Dihydropyrimidine Dehydrogenase (DPYD), 3 Variants

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](http://www.pharmgkb.org/gene/PA145)

Genetics

Gene

DPYD

Variants Tested

<table>
<thead>
<tr>
<th>DPYD Variant</th>
<th>Alternative Name(s)</th>
<th>Predicted Consequence in Patients Receiving 5-FU</th>
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Tests to Consider

Dihydropyrimidine Dehydrogenase (DPYD), 3 Variants 2012166

Method: Polymerase Chain Reaction/Fluorescence Monitoring

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


### Related Information

**Colorectal (Colon) Cancer**
**Germline Pharmacogenetics - PGx**