Cytochrome P450 2C19 (CYP2C19) Pharmacogenetic Competency
A patient has a reported pharmacogenetic test result of \textit{CYP2C19} *1/*12. What is the assigned phenotype?

a) Ultra-rapid metabolizer (UM)  
b) Intermediate metabolizer (IM)  
c) Poor metabolizer (PM)  
d) Indeterminate
A patient with a reported pharmacogenetic test result of \textit{CYP2C19} *2A/*2A who is receiving clopidogrel is at \___ risk of suffering from an adverse cardiovascular event (e.g. thrombosis) due to treatment failure.

a) Increased  
b) Moderate  
c) Decreased
JH has an indication to start clopidogrel therapy. He has a reported pharmacogenetic test result of CYP2C19 *2A/*3. What is your recommendation to the physician regarding the use of clopidogrel?

a) Use clopidogrel at an increased dose
b) Use clopidogrel at a reduced dose
c) Use clopidogrel at a standard dose
d) Use an alternative antiplatelet agent
Which of the following statements is most correct about a *CYP2C19* *17/*17 genotype?

a) Patients convert clopidogrel to an inactive metabolite to a greater extent than *1/*1 and therefore a decrease in clopidogrel dose is recommended

b) Patients convert clopidogrel to an active metabolite to a greater extent than *1/*1 but no change in clopidogrel dose is recommended

c) Patients convert clopidogrel to an active metabolite to a lesser extent than *1/*1 and therefore a decrease in clopidogrel dose is recommended

d) Patients convert clopidogrel to an active metabolite to a lesser extent than *1/*1 and therefore a change in therapy is recommended
Objectives

• Upon completion of this competency, participants will be able to:
  – Recognize the different CYP2C19 allele variants
  – Describe the different CYP2C19 phenotypes
  – Assign the correct phenotype based upon the allele variants
  – Make therapeutic recommendations for clopidogrel dosing based on a patient's predicted CYP2C19 phenotype
Patient Case

- A 74-year-old patient with severe coronary artery disease started on clopidogrel following a percutaneous coronary intervention (PCI).
- After multiple episodes of restenosis, clopidogrel resistance was suspected.
- Platelet reactivity testing measured while on clopidogrel returned was high (suggestive of resistance).
- \textit{CYP2C19} genotyping revealed that the patient was homozygous for two non-functional alleles (*2/*2 genotype). The patient was classified as having a CYP2C19 poor metabolizer phenotype.
- Switched to prasugrel, reduction in platelet reactivity by 86% and no cardiovascular events since switching agents.

CYP2C19 Pharmacogenetics
CYP2C19

• CYP2C19 is an enzyme that metabolizes some commonly prescribed drugs

• Metabolism by CYP2C19 can either activate or inactivate a drug
  – Clopidogrel is a prodrug that is metabolized to an active form by CYP2C19
  – Amitriptyline is metabolized by CYP2C19 to a less active form
Genetic variations in the *CYP2C19* gene may lead to changes in metabolic activity of the CYP2C19 enzyme (increased or reduced function)
CYP2C19 Allele Variants

• *CYP2C19* alleles are characterized into different groups:
  – Wild-type (normal function) alleles
  – Reduced function alleles
  – Increased function alleles
  – Uncharacterized alleles
• **CYP2C19** wild-type (normal function) allele:
  – This allele encodes for CYP2C19 enzymes with normal metabolic function
  – *1

Certain *CYP2C19* alleles are characterized as reduced function alleles

- These alleles will encode for a CYP2C19 enzyme that has little or no metabolic function

Reduced function *CYP2C19* alleles include:

• **CYP2C19** has an allele characterized by a increased expression of the enzyme
  – This results in increased CYP2C19 metabolic activity compared to the wild-type (normal function) allele

• The **CYP2C19** gain-of-function allele that is test for the most in clinical practice is the *17 allele

For certain CYP2C19 alleles, the function of the enzyme is unknown and considered uncharacterized.

CYP2C19 uncharacterized alleles include:


Assigning a CYP2C19 Phenotype
The assignment of CYP2C19 phenotype is based on the two alleles that the patient carries (also called genotype or diplotype).

There are four CYP2C19 phenotypes:
- Ultra-rapid metabolizer (UM)
- Extensive metabolizer (EM)
- Intermediate metabolizer (IM)
- Poor metabolizer (PM)

# CYP2C19 Phenotypes

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Definition</th>
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| Ultra-rapid Metabolizer (UM) | - Two copies of an increased function allele.  
                              | - One copy of a normal function allele and one copy of an increased function allele. |
| Extensive Metabolizer (EM)  | - Two copies of a normal function allele.                                  |
| Intermediate Metabolizer (IM) | - One copy of a reduced function allele and one copy of a normal function allele.  
                                     | - One copy of an increased function allele (*17) with one copy of a reduced function allele (either *2, *2A and *2B). |
| Poor Metabolizer (PM)       | - Two copies of a reduced function allele.                                 |
| Indeterminate              | - Two copies of an indeterminate function allele.  
                              | - One copy of an indeterminate function allele with one copy of a known function allele.  
                              | - One copy of an increased function allele with one copy of a reduced function allele (other than *2, *2A and *2B). |

1 As per the CYP2C19/Clopidogrel CPIC guideline update (2013): The currently available evidence indicates that the *17 gain-of-function allele is unable to completely compensate for the *2 loss-of-function allele; however, these data have not been consistently replicated and is therefore a provisional classification.
CYP2C19 Phenotypes

• **Ultra-rapid Metabolizers (UM)**
  — Have CYP2C19 enzyme function higher than normal
  — Approximately 17% of the population
  — Diploptype examples:
    • *17/*17
    • *1/*17
CYP2C19 Phenotypes

