THE PATHCARE NEWS

DPYD RESULT INTERPRETATION

INTERPRETATION OF DPYD GENOTYPING RESULTS

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[1].

PathCare tests for four DPYD variants, as recommended by SAHPRA[2].

INTERPRETATION OF DPYD GENOTYPING RESULTS

1. **An individual's likely phenotype can be calculated as the sum of the two lowest individual variant activity values.**

VARIANT RESULTS:	
DPYD c.1905+1G>A (*2A).	NOT DETECTED
	Allele functional status: Normal function (Activity value = 1).
DPYD c.1679T>G (*13):	NOT DETECTED
	Allele functional status: Normal function (Activity value = 1).
DPYD c.2846A>T:	NOT DETECTED
	Allele functional status: Normal function (Activity value = 1).
DPYD HapB3:	NOT DETECTED
	Allele functional status: Normal function (Activity value = 1).

2. **Refer to Table 1 of the CPIC Guidelines to determine the assignment of the individual's likely phenotype.**

Table 1 Assignment of likely DPD phenotypes based on *DPYD* genotypes

Likely phenotype	Activity score[a]	Genotypes[b]	Examples of genotypes[c]
DPYD normal metabolizer	2	An individual carrying two normal function alleles.	c.[=];[=], c.[85T>C];[=], c.[1627A>G];[=]
DPYD intermediate metabolizer	1 or 1.5	An individual carrying one normal function allele plus one no function allele or one decreased function allele, or an individual carrying two decreased function alleles.	c.[1905+1G>A];[=], c.[1679T>G];[=], c.[2846A>T];[=]; c.[1129–5923C>G];[=][d]; c.[1129–5923C>G];[1129–5923C>G][d]; c.[2846A>T];[2846A>T]
DPYD poor metabolizer	0 or 0.5	An individual carrying two no function alleles or an individual carrying one no function plus one decreased function allele.	c.[1905+1G>A];[1905+1G>A], c.[1679T>G];[1679T>G], c.[1905+1G>A];[2846A>T] c.[1905+1G>A]; [1129-5923C>G]

[a]Calculated as the sum of the two lowest individual variant activity scores. See text for further information. [b]Allele definitions, assignment of allele function and references can be found on the CPIC website (*DPYD* Allele Functionality Table available at [ref 4]) [c]HGVS nomenclature using the reference sequence NM_000110.3 [d]Likely HapB3 causal variant. See *DPYD* Allele Functionality Table available at [ref 4] for other HapB3 proxy SNPs.

3. **Refer to Table 2 of the CPIC Guidelines to view the recommended dosing.**

Table 2 Recommended dosing of fluoropyrimidines[a] by DPD phenotype

Phenotype	Implications for phenotypic measures	Dosing recommendations	Classification of recommendations[b]
DPYD normal metabolizer	Normal DPD activity and "normal" risk for fluoropyrimidine toxicity.	Based on genotype, there is no indication to change dose or therapy. Use label-recommended dosage and administration.	Strong
DPYD intermediate metabolizer	Decreased DPD activity (leukocyte DPD activity at 30% to 70% that of the normal population) and increased risk for severe or even fatal drug toxicity when treated with fluoropyrimidine drugs.	Reduce starting dose based on activity score followed by titration of dose based on toxicity[c] or therapeutic drug monitoring (if available). **Activity score 1:** Reduce dose by 50% **Activity score 1.5:** Reduce dose by 25% to 50%	**Activity score 1:** Strong **Activity score 1.5:** Moderate
DPYD poor metabolizer	Complete DPD deficiency and increased risk for severe or even fatal drug toxicity when treated with fluoropyrimidine drugs.	**Activity score 0.5:** Avoid use of 5-fluorouracil or 5-fluorouracil prodrug-based regimens. In the event, based on clinical advice, alternative agents are not considered a suitable therapeutic option, 5-fluorouracil should be administered at a strongly reduced dose[d] with early therapeutic drug monitoring.[e] **Activity score 0:** Avoid use of 5-fluorouracil or 5-fluorouracil prodrug-based regimens.	Strong

[a]5-fluorouracil or capecitabine. [b]Rating scheme described in Supplement. [c]Increase the dose in patients experiencing no or clinically tolerable toxicity in the first two cycles to maintain efficacy; decrease the dose in patients who do not tolerate the starting dose to minimize toxicities. [d]If available, a phenotyping test (see main text for further details) should be considered to estimate the starting dose. In the absence of phenotyping data, a dose of <25% of the normal starting dose is estimated assuming additive effects of alleles on 5-FU clearance. [e]Therapeutic drug monitoring should be done at the earliest timepoint possible (e.g., minimum timepoint in steady state) in order to immediately discontinue therapy if the drug level is too high.

