MAYO CLINIC LABORATORIES

Test Definition: DPYDG

DPYD Full Gene Sequencing

Overview

Useful For

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

May be useful in identifying variants associated with decreased or absent dihydropyrimidine dehydrogenase enzyme activity for an individual with this deficiency suspected

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 (DPD) deficiency.(1) Individuals who have variations identified in the *DPYD* may benefit from genetic consultation.

Special Instructions

- Informed Consent for Genetic Testing
- Multiple Whole Blood EDTA Genotype Tests
- Pharmacogenomic Associations Tables
- Informed Consent for Genetic Testing (Spanish)

Method Name

Polymerase Chain Reaction (PCR) followed by DNA Sequence Analysis

NY State Available

Yes

Specimen

Specimen Type

Varies

Specimen Required

Multiple whole blood EDTA genotype tests can be performed on a single specimen after a single extraction. See Multiple Whole Blood EDTA Genotype Tests in Special Instructions for a list of tests that can be ordered together.

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 specimen in original tube.

Specimen Stability Information: Ambient (preferred) 9 days/Refrigerated 30 days

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

Specimen Type: Extracted DNA

Container/Tube: 2 mL screw top tube

Specimen Volume: 100 mcL (microliters)

Collection Instructions:

1. The preferred volume is 100 mcL at a concentration of 250 ng/mcL.

2. Include concentration and volume on tube.

Specimen Stability Information: Frozen (preferred)/Ambient/Refrigerated

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) form with the specimen.

Reject Due To

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

Specimen Minimum Volume

Blood: 0.45 mL

Saliva: 1 swab

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Varies (preferred)		

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 dihydropyrimidine dehydrogenase (*DPYD*) gene encodes the rate-limiting enzyme for fluoropyrimidine catabolism and eliminates over 80% of administered 5-FU. Dihydropyrimidine dehydrogenase (DPYD) activity is subject to wide variability, mainly due to genetic variation (table 1). This results in a broad range of enzymatic deficiency from partial (3%-5% of population) to complete loss (0.2% of population) of enzyme activity.(2,3) Patients who are deficient in DPYD are at an increased risk for side effects and toxicity when undergoing 5-FU treatment.(4) In addition, pathogenic homozygous or compound heterozygous variants within *DPYD* are associated with dihydropyrimidine dehydrogenase (DPD) deficiency. DPD deficiency shows large phenotypic variability, ranging from no symptoms to a convulsive disorder with motor and mental retardation.

Table 1. Known Genetic Variations Associated with Fluoropyrimidine Treatment

Gene	cDNA numbering	Alternative name	Enzyme activity	Phenotype
DPYD	No variations identified	*1		
	c.1905+1G->A	*2A	No activity or significantly reduced activity	High risk for fluoropyrimidine toxicity
	c.1679T->G	*13		
	c.1898delC	*3		
	c.299_302delTCAT	*7		
	c.1156G->T	*12		
	c.2846A->T	rs67376798	Reduced activity	Increased risk for fluoropyrimidine toxicity
	c.1129-5923C->G	rs75017182		
	c.703C->T	*8	Probable reduced function	Increased risk for fluoropyrimidine toxicity
	c.2983G->T	*10		
	c.1003G->T	*11		
	c.557A->G	rs115232898		
	c.1601C->T	*4	Normal activity**	Normal risk for fluoropyrimidine toxicity
	c.1627A->G	*5		
	c.2194C->T	*6		
	c.85T->C	*9A		

*Other or novel variations, besides those listed here, may also impact fluoropyrimidine-related side effects and tumor response and will be reported if detected.

**Alleles that are categorized as having normal enzyme activity (eg, *4, *5, *6, *9A) will not be reported if detected because variants with normal enzyme activity are not expected to impact fluoropyrimidine-related side effects and tumor response.

The *DPYD* gene is located on chromosome 1 and contains 2 transcripts. The longer transcript (NM_000110.3) contains 23 exons, and the shorter transcript (NM_001160301.1) contains 6 exons, with exon 6 being unique to this transcript. All exons from the longer transcript (NM_000110.3) and exon-intron boundaries are assessed.

Genetic variations involved in the metabolic pathway of fluoropyrimidines have been shown to contribute to the differences in clinical outcomes including toxicity and tumor response.

Reference Values

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.

For additional information regarding pharmacogenomic genes and their associated drugs, see the Pharmacogenomic Associations Tables in Special Instructions. 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 heterologous blood transfusions or allogeneic blood or marrow 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 blood or marrow transplantation, a pretransplant DNA specimen is recommended for testing.

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

Rare genetic variants exist that could lead to false-negative or false-positive results. Other variants in the primer binding regions can affect the testing, and ultimately, the genotype assessment made.

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 DPYD protein expression and their impact on fluoropyrimidine related side effects and 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 April 18, 2012. Accessed December 4, 2020. Available from https://www.omim.org/entry/274270

2. 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

3. Morel A, Boisdron-Celle M, Fey L, et al: Clinical relevance of different dihyropyrimidine dehydrogenase gene single nucleotide polymorphisms on 5-fluorouracil tolerance. Mol Cancer Ther. 2006 Nov;5(11):2895-2904

4. U.S. Food and Drug Administration (FDA): Table of Pharmacogenomic Biomarkers in Drug Labeling. FDA; Updated June 2020, Accessed December 4, 2020. 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. The dihydropyrimidine dehydrogenase (*DPYD*) 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 the exons and intron/exon boundaries of all 23 exons of the *DPYD* gene (using gene transcript NM_000110.3) using mutation detection software and visual inspection.(Unpublished Mayo method)

PDF Report

No

Specimen Retention Time

Whole blood/Saliva: 2 weeks; Extracted DNA: 2 months

Performing Laboratory Location

Rochester

Fees & Codes

Test Classification

This test was developed, and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test 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
DPYDG	DPYD Full Gene Sequencing	94198-9

Result ID	Reporting Name	LOINC®
48263	DPYD Predicted Toxicity Risk	83009-1
48264	Result Details	82939-0
48268	Interpretation	69047-9
48266	Method	85069-3
48269	Disclaimer	62364-5
48270	Reviewed by	18771-6
92011	Additional Information	48767-8