Test Definition: DPYDZ

Dihydropyrimidine Dehydrogenase, DPYD Full Gene Sequencing, Varies

Overview

Useful For

Identifying individuals at increased risk of toxicity when considering 5-fluorouracil and capecitabine chemotherapy treatment

Identifying common and rare variants associated with decreased or absent dihydropyrimidine dehydrogenase (DPD) enzyme activity in individuals with suspected DPD deficiency

Genetics Test Information

This is a pharmacogenomics test associated with 5-fluorouracil and capecitabine drug sensitivity. Biallelic variation in the *DPYD* gene is also associated with dihydropyrimidine dehydrogenase deficiency.(1) Individuals who have variations identified in *DPYD* may benefit from genetic consultation.

This full gene sequencing test detects common, established *DPYD* variants known to impact enzyme activity (eg, *2A, *7, *8, *10, *13, rs67376798, rs75017182, rs115232898) as well as rare sequence variants classified as variant of uncertain significance, likely pathogenic, or pathogenic.

Special Instructions

- Informed Consent for Genetic Testing
- Pharmacogenomic Association Tables
- Blood Spot Collection Card-Spanish Instructions
- Blood Spot Collection Card-Chinese Instructions
- Informed Consent for Genetic Testing (Spanish)
- Blood Spot Collection Instructions

Method Name

Polymerase Chain Reaction (PCR) followed by DNA Sequence Analysis

NY State Available

Yes

Specimen

Specimen Type

Varies

Ordering Guidance

This test and DPYDQ / Dihydropyrimidine Dehydrogenase Genotype, Varies are both used to test for genetic variants in the *DPYD* gene that are associated with fluoropyrimidine toxicity. This test can detect rare variants in addition to

common variants and is the appropriate test for diagnosis of dihydropyrimidine dehydrogenase deficiency. Additionally, this test is expected to have an overall higher detection rate than DPYDQ, particularly for individuals of non-European ancestry.

Shipping Instructions

Specimen preferred to arrive within 96 hours of collection.

Specimen Required

Submit only 1 of the following specimens:

Specimen Type: Whole blood
Container/Tube: Lavender top (EDTA)
Specimen Volume: 3 mL
Collection Instructions:
1. Invert several times to mix blood.
2. Send whole blood specimen in original tube. **Do not aliquot.**
Specimen Stability Information: Ambient (preferred) 9 days/Refrigerated 30 days
Additional Information: To ensure minimum volume and concentration of DNA is met, the preferred volume of blood must be submitted. Testing may be canceled if DNA requirements are inadequate.

Specimen Type: Saliva
Patient Preparation: Patient should not eat, drink, smoke, or chew gum 30 minutes prior to collection.
Supplies: Saliva Swab Collection Kit (T786)
Specimen Volume: 1 Swab
Collection Instructions: Collect and send specimen per kit instructions.
Specimen Stability Information: Ambient 30 days
Additional Information: Due to lower quantity/quality of DNA yielded from saliva, some aspects of the test may not perform as well as DNA extracted from a whole blood sample. When applicable, specific gene regions that were unable to be interrogated will be noted in the report. Alternatively, additional specimen may be required to complete testing.

Forms

1. **New York Clients-Informed consent is required.** Document on the request form or electronic order that a copy is on file. The following documents are available in Special Instructions:
-Informed Consent for Genetic Testing (T576)
-Informed Consent for Genetic Testing (Spanish) (T826)
2. If not ordering electronically, complete, print, and send a Therapeutics Test Request (T831) with the specimen.

Specimen Minimum Volume

Blood: 0.45 mL; Saliva: See Specimen Required

Reject Due To

All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Varies		

Clinical & Interpretive

Clinical Information

5-Fluorouracil (5-FU) and its orally administered prodrug, capecitabine, are fluoropyrimidine-based chemotherapeutic agents that are widely used for the treatment of colorectal cancer and other solid tumors.

The *DPYD* gene encodes dihydropyrimidine dehydrogenase (DPD), the rate-limiting enzyme for fluoropyrimidine catabolism, which eliminates over 80% of administered 5-FU. Genetic variation in *DYPD* is the main cause for variability in DPD activity and can lead to partial or complete enzymatic deficiency (3-5% or 0.2% of the population, respectively).(2,3) Patients who are deficient in DPD are at an increased risk for adverse effects and toxicity when undergoing 5-FU treatment.(4) In addition, disease-causing homozygous or compound heterozygous variants within *DPYD* are associated with DPD deficiency. DPD deficiency shows a wide range of severity, from asymptomatic (albeit at risk for drug toxicity) to neurological problems, including seizures and intellectual disability, delayed motor development, and microcephaly.

