Dihydropyrimidine Dehydrogenase (*DPYD*) Pharmacogenetic Competency

Updated on 6/2015

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

Pre-test Question # 1

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

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

Pre-test Question # 2

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

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

Pre-test Question # 3

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

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

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**

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

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

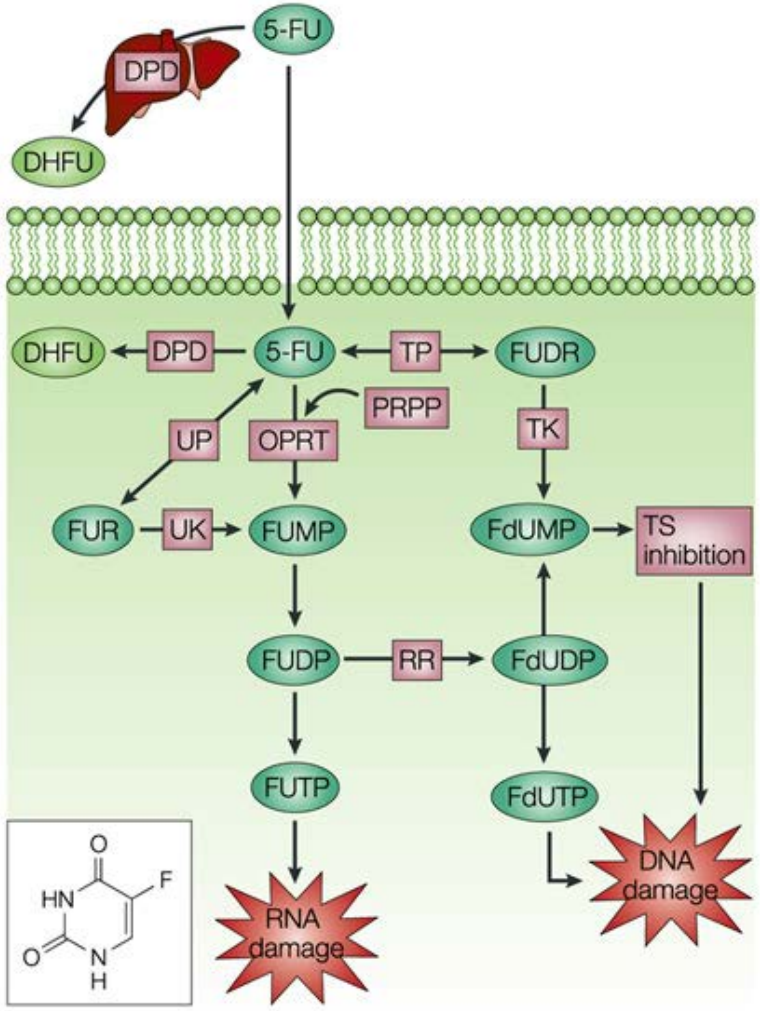
Saif MW, et al. *Cancer Chemother Pharmacol*. 2007;60:503–7.

DPYD Advanced Pharmacogenetics

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

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)



Nature Reviews | Cancer

Longley DB, et al. *Nat Rev Cancer*. 2003;3:330-8.

DPYD ALLELE VARIANTS

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

Genotype Sensitivity

- 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%.

Caudle KE, et al. *Clin Pharmacol Ther*. 2013;94:640-5.
Relling MV, et al. *Clin Pharmacol Ther.* 2014;93:324-5.

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

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

Caudle KE, et al. *Clin Pharmacol Ther*. 2013;94:640-5.

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

DPYD

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

Functional Status	**Alleles**
Functional	*1, *9A, *4, *5, *6
Non-functional	*2, *2A, *13, rs67376798
Possible non-functional	*3, *7, *8, *9B, *10, *11, *12

Adapted from Caudle KE, et al. *Clin Pharmacol Ther*. 2013;94:640-5.

ASSIGNING DPYD PHENOTYPES

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

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

Caudle KE, et al. *Clin Pharmacol Ther*. 2013;94:640-5.

