Dihydropyrimidinedehydrogenase (DPYD) Pharmacogenetic Competency
A patient has a reported pharmacogenetic test result of *DPYD* *1/*2. What is the assigned phenotype?

a) Normal function
b) Low function
c) Deficient function
d) Indeterminate function
A patient with a reported pharmacogenetic test result of DPYD *2/*2 who is receiving capecitabine is at ____ risk of suffering from toxicity (e.g. neurotoxicity, myelosuppression, diarrhea).

a) Increased
b) Moderate
c) Decreased
HM is a 55 yo male presenting with an indication for capecitabine. He has normal kidney and liver function and has a reported pharmacogenetic test result of *DPYD* *1/*9A. What is your recommendation to the physician regarding the use of capecitabine?

a) Use capecitabine with a dosage increase
b) Use capecitabine with a dosage decrease
c) Use capecitabine with standard dosing
d) Use an alternative anticancer agent
Objectives

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

- A 75-year-old patient with metastatic pancreatic adenocarcinoma received a fluorouracil-containing chemotherapy regimen. He developed grade 3 coagulopathy and neurologic toxicity, grade 4 thrombocytopenia and died of the side effects of fluorouracil (5-FU)
- He was found to be a carrier of a non-functional allele (*2) and a low DPYD function phenotype

DPYD Advanced Pharmacogenetics
DPYD

- DPYD is an enzyme that metabolizes fluoropyrimidines like fluorouracil (5-FU) and capecitabine to an inactive metabolite: DHFU
- Genetic variations in the *DPYD* gene can alter DPYD enzyme function (sometimes called DPD)

DPYD ALLELE VARIANTS
The sensitivity for the *DPYD* genotype test is 31%; therefore, the absence of variant alleles does not rule out a DPYD deficiency.

The sensitivity is lower than in other genes. For example the *TPMT* genotype test has a sensitivity of ~90%.

DPYD Allele Variants

• *DPYD* alleles are characterized into different groups:
  – Normal function alleles
  – Non-functional alleles
  – Possible non-functional alleles
    • These alleles have reduced or undetectable function in a few case reports
  – Indeterminate function alleles

The following table summarizes *DPYD* alleles and their known associated *DPYD* function:

<table>
<thead>
<tr>
<th>Functional Status</th>
<th>Alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-functional</td>
<td>*2, *2A, *13, rs67376798</td>
</tr>
</tbody>
</table>
ASSIGNING DPYD PHENOTYPES
The assignment of a DPYD phenotype is based on the function of the two alleles that the patient carries (also called genotype or diplotype).

There are 3 possible phenotypes for DPYD:

- Normal function
- Low function
- Deficient function

In some instances the DPYD phenotype may be unknown and the following phenotype terminology is used:

- Indeterminate DPYD function

DPYD Phenotypes

• Normal DPYD function
  – Approximately 96% of patients
  – Example diplotype: *1/*1, *1/*9A

DPYD Phenotypes

• Low DPYD function
  – Approximately 4% of patients
  – An individual carrying one functional allele (*1, *9A) and one non-functional allele (*2, *2A, *13, or rs67376798)
  – Example diplotype: *1/*2, *1/*13

DPYD Phenotypes

- Deficient DPYD function
  - Approximately 0.2% of patients
  - An individual carrying two copies of a non-functional allele (e.g. *2, 2A, *13, or rs67376798)
  - Example diplotypes: *2/*2, *2/*13
DPYD Phenotypes

• Indeterminate DPYD function
  • Expected phenotype cannot be determined based upon the *DPYD* genotype result
  • An individual carrying one or more alleles with indeterminate function