DPYD variants impacting the metabolic pathway of fluoropyrimidines have been shown to contribute to the differences in clinical outcomes, including toxicity and tumor response. Common *DPYD* variants that result in no activity include c.1905+1G>A (*2A), c.299_302del (*7), c.703C>T (*8), c.2983G>T (*10), and c.1679T>G (*13). Common *DPYD* variants resulting in reduced activity include c.2846A>T (rs67376798), c.1129-5923C>G (rs75017182, also part of the HapB3 haplotype), and c.557A>G (rs115232898). In addition to these common variants, this sequencing test may also detect rare variants that impact DPD activity.

Reference Values

DPYD Total Activity Score: 2

DPYD Phenotype: Normal metabolizer

An interpretive report will be provided.

Interpretation

Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics recommendations as a guideline.(5) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Additionally variant functional status and activity score are assigned using the most recent published Clinical Pharmacogenetics Implementation Consortium (CPIC) recommendations as a guideline.(2)

For additional information regarding pharmacogenomic genes and their associated drugs, see the Pharmacogenomic Association Tables. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

Cautions

Samples may contain donor DNA if obtained from patients who received non-leukocyte reduced blood transfusions or allogeneic hematopoietic stem cell transplantation. Results from samples obtained under these circumstances may not accurately reflect the recipient's genotype. For individuals who have received blood transfusions, the genotype usually reverts to that of the recipient within 6 weeks. For individuals who have received allogeneic hematopoietic stem cell transplantation, a pretransplant DNA specimen is recommended for testing.

DPYD genetic test results in patients who have undergone liver transplantation may not accurately reflect the patient's dihydropyrimidine dehydrogenase (DPD) status.

Rare genetic variants in the primer binding regions can affect the testing, and ultimately, the genotype assessment made, including false-negative or false-positive results.

Test results should be interpreted in the context of clinical findings, family history, and other laboratory data. Large deletions or rearrangements are not detected by this assay, and these may affect DPD protein expression and fluoropyrimidine-related adverse effects or tumor response.

Sometimes a genetic alteration of unknown significance may be identified. In this case, testing of appropriate family members may be useful to determine pathogenicity of the alteration.

This test is not designed to provide specific dosing or drug selection recommendations and is to be used as an aid to clinical decision making only. Drug-label guidance should be used when dosing patients with medications regardless of the predicted phenotype.

Clinical Reference

1. OMIM. 274270 Dihydropyrimidine dehydrogenase deficiency. Johns Hopkins University; 1986. Updated October 4, 2023. Accessed June 4, 2024. Available from www.omim.org/entry/274270
2. Amstutz U, Henricks LM, Offer SM, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing: 2017 Update. Clin Pharmacol Ther. 2018;103(2):210-216
3. Morel A, Boisdron-Celle M, Fey L, et al. Clinical relevance of different dihydropyrimidine dehydrogenase gene single nucleotide polymorphisms on 5-fluorouracil tolerance. Mol Cancer Ther. 2006;5(11):2895-2904
4. U.S. Food and Drug Administration (FDA). Table of Pharmacogenomic Biomarkers in Drug Labeling. FDA; Updated February 2, 2024. Accessed June 4, 2024. Available at: www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm
5. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424
6. Offer SM, Fossum CC, Wegner NJ, et al. Comparative functional analysis of DPYD variants of potential clinical relevance to dihydropyrimidine dehydrogenase activity. Cancer Res. 2014;74(9):2545-2554

Performance

Method Description
Genomic DNA is extracted from whole blood or saliva. The *DPYD* (NM_000110.3) gene is amplified by polymerase chain reaction (PCR). The PCR products are then purified and sequenced in both directions using fluorescent dye-terminator chemistry. Sequencing products are separated on an automated sequencer and trace files analyzed for variations in all exons and intron/exon boundaries, plus the deeply intronic variant c.1129-5923C>G (rs75017182), using mutation detection software and visual inspection.(Unpublished Mayo method)

PDF Report
No

Day(s) Performed
Monday through Friday

Report Available
5 to 10 days

Specimen Retention Time
Whole blood/Saliva: 2 weeks; Extracted DNA: 3 months

Performing Laboratory Location
Mayo Clinic Laboratories - Rochester Main Campus

Fees & Codes

Fees
- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact Customer Service.

Test Classification
This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. It has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information
81232

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
DPYDZ	DPYD Full Gene Sequencing, V	94198-9

Result ID	Test Result Name	Result LOINC® Value

618600	DPYD Total Activity Score	104665-5
618601	DPYD Phenotype	79719-1
618602	Result Details	82939-0
618603	Interpretation	69047-9
618604	Method	85069-3
618605	Disclaimer	62364-5
618606	Additional Information	48767-8
618607	Reviewed by	18771-6