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

DPYD Phenotypes

- Normal DPYD function
  - Approximately 96% of patients
  - An individual carrying two copies of a functional allele (*1, *9A, *4, *5, *6)
  - Example diplotype: *1/*1, *1/*9A

Caudle KE, et al. *Clin Pharmacol Ther*. 2013;94:640-5.

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

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

Caudle KE, et al. *Clin Pharmacol Ther*. 2013;94:640-5.

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

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

Caudle KE, et al. *Clin Pharmacol Ther*. 2013;94:640-5.

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

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

Caudle KE, et al. *Clin Pharmacol Ther*. 2013;94:640-5.

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

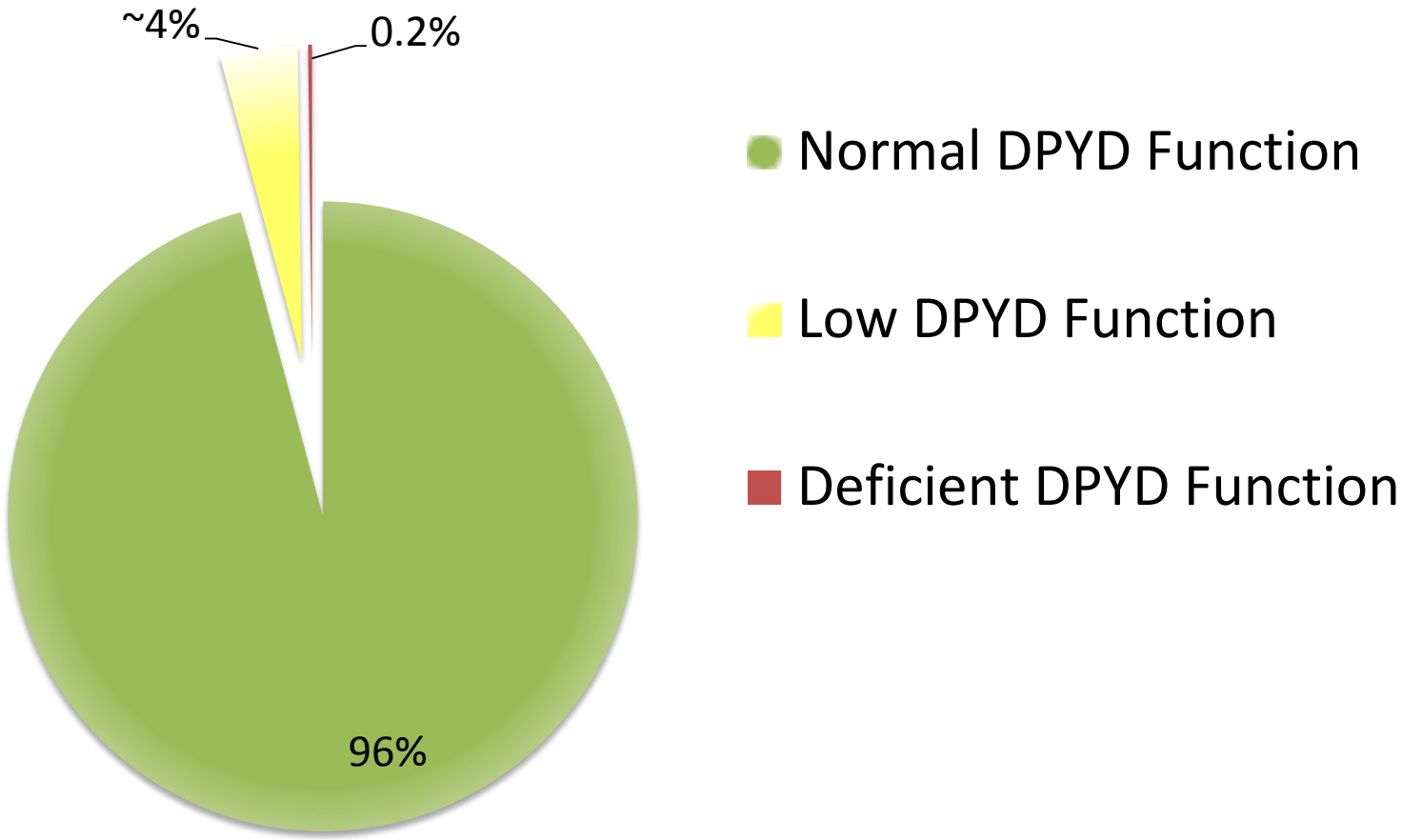
DPYD Phenotypes: Summary

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

Adapted from Caudle KE, et al. *Clin Pharmacol Ther*. 2013;94:640-5.