### DPYD Phenotypes: Summary

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal function</td>
<td>An individual carrying two copies of a functional allele (e.g. *1/*1, *1/*9A)</td>
</tr>
<tr>
<td>Low function</td>
<td>An individual carrying one functional allele (e.g. *1) plus one non-functional allele (e.g. *2, *2A *13, or rs67376798)</td>
</tr>
<tr>
<td>Deficient function</td>
<td>An individual carrying two copies of a non-functional allele (e.g. *2, *2A, *13, or rs67376798)</td>
</tr>
<tr>
<td>Indeterminate function</td>
<td>An individual carrying one or more alleles with indeterminate function</td>
</tr>
</tbody>
</table>

DPYD Phenotypes

* The exact percent of each phenotype group varies by ethnicity

GENOTYPE-BASED DOSING RECOMMENDATIONS FOR FLUOROPYRIMIDINES
Fluorouracil/Capecitabine

Capecitabine is a pro-drug that is converted to 5-FU when it enters into the cell.

5-FU is then converted into FUTP and FdUTP leading to premature termination of RNA and DNA synthesis.

FdUMP, another product of 5-FU, inhibits thymidylate synthetase depleting the pool of nucleotides for DNA synthesis.

DPYD inactivates 5-FU in the liver and intracellularly.

Low DPYD function caused by variations in the DPYD gene results in increased availability of 5-FU to exert its activity, increasing the potential for toxicity.
• Normal DPYD function (96% of population)
  – Normal DPYD function puts the patient at “normal” risk for fluoropyrimidine toxicity (*1/*1, *1/*9A)
    • Myelosuppression, mucositis, neurotoxicity, hand-foot syndrome, and diarrhea
  – No reason to adjust the dose based on DPYD genotype
  – Note: Currently, DPYD genotype tests have a high false negative rate.
    • A normal function genotype means that none of other variants tested for by the assay were detected; it is a diagnosis of exclusion. The patient may have reduced function variants that are not detected by the assay
    • To determine whether a patient’s DPYD activity is low in such patients, one must measure DPYD activity in the blood. Unfortunately at this time, it is not possible to verify a patient’s phenotype via a CLIA certified assay

• Low DPYD function (4% of population)
  – Decreased DPYD function (30–70% of normal)
  – Increased risk for severe or fatal drug toxicity when treated with fluoropyrimidine drugs:
    • Myelosuppression, mucositis, neurotoxicity, hand-foot syndrome, and diarrhea
  – Consider at least a 50% reduction in starting dose or non-fluoropyrimidine containing regimen
  – Titrate dose based on toxicity and tolerance

Deficient DPYD function (0.2% of population)

- Complete DPYD deficiency (*2/*2, *13/*13)
- These patients may have neurological signs and symptoms (such as seizures and mental retardation) even in the absence of drug exposure
- Increased risk for severe or even fatal drug toxicity when treated with fluoropyrimidine drugs:
  - Myelosuppression, mucositis, neurotoxicity, hand-foot syndrome, and diarrhea
- Do not use a fluoropyrimidine

• For more information about DPYD and fluoropyrimidines here.

• For more information about pharmacogenetics visit the following website: www.pharmgkb.org

• For more pharmacogenetic service implementation resources visit the following website: www.stjude.org/pg4kds/implement
A patient has a reported pharmacogenetic test result of $DPYD \, *1/*2$. What is the assigned phenotype?

a) Normal function
b) Low function
c) Deficient function
d) Indeterminate function

Correct answer: b
A patient with a reported pharmacogenetic test result of $DPYD\ *2/*2$ who is receiving capecitabine is at ____ risk of suffering from toxicity (e.g. neurotocixity, myelosuppression, diarrhea).

a) Increased

b) Moderate

c) Decreased

Correct answer: a
HM is a 55 yo male presenting with an indication for capecitabine. He has normal kidney and liver function and has a reported pharmacogenetic test result of *DPYD* *1/*9A. What is your recommendation to the physician regarding the use of capecitabine?

a) Use capecitabine with a dosage increase
b) Use capecitabine with a dosage decrease
c) Use capecitabine with standard dosing
d) Use an alternative anticancer agent

Correct answer: c
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