Dihydropyrimidine Dehydrogenase (DPYD)

Last Literature Review: April 2019 Last Update: December 2025

Dihydropyrimidine dehydrogenase, an enzyme encoded by the *DPYD* gene, is responsible for metabolizing 5-fluorouracil (5-FU), a chemotherapeutic drug frequently used to treat many types of cancer, including colorectal adenocarcinomas. Germline variants in *DPYD* affect enzyme production, which may result in dose-related toxicity or in a reduction of treatment effectiveness.[1]

For more information on pharmacogenetic testing, refer to the ARUP Consult Germline Pharmacogenetics - PGx topic.

Featured ARUP Testing

Dihydropyrimidine Dehydrogenase (DPYD) 2012166

Method: Polymerase Chain Reaction (PCR)/Fluorescence Monitoring

The test predicts risk of dose-related toxicity to 5-FU therapy.

For more information about combined *DPYD* and *UGT1A1* testing, refer to the Dihydropyrimidine Dehydrogenase (*DPYD*) and UPD Glucuronosyltransferase 1A1 (*UGT1A1*) Genotyping Test Fact Sheet.

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
- Heterozygous *DPYD* gene variants
  - Associated with 30-70% of normal DPD activity
- Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing available at ClinPGx[2]

Genetics

Gene

DPYD

Variants Tested

DPYD Gene Variants		
***DPYD* Variant**	**Alternative Name(s)**	**Predicted Consequence in Patients Receiving 5-FU**
c.1024G>A	rs183385770	No DPD activity; increased toxicity risk
c.1129-5923C>G	rs75017182	Decreased DPD activity; increased toxicity risk
c.1774C>T	rs59086055	No DPD activity; increased toxicity risk
c.2279C>T	rs112766203	Decreased DPD activity; increased toxicity risk
c.557A>G	rs115232898	Decreased DPD activity; increased toxicity risk
c.868A>G	rs146356975	Decreased DPD activity; increased toxicity risk
c.1679T>G	*DPYD*13*, rs55886062	No DPD activity; increased toxicity risk
c.1905+1G>A	*DPYD*2A*, rs3918290	No DPD activity; increased toxicity risk
c.2846A>T	rs67376798	Decreased DPD activity; increased toxicity risk

See ClinPGx[3] 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 allele

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

References

1. Dean L, Kane M. Fluorouracil therapy and DPYD genotype. In: Pratt VM, Scott SA, Pirmohamed M, et al, eds. *Medical Genetics Summaries*. Bethesda, Maryland. Updated Jan 2021; accessed Aug 2024.

2. ClinPGx. DPYD. Accessed Feb 2025.

3. ClinPGx. Accessed Nov 2024.

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