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

DPYD Phenotypes



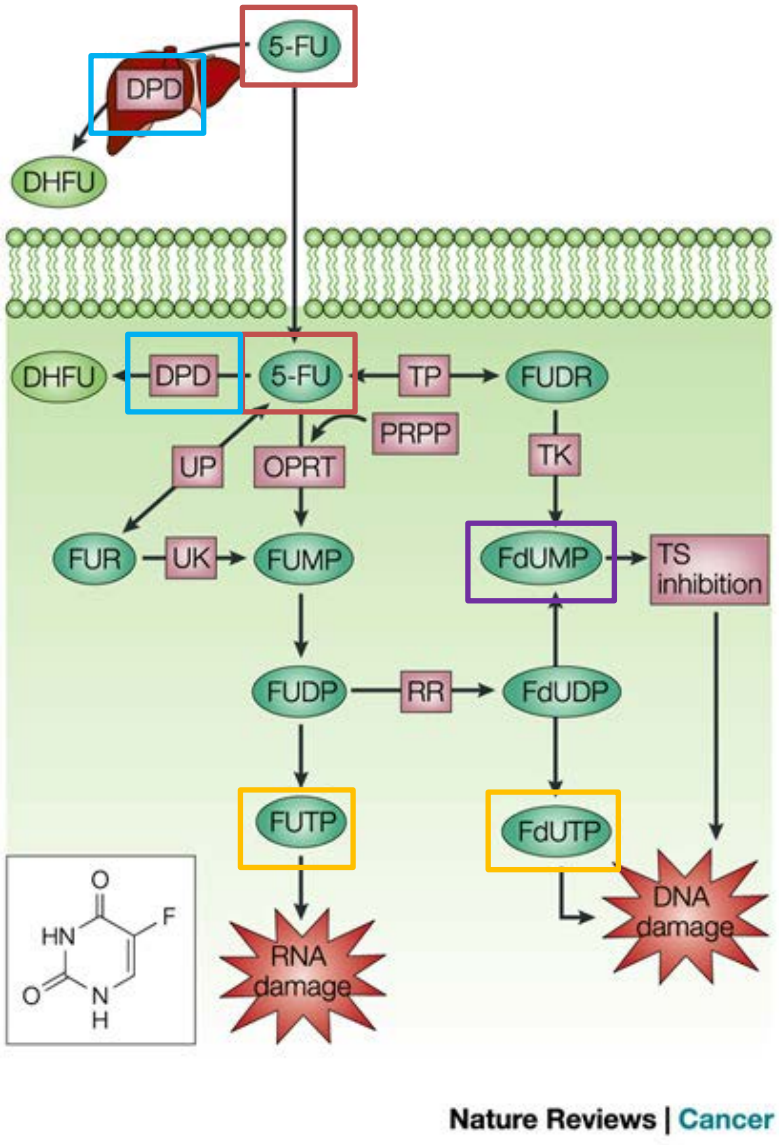
*** The exact percent of each phenotype group varies by ethnicity**

Caudle KE, et al. *Clin Pharmacol Ther*. 2013;94:640-5.

GENOTYPE-BASED DOSING RECOMMENDATIONS FOR FLUOROPYRIMIDINES

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

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.

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

Fluorouracil/Capecitabine

- 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

Caudle KE, et al. *Clin Pharmacol Ther*. 2013;94:640-5.

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

Fluorouracil/Capecitabine

- 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

Caudle KE, et al. *Clin Pharmacol Ther*. 2013;94:640-5.

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

Fluorouracil/Capecitabine

- 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

Caudle KE, et al. *Clin Pharmacol Ther*. 2013;94:640-5.

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

For More Information…

- **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**

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

Question # 1

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

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

Question # 2

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

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

Question # 3

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

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

Legal Disclaimer

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.