DPYD Genotyping

Background:

The *DPYD* gene encodes dihydropyrimidine dehydrogenase (DPD), the enzyme involved in fluoropyrimidine (5-fluorouracil, capecitabine, and other analogs) metabolism. For clinical correlation, drug-specific guidelines are available[1] to provide therapeutic recommendations based on phenotype. Patients who carry *DPYD* genetic variants associated with altered metabolism may be at risk for an adverse or poor response to drugs that are predominantly metabolized by DPD. Adverse effects may include severe life-threatening neutropenia, mucositis, and/or diarrhea. Such adverse effects are more likely for patients who are DPD intermediate or poor metabolizers. For patients with altered DPD activity, alternative pharmacological agents or dosing adjustments may be needed for medications metabolized by DPD to avoid an unexpected, adverse response.

DPYD genotyping should not be ordered on a patient with a history of an allogeneic bone marrow transplant or liver transplant as genotype results from peripheral blood may not reflect that patient's liver enzyme function.

In addition to increased risk of 5-flourouracil toxicity, variants in the *DPYD* gene may be associated with DPD deficiency, an autosomal recessive inborn error of metabolism (OMIM: 274270). DPD deficiency exhibits a wide range of phenotypic variability, from no symptoms to a very rare severe neurological disorder with onset in infancy or childhood (prevalence unknown). For the vast majority of affected individuals, the first and only symptom is sensitivity to 5-fluorouracil and capecitabine. It is possible that individuals with DPD deficiency may be identified by the presence of two "no-function" *DPYD* variants (activity score = 0). However, this test is designed as a pharmacogenomic test and is not intended as a diagnostic or carrier test for DPD deficiency. A formal genetics consultation is recommended for those with concerns regarding DPD deficiency.

Clinical Indication:

DPYD genotyping is intended for those individuals for whom fluoropyrimidine medication is being or may be considered as part of their treatment.

Interpretation:

This *DPYD* genotyping test predicts metabolizer status based on the activity score associated with the known pharmacogenomic, clinically relevant, targeted variants (alleles). The absence of an abnormal variant in this test is interpreted as a "normal function" phenotype. The most common phenotype and metabolizer status is a DPD normal metabolizer characterized by two "normal function" alleles (activity score = 2.0). DPD intermediate metabolizers have one "normal function" allele and either one "decreased function" or one "no-function" allele (activity score 1.0 – 1.5). DPD poor metabolizers have one "no-function" allele and either one "decreased function" or a second "no-function" allele (activity score 0 – 0.5). There are several "decreased function" alleles but the total frequency for all combined "decreased function" alleles is low (<5% of the general population). The "no-function" alleles are very uncommon and the specific frequency for some are not known (see Table 2, *DPYD* Targeted Variants).

Table 1: Interpretation Summary:

Activity Score	Predicted Phenotype	Interpretation Summary*
Combination of alleles activity score = 2	Normal metabolizer	Normal dosing recommendations for medications metabolized by DPD.
Combination of alleles activity score = 1 or 1.5	Intermediate metabolizer	May be at risk of adverse or poor drug reaction to medications metabolized by DPD
Combination of alleles activity score = 0.5	Poor metabolizer	May be at risk of adverse or poor drug reaction to medications metabolized by DPD
Combination of alleles activity score = 0	Poor metabolizer	At risk of adverse drug reactions to medications metabolized by DPD

*Consult a clinical pharmacist with questions regarding drug therapy.

Methodology:

Purified genomic DNA is subjected to polymerase chain reaction-based amplification. Primer extension products are analyzed using matrix-assisted laser desorption/ ionization mass spectrometry, was used to detect specific *DPYD* genotypes (NM_000110.3). Interrogation for known clinically relevant variants (see list below) is performed and the appropriate activity score is derived. The reference genome used is GRCh38/hg38.

Test Limitations:

DNA studies do not provide a definitive genetic or pharmacogenomic risk for all individuals. This test is designed to detect a specific set of variants (Table 2) in the *DPYD* gene (OMIM 612779). This test does not detect all *DPYD* sequence variants. Uncommon variants or single nucleotide polymorphisms may affect binding of primers and probes and may result in false negative, false positive, or indeterminate results. The absence of abnormal variants in this test is interpreted as the presence of two "normal function" alleles. The predicted phenotype provided in the interpretation may be impacted by undetected genetic and/or non-genetic factors such as drug-drug interactions.

DPYD genotyping is a pharmacogenomic test. It is not intended as a carrier screen and should not be used to determine reproductive risk for DPD deficiency.

Table 2: *DPYD* targeted variants:

RefSNP ID	Legacy Name	Allele Function (Activity Score)	Total Allele Frequency, General Population* (gnomAD)
No variant detected	*1	Normal function	
rs3918290	*2A	"no-function" (0)	0.4%
rs72549303	*3	"no-function" (0)	0.0007%
rs72549309	*7	"no-function" (0)	0.01%
rs1801266	*8	"no-function" (0)	0.004%
rs1801265	*9A	"normal function" (1)	27.3%
rs1801268	*10	"no-function" (0)	n/a
rs78060119	*12	"no-function" (0)	0.0007%
rs55886062	*13	"no-function" (0)	0.04%
rs115232898	Y186C	Decreased function (0.5)	0.6%
rs67376798	c.2846A>T	Decreased function (0.5)	0.3%
rs75017182	HapB3	Decreased function (0.5)	1.3%
rs56038477	c.1236G>A	Decreased function (0.5)	1.3%

*Population frequencies may be higher or lower in specific ethnic groups. This allele frequency shown is the total allele frequency in all populations.

References:

1. 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.
2. Clinical Pharmacogenetics Implementation Consortium (CPIC): www.CPICpgx.org
3. Pharmacogene Variation Consortium (PharmVar): www.PharmVar.org
4. Whirl-Carrillo M, McDonagh EM, Hebert JM, *et al.* Pharmacogenomics Knowledge for Personalized Medicine. *Clinical Pharmacology & Therapeutics* (2012) 92(4): 414-417.
5. Medlineplus, National Library of Medicine 2020. Dihydropyrimidine dehydrogenase deficiency, accessed 23 April 2021, https://medlineplus.gov/genetics/condition/dihydropyrimidine-dehydrogenase-deficiency/#resources
6. Kamatani N, Jinnah HA, Hennekam RCM, van Kuilenburg ABP. Purine and Pyrimidine Metabolism: Pyrimidine Metabolism: Dihydropyrimidine Dehydrogenase. *Emery and Rimoin's Principles and Practice of Medical Genetics and Genomics: Metabolic Disorders, Seventh Edition.* Edited by Pyeritz, RE et al, *Elsevier*. 2021. Sections 6.3.4–6.3.4.4 https://www-clinicalkey-com.ccmain.ohionet.org/#!/content/book/3-s2.0-B9780128125359000066?scrollTo=%23hl0001075

Test Overview

Test Name	Pharmacogenomics (PGx) DPYD Genotyping
Ordering Mnemonic	DPYD
Specimen	Peripheral Blood: 4 ml in an EDTA tube (lavender top)
Stability	Ambient: 24 hours Frozen: Unacceptable Refrigerated: 5 days
Reference Range	No variant detected = *1/*1
CPT Codes	81232

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