neuropathic pain, patients usually receive a lower dose
• Therapeutic drug monitoring is available for amitriptyline, and may be a useful adjunct to genetic testing especially in poor, intermediate and ultra-rapid CYP2D6 metabolizers
Amitriptyline

- Amitriptyline’s efficacy is closely related to CYP2D6 and CYP2C19 metabolism
  - Ultra-rapid metabolizers of CYP2C19 and/or CYP2D6
    - Convert amitriptyline to nortriptyline at a greater extent than extensive metabolizers (for CYP2C19)
    - Increased metabolism of amitriptyline to less active compounds compared to extensive metabolizers (for CYP2D6)
    - Lower plasma concentrations increase the probability of therapeutic failure
- Consider an alternative agent not metabolized by CYP2C19 or CYP2D6

Amitriptyline’s efficacy is closely related to CYP2D6 and CYP2C19 metabolism

- **Extensive metabolizers of CYP2C19 or CYP2D6**
  - Normal bioactivation
  - No recommended dosage change

Amitriptyline’s efficacy is closely related to CYP2D6 and CYP2C19 metabolism

- Intermediate metabolizers of CYP2C19 or CYP2D6
  - Reduced metabolism of amitriptyline when compared to extensive metabolizers
  - For CYP2D6 IM patients, consider a 25% reduction of the initial amitriptyline dose and titrate to effect. Utilize therapeutic drug monitoring as appropriate
  - For CYP2C19 IM patients, initiate therapy with the recommended starting doses of amitriptyline

Amitriptyline

- Amitriptyline’s efficacy is closely related to CYP2D6 and CYP2C19 metabolism
  
  - Poor metabolizers of CYP2C19 or CYP2D6
    
    - Greatly reduced metabolism of amitriptyline when compared to extensive metabolizers and an increased likelihood of side effects
    
    - Consider an alternative agent not metabolized by CYP2C19 or CYP2D6
  
- A table providing recommendations for dosing of amitriptyline according to the CYP2D6 and CYP2C19 genotype test results can be found [here](#).

• For more information about CYP2D6 and drug dosing click [here](#).

• For more information about pharmacogenetics visit the following website: [www.pharmgkb.org](http://www.pharmgkb.org)

• For more pharmacogenetic service implementation resources visit the following website: [www.stjude.org/pg4kds/implement](http://www.stjude.org/pg4kds/implement)
What is the activity score for the pharmacogenetic test result of CYP2D6 (*1/*1)2N?

a) 0.5  
b) 1.0  
c) 1.5  
d) 2.0

Correct answer: d
What is the predicted CYP2D6 phenotype for the test result of $CYP2D6\ (*2/*17)2N$?

a) Ultra-rapid metabolizer
b) Extensive metabolizer
c) Intermediate metabolizer
d) Poor metabolizer

Correct answer: b
ZB is experiencing pain following a minor surgical procedure. A clinician wants to prescribe codeine to treat the pain and asks you for the appropriate dose. The patient has a pharmacogenetic test result of *CYP2D6 (*4/*4) duplication.

Based on the pharmacogenetic test result, what recommendation would you give to the clinician?

a) Use label recommended dosing
b) Reduce the initial starting codeine dose by 50%
c) Avoid codeine due an increased risk of adverse events
d) Avoid codeine due to a lack of analgesic effects

Correct answer: d
MJ is about to be prescribed amitriptyline for treatment of depression. The patient has a reported pharmacogenetic test result of $CYP2D6\,*1/**4)2N$. Based on the pharmacogenetic test result, which of the following statements is correct?

a) The patient should not receive amitriptyline due to decreased plasma concentrations of the drug and likely therapeutic failure

b) The patient should not receive amitriptyline due to increased plasma concentrations of the drug and likely development of side effects

c) There is no reason to adjust the dose of amitriptyline based on the $CYP2D6$ genotype test result

d) The patient’s initial dose should be increased by 25%

Correct answer: c
The information in this competency, including but not limited to any text, graphics or images, is for informational and educational purposes only. Although reasonable efforts have been made to ensure that the information provided is current, complete and, where appropriate, based on scientific evidence, St. Jude Children's Research Hospital makes no assurances as to whether the provided information will at all times be current or complete. St. Jude Children's Research Hospital, in offering this document, is not providing medical advice or offering a consultative opinion, and is not establishing a treatment relationship with any given individual. You, therefore, should not substitute information contained herein for your own professional judgment, nor should you rely on information provided herein in rendering a diagnosis or choosing a course of treatment for a particular individual.