Example 1:

1. An individual's likely phenotype can be calculated as the sum of the two lowest individual variant activity values (highlighted below):

P.C.R. Department

Test Name	Result	Flag	Reference Range
DPYD genotyping panel			
RESULT SUMMARY	NO VARIANTS DETECTED		
VARIANT RESULTS:			
DPYD c.1905+1G>A (*2A):	NOT DETECTED		
	Allele functional status: Normal function (Activity value = 1).		
DPYD c.1679T>G (*13):	NOT DETECTED		
	Allele functional status: Normal function (Activity value = 1).		
DPYD c.2846A>T:	NOT DETECTED		
	Allele functional status: Normal function (Activity value = 1).		
DPYD HapB3:	NOT DETECTED		
	Allele functional status: Normal function (Activity value = 1).		

1 + 1 = 2

2. Refer to Table 1 of the CPIC Guidelines to determine the assignment of the individual's likely phenotype:

Table 1 Assignment of likely DPD phenotypes based on *DPYD* genotypes

Likely phenotype	Activity score[a]	Genotypes[b]	Examples of genotypes[c]
DPYD normal metabolizer	2	An individual carrying two normal function alleles.	c.[=];[=], c.[85T>C];[=], c.[1627A>G];[=]
DPYD intermediate metabolizer	1 or 1.5	An individual carrying one normal function allele plus one no function allele or one decreased function allele, or an individual carrying two decreased function alleles.	c.[1905+1G>A];[=], c.[1679T>G];[=], c.[2846A>T];[=]; c.[1129–5923C>G];[=][d]; c.[1129–5923C>G];[1129–5923C>G][d]; c.[2846A>T];[2846A>T]
DPYD poor metabolizer	0 or 0.5	An individual carrying two no function alleles or an individual carrying one no function plus one decreased function allele.	c.[1905+1G>A];[1905+1G>A], c.[1679T>G];[1679T>G], c.[1905+1G>A];[2846A>T] c.[1905+1G>A]; [1129-5923C>G]

[a]Calculated as the sum of the two lowest individual variant activity scores. See text for further information. [b]Allele definitions, assignment of allele function and references can be found on the CPIC website (*DPYD* Allele Functionality Table available at [ref 4]) [c]HGVS nomenclature using the reference sequence NM_000110.3 [d]Likely HapB3 causal variant. See *DPYD* Allele Functionality Table available at [ref 4] for other HapB3 proxy SNPs.

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DPYD intermediate metabolizer	Decreased DPD activity (leukocyte DPD activity at 30% to 70% that of the normal population) and increased risk for severe or even fatal drug toxicity when treated with fluoropyrimidine drugs.	Reduce starting dose based on activity score followed by titration of dose based on toxicity[c] or therapeutic drug monitoring (if available). **Activity score 1:** Reduce dose by 50% **Activity score 1.5:** Reduce dose by 25% to 50%	**Activity score 1:** Strong **Activity score 1.5:** Moderate
DPYD poor metabolizer	Complete DPD deficiency and increased risk for severe or even fatal drug toxicity when treated with fluoropyrimidine drugs.	**Activity score 0.5:** Avoid use of 5-fluorouracil or 5-fluorouracil prodrug-based regimens. In the event, based on clinical advice, alternative agents are not considered a suitable therapeutic option, 5-fluorouracil should be administered at a strongly reduced dose[d] with early therapeutic drug monitoring.[e] **Activity score 0:** Avoid use of 5-fluorouracil or 5-fluorouracil prodrug-based regimens.	Strong

[a]5-fluorouracil or capecitabine. [b]Rating scheme described in Supplement. [c]Increase the dose in patients experiencing no or clinically tolerable toxicity in the first two cycles to maintain efficacy; decrease the dose in patients who do not tolerate the starting dose to minimize toxicities. [d]If available, a phenotyping test (see main text for further details) should be considered to estimate the starting dose. In the absence of phenotyping data, a dose of <25% of the normal starting dose is estimated assuming additive effects of alleles on 5-FU clearance. [e]Therapeutic drug monitoring should be done at the earliest timepoint possible (e.g., minimum timepoint in steady state) in order to immediately discontinue therapy if the drug level is too high.

