THE PATHCARE NEWS

Dihydropyrimidine dehydrogenase (DPYD) genotyping to guide dosing of fluoropyrimidines

Background:

DPYD, the gene encoding dihydropyrimidine dehydrogenase (DPD) is the rate-limiting enzyme for fluoropyrimidine catabolism. In the context of 5-fluorouracil, four decreased function DPYD variants are of primary relevance due to their population frequency and established impact on enzyme function and toxicity risk:

DPYD allele	rs number	Other names	Allele functional status	Activity score
c.190511G>A	rs3918290	DPYD*2A, DPYD:IVS14+1G>A	No function	0
c.1679T>G	rs55886062	DPYD *13, p.I560S	No function	0
c.2846A>T	rs67376798	p.D949V	Decreased function	0.5
c.1129-5923C>G, c.1236G>A, c.483+18G>A	rs75017182, rs56038477, rs56276561	HapB3	Decreased function	0.5

The Clinical Pharmacogenetics Implementation Consortium (CPIC) has well-established guidelines for DPYD genotyping and fluoropyrimidine dosing based on genetic testing results[1]. Impaired DPD enzyme function leads to an increased risk for severe or life-threatening toxicity in patients treated with 5-FU or its prodrugs.

South African recommendations:

In collaboration with the South African Health Products Regulatory Authority (SAHPRA), numerous pharmaceutical companies have recommended that DPYD pre-testing be performed to identify patients at increased risk of severe toxicity due to fluoropyrimidine containing medicines[2]. Both genotyping of the DPYD variants listed above and phenotyping by measurement of blood uracil levels are listed as acceptable methods.

Genetic testing considerations:

Individuals who harbour one copy of a no function DPYD variant are considered to be carriers for an inborn error of metabolism and consideration should be given to the potential risk to future children (if both parents are carriers). Patients homozygous for inactivating variants of DPYD have complete dihydropyrimidine dehydrogenase deficiency, a clinically heterogeneous autosomal recessive disorder of pyrimidine metabolism that shows wide variability of clinical presentations, ranging from no symptoms to severe convulsive disorders with global developmental delay and intellectual disability[1]. It is recommended that these results are communicated to the patient in a setting that includes appropriate genetic counselling.

How to request:

- PathCare tests for four DPYD variants, as recommended by SAHPRA.
- The DPYD genotyping test is a simple blood test that can be requested via any PathCare/Vermaak depot.
- Test mnemonic: L3492 (PPCRDPD)
- Result availability: 1-2 weeks

Cost:

The price of this test depends on your patient's medical aid – please contact the PathCare Debtors department for a quote for your patient (drsystems@pathcare.co.za)

If you require any additional information, please email geneticconsult@pathcare.co.za or molecularoncology@pathcare.co.za.

References:

1. Amstutz U, Henricks LM, Offer SM, Barbarino J, Schellens JH, Swen JJ, Klein TE, McLeod HL, Caudle KE, Diasio RB, Schwab M. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing: 2017 update. Clinical Pharmacology & Therapeutics. 2018 Feb;103(2):210-6. https://cpicpgx.org/guidelines/guideline-for-fluoropyrimidines-and-dpyd/

2. www.sahpra.org.za/wp-content/uploads/2020/10/20200924-Fluoropyrimidine_Proposed-DHCPL-DPD-defiency-Final-1.pdf