- Extensive (normal) metabolizers (EM)
  - Have normal CYP2C19 enzyme function
  - Homozygous wild-type/normal
  - Approximately 43% of the population
  - Patient carrying two functional alleles
  - Diplotype examples:
    - *1/*1
**CYP2C19 Phenotypes**

- **Intermediate metabolizers (IM)**
  - Have decreased CYP2C19 enzyme function. The activity is in between extensive and poor metabolizer patients
  - Approximately 30% of the population
  - Diplotype examples:
    - *1/*2A
    - *2A/*17
CYP2C19 Phenotypes

• Poor metabolizers (PM)
  — Have little or no CYP2C19 enzyme function
  — Approximately 10% of the population
  — Patient carrying two reduced-function alleles
  — Diploftype examples:
    • *2A/*2A
    • *2A/*2B
CYP2C19 Phenotypes

- **Indeterminate**
  - The expected phenotype cannot be determined based upon the *CYP2C19* genotype result
  - For example, a patient may have two copies of an indeterminate function allele or one copy of an indeterminate function allele and one copy of a known function allele
    - *1/*12
    - *12/*14
CYP2C19 Phenotypes

• Phenotypes associated with *17 allele
  – Only a few diplotypes which include the *17 allele have known functional activity:
    • *1/*17 is assigned an ultra-rapid metabolizer phenotype
    • *2/*17, *2A/*17 and *2B/*17 are assigned an intermediate function phenotype

  – *17 plus any other allele is assigned an indeterminate phenotype
CYP2C19 Phenotypes

- Ultrarapid Metabolizer - very high activity
- Extensive Metabolizer - normal activity
- Intermediate Metabolizer - lower activity
- Poor Metabolizer - low or no activity

* The exact percent of each phenotype group varies by ethnicity
• **CYP2C19** allele frequencies are dependent on ethnicity

• *2 and *3 alleles are the most common variations
  – *2 allele:
    • ~30% of Asians
    • ~15% of Caucasians and African-Americans
  – *3 allele:
    • ~8% of Asians
    • Less than 1% in Caucasians and African-Americans

• Prevalence of poor metabolizer phenotype:
  – Up to 25% of Asians
  – ~5% of Caucasians and African-Americans
Gene-Based Dosing Recommendations
Clopidogrel
• Clopidogrel is an antiplatelet drug which inhibits ADP-induced platelet aggregation

• Clopidogrel is commonly used in patients undergoing percutaneous coronary intervention (PCI) with stent placement

• Other indications:
  – Acute coronary syndrome (ACS)
  – Stroke
  – Peripheral artery disease

• The 2013 CPIC guideline on clopidogrel and CYP2C19 mainly focuses on ACS/PCI patients

Clopidogrel

- Clopidogrel is a pro-drug that requires hepatic bioactivation
  - 85% of the drug is hydrolyzed by carboxylesterase 1, leaving only 15% to be converted to the active form
- The activation of clopidogrel is a two step process
  - Clopidogrel is converted to 2-oxoclopidogrel via CYP2C19 (45%), CYP1A2 (36%), and CYP2B6 (19%)
  - 2-oxoclopidogrel is converted to the active thiol metabolite via CYP3A4/5 (40%), CYP2B6 (33%), CYP2C19 (21%), and CYP2C9 (7%)

Clopidogrel

Clopidogrel’s anti-platelet effect is closely related to CYP2C19 metabolism

- **Ultra-rapid metabolizers**
  - Convert clopidogrel to the active metabolite at a greater extent than normal
  - Possible increase in antiplatelet activity
  - No recommended dosage change

- **Extensive metabolizers**
  - Normal bioactivation
  - No recommended dosage change
• Clopidogrel anti-platelet effect is closely related to CYP2C19 metabolism
  
  – **Intermediate metabolizers**
  
  • Reduced bioactivation of clopidogrel to the active metabolite
  
  • Decreased platelet inhibition leading to increased residual platelet aggregation
  
  • Increased risk for adverse cardiovascular events (e.g., thrombosis)

• **CYP2C19 intermediate metabolizers generally should NOT receive clopidogrel**
  
  • Consider alternatives such as prasugrel or ticagrelor
Clopidogrel

- Clopidogrel anti-platelet effect is closely related to CYP2C19 metabolism
  - **Poor metabolizers**
    - Poor bioactivation of clopidogrel to the active metabolite
    - Significantly reduced platelet inhibition leading to increased residual platelet aggregation
    - Significant increased risk for adverse cardiovascular events (e.g., thrombosis)
- **CYP2C19 poor metabolizers should NOT receive clopidogrel**
  - Consider alternatives such as prasugrel or ticagrelor
Amitriptyline
• CYP2C19 metabolizes amitriptyline to an active metabolite: nortriptyline

• CYP2D6 metabolizes amitriptyline and nortriptyline to less active hydroxy-metabolites

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 CYP2C19 and clopidogrel dosing click [here](#).

• For more information about CYP2C19 and amitriptyline 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)
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d) Indeterminate

Correct answer: d
A patient with a reported pharmacogenetic test result of CYP2C19 *2A/*2A who is receiving clopidogrel is at ____ risk of suffering from an adverse cardiovascular event (e.g. thrombosis) due to treatment failure.

a) Increased
b) Moderate
c) Decreased

Correct answer: a
JH has an indication to start clopidogrel therapy. He has a reported pharmacogenetic test result of CYP2C19 *2A/*3. What is your recommendation to the physician regarding the use of clopidogrel?

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c) Use clopidogrel at a standard dose
d) Use an alternative antiplatelet agent

Correct answer: d
Which of the following statements is most correct about a CYP2C19 *17/*17 genotype?

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Correct answer: b
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