Example 2:

1. An individual's likely phenotype can be calculated as the sum of the two lowest individual variant activity values (highlighted below):

P.C.R. Department

Test Name	Result	Flag	Reference Range
DPYD genotyping panel			
RESULT SUMMARY	VARIANT/S DETECTED		
VARIANT RESULTS:			
DPYD c.1905+1G>A (*2A):	NOT DETECTED		
Allele functional status: Normal function (Activity value = 1).			
DPYD c.1679T>G (*13):	NOT DETECTED		
Allele functional status: Normal function (Activity value = 1).			
DPYD c.2846A>T:	NOT DETECTED		
Allele functional status: Normal function (Activity value = 1).			
DPYD HapB3:	HETEROZYGOUS		
Allele functional status: Decreased function (Activity value = 0.5).			

1 + 0.5 = 1.5

2. Refer to Table 1 of the CPIC Guidelines to determine the assignment of the individual's likely phenotype:

Table 1 Assignment of likely DPD phenotypes based on *DPYD* genotypes

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DPYD normal metabolizer	2	An individual carrying two normal function alleles.	c.[=];[=], c.[85T>C];[=], c.[1627A>G];[=]
DPYD intermediate metabolizer	1 or 1.5	An individual carrying one normal function allele plus one no function allele or one decreased function allele, or an individual carrying two decreased function alleles.	c.[1905+1G>A];[=], c.[1679T>G];[=], c.[2846A>T];[=]; c.[1129–5923C>G];[=][d]; c.[1129–5923C>G];[1129–5923C>G][d]; c.[2846A>T];[2846A>T]
DPYD poor metabolizer	0 or 0.5	An individual carrying two no function alleles or an individual carrying one no function plus one decreased function allele.	c.[1905+1G>A];[1905+1G>A], c.[1679T>G];[1679T>G], c.[1905+1G>A];[2846A>T] c.[1905+1G>A]; [1129-5923C>G]

[a]Calculated as the sum of the two lowest individual variant activity scores. See text for further information. [b]Allele definitions, assignment of allele function and references can be found on the CPIC website (*DPYD* Allele Functionality Table available at [ref 4]) [c]HGVS nomenclature using the reference sequence NM_000110.3 [d]Likely HapB3 causal variant. See *DPYD* Allele Functionality Table available at [ref 4] for other HapB3 proxy SNPs.

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Example 3:

1. An individual's likely phenotype can be calculated as the sum of the two lowest individual variant activity values (highlighted below):

P.C.R. Department

Test Name	Result	Flag	Reference Range
DPYD genotyping panel			
RESULT SUMMARY	VARIANT/S DETECTED		
VARIANT RESULTS:			
DPYD c.1905+1G>A (*2A):	HETEROZYGOUS		
	Allele functional status: No function (Activity value = 0).		
DPYD c.1679T>G (*13):	NOT DETECTED		
	Allele functional status: Normal function (Activity value = 1).		
DPYD c.2846A>T:	NOT DETECTED		
	Allele functional status: Normal function (Activity value = 1).		
DPYD HapB3:	HETEROZYGOUS		
	Allele functional status: Decreased function (Activity value = 0.5).		

$0 + 0.5 = 0.5$

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DPYD poor metabolizer	0 or 0.5	An individual carrying two no function alleles or an individual carrying one no function plus one decreased function allele.	c.[1905+1G>A];[1905+1G>A], c.[1679T>G];[1679T>G], c.[1905+1G>A];[2846A>T] c.[1905+1G>A]; [1129-5923C>G]

[a]Calculated as the sum of the two lowest individual variant activity scores. See text for further information. [b]Allele definitions, assignment of allele function and references can be found on the CPIC website (*DPYD* Allele Functionality Table available at [ref 4]) [c]HGVS nomenclature using the reference sequence NM_000110.3 [d]Likely HapB3 causal variant. See *DPYD* Allele Functionality Table available at [ref 4] for other HapB3 proxy SNPs.

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References:

1. CPIC® Guidelines for Fluoropyrimidines and DPYD
2. SAHPRA document: Fluoropyrimidine Containing Medicines And Related Substances: Increased Drug Exposure And Toxicity In Patients With Dihydropyrimidine Dehydrogenase (DPD) Deficiency