

Dihydropyrimidine Dehydrogenase (DPYD), 3 Variants

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Dihydropyrimidine dehydrogenase is an enzyme encoded by the *DPYD* gene and is responsible for the metabolism of 5-fluorouracil (5-FU), the most frequently used chemotherapeutic drug in the treatment of colorectal adenocarcinomas. Germline variants in *DPYD* affect enzyme production, which may result in dose-related toxicity or in a reduction of treatment effectiveness.

Disease Overview

Physiology

When 5-FU is metabolized in the body

- Approximately 80% is catabolized by the enzyme dihydropyrimidine dehydrogenase (DPD) into an *inactive* form, dihydro 5-FU, and excreted in urine
- Remaining drug is metabolized into an *active* form which inhibits the synthesis of both DNA and RNA by
 - Direct incorporation of cytotoxic metabolites (5-FUTP and 5-FdUTP) into nucleic acids
 - Competitive inhibition of the thymidylate synthase (TYMS) enzyme

Treatment Issues

- Intravenous 5-FU: Adrucil (5-fluorouracil)
- Oral 5-FU prodrugs: Xeloda (capecitabine), Uftoral (tegafur/uracil)
- Grade III-IV drug toxicity attributed to 5-FU occurs in approximately 16% of individuals
- Germline variants in the *DPYD* gene can lead to reduced 5-FU catabolism and result in grade III-IV 5-FU toxicity
 - Complications include hematologic, gastrointestinal, and dermatologic symptoms as well as toxicity-related death
 - Clinical testing for variants that alter 5-FU metabolism may aid in patient care

Clinical Issues (5-FU Dosing)

- Homozygous or compound heterozygous *DPYD* gene variants
 - Associated with DPD enzyme deficiency
 - Avoidance of fluoropyrimidine therapy is recommended
 - An alternate drug should be selected
- Heterozygous *DPYD* gene variants
 - Associated with 30-70% of normal DPD activity
 - Fluoropyrimidine therapy should be initiated with reduced dosing
 - Approximately 25-50% of a standard dose is recommended
 - Titration of dose based on patient tolerability and therapeutic drug monitoring
- Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing available at www.pharmgkb.org/gene/PA145

Genetics

Gene

DPYD

Variants Tested

Featured ARUP Testing

[Dihydropyrimidine Dehydrogenase \(DPYD\), 3 Variants 2012166](#)

Method: Polymerase Chain Reaction (PCR)/Fluorescence Monitoring

Predicts risk of dose-related toxicity to 5-FU therapy

DPYD Gene Variants		
DPYD Variant	Alternative Name(s)	Predicted Consequence in Patients Receiving 5-FU
c.1679T>G	DPYD*13, rs55886062	No DPD activity; increased toxicity risk
c.1905+1G>A	DPYD*2A, IVS14+1 G>A, rs3918290	No DPD activity; increased toxicity risk
c.2846A>T	rs67376798	Decreased DPD activity; increased toxicity risk

See www.pharmgkb.org for allele frequency and other data about these variants.

Test Interpretation

Results

Positive

- *DPYD* gene variant detected
 - Predicts decreased DPD enzymatic activity
 - Associated with an increased risk for grade III-IV 5-FU toxicity

Negative

- No variants detected in *DPYD*: predictive of *1 functional alleles

Limitations

- Only targeted variants in the *DPYD* gene will be detected
- Rare diagnostic errors may occur due to rare sequence variations
- Genetic and/or nongenetic factors not detected by this test may affect 5-FU drug metabolism and efficacy and the risk for toxicity
- Genotyping does not replace the need for therapeutic drug monitoring or clinical observation
- Lack of detection of the targeted *DPYD* variants does not rule out risk for 5-FU toxicity or predict degree of responsiveness to 5-FU

Additional Resources

Caudle KE, Thorn CF, Klein TE, et al. [Clinical Pharmacogenetics Implementation Consortium guidelines for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing](#). *Clin Pharmacol Ther*. 2013;94(6):640-645.

Related Information

[Colorectal \(Colon\) Cancer](#)
[Germline Pharmacogenetics - PGx](#)

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