Ontario Health
Cancer Care Ontario

Fluoropyrimidine Treatment in Patients with Dihydropyrimidine Dehydrogenase (DPD) Deficiency – Summary of Pre-treatment Dosing Recommendations

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Functional Status of *DPYD* Variant Alleles

Table 1 – Reduction in DPD activity associated with known *DPYD* variants

DPYD* Variant	**Activity Score****	**Functional Status[3]*****	**Reduction in DPD Enzymatic Activity – Heterozygous carriers[3]**	**Reduction in DPD Enzymatic Activity – Homozygous carriers[11]**
Wild-type e.g. c.1627A>G (*DPYD**5) c.85T>C (*DPYD**9A)	1	Normal activity	None	None
c.2846A>T (D949V, rs67376798)	0.5	Decreased activity	30%	50%
c.1236G>A (rs56038477, E412E); same variant as **c.1129-5923C>G** (rs75017182) haplotype B3 (HapB3)	0.5	Decreased activity	35%	20-70%
c.1905+1G>A (***DPYD**2A***, IVS14+1G>A, rs3918290)	0	No activity	50%	100%
c.1679T>G (*DPYD13,** I560S, rs55886062)	0	No activity	68%	75%

*Various versions of nomenclature are used for *DPYD* variants; the most commonly used are bolded

** Individual variant allele activity scores; see Appendix 2 for a definition of Activity Score

***Variant allele definitions and assignment of allele function can be found in the *DPYD* Allele Functionality Table (https://cpicpgx.org/guidelines/guideline-for-fluoropyrimidines-and-dpyd/)

Please see the full report, "Fluoropyrimidine Treatment in Patients with Dihydropyrimidine Dehydrogenase (DPD) Deficiency: Guidance for Clinicians" for more information, including references and limitations. *Please note*: Recommendations are based on data largely derived from individuals of European ancestry. Other clinically relevant variants of the *DPYD* gene that have yet to be identified or for which association with enzyme activity have not yet been established are not assessed by the current test. Clinical judgement should be exercised when interpreting results, especially in racial/ethnic groups that have not been studied as extensively.

Genotype-Guided Dosing Recommendations for Planned Fluoropyrimidine Treatment

Table 2 – Initial Genotype-Guided Fluoropyrimidine Dosing Recommendations by *DPYD* Variant

***DPYD* Variant 1**	***DPYD* Variant 2**	**Activity Score[a]**	***DPYD* Metabolizer[b]**	**Starting Dose Recommendation[c]**
any normal function variant	any normal function variant	2	Normal	No dose adjustment
c.1905+1G>A (*2A)	any normal function variant	1	Intermediate	Reduce[c] starting dose by 50%
c.1905+1G>A (*2A)	c.1905+1G>A (*2A)	0	Poor	Avoid use of 5-FU or 5-FU prodrug-based regimens.
c.1905+1G>A (*2A)	c.1129-5923C>G, c.1236G>A (HapB3)	0.5	Poor	Avoid use of 5-FU or 5-FU prodrug-based regimens. If alternative agents are not considered a suitable therapeutic option, 5-FU should be administered at a strongly reduced dose (by > 75%) with toxicity monitoring
c.1905+1G>A (*2A)	c.1679T>G (*13)	0	Poor	Avoid use of 5-FU or 5-FU prodrug-based regimens.
c.1905+1G>A (*2A)	c.2846A>T	0.5	Poor	Avoid use of 5-FU or 5-FU prodrug-based regimens. If alternative agents are not considered a suitable therapeutic option, 5-FU should be administered at a strongly reduced dose (by > 75%) with toxicity monitoring
c.1679T>G (*13)	any normal function variant	1	Intermediate	Reduce[d] starting dose by 50%
c.1679T>G (*13)	c.1679T>G (*13)	0	Poor	Avoid use of 5-FU or 5-FU prodrug-based regimens.

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DPYD Variant 1	*DPYD* Variant 2	Activity Score[a]	*DPYD* Metabolizer[b]	Starting Dose Recommendation[c]
c.1679T>G (*13)	c.1129-5923C>G, c.1236G>A (HapB3)	0.5	Poor	Avoid use of 5-FU or 5-FU prodrug-based regimens. If alternative agents are not considered a suitable therapeutic option, 5-FU should be administered at a strongly reduced dose (by > 75%) with toxicity monitoring
c.1679T>G (*13)	c.2846A>T	0.5	Poor	Avoid use of 5-FU or 5-FU prodrug-based regimens. If alternative agents are not considered a suitable therapeutic option, 5-FU should be administered at a strongly reduced dose (by > 75%) with toxicity monitoring
c.1129-5923C>G, c.1236G>A (HapB3)	any normal function variant	1.5	Intermediate	Reduce[d] starting dose by 50%
c.1129-5923C>G, c.1236G>A (HapB3)	c.1129-5923C>G, c.1236G>A (HapB3)	1	Intermediate	Reduce[d] starting dose by 50%
c.1129-5923C>G, c.1236G>A (HapB3)	c.2846A>T	1	Intermediate	Reduce[d] starting dose by 50%
c.2846A>T	any normal function variant	1.5	Intermediate	Reduce[d] starting dose by 50%
c.2846A>T	c.2846A>T	1	Intermediate	Reduce[d] starting dose by 50%[e]

[a] Activity score is calculated as the sum of the two individual variant allele activity scores (1=fully functional, 0.5=reduced function, and 0=non-functional)

[b] Likely phenotype; extent to which the variant alleles influence enzyme activity

[c] For standard dosing of 5-FU or capecitabine. Excludes low (metronomic) dosing as this was not represented in studies; dose adjustments in these patients should be based on clinical judgement.

[d] Followed by titration of dose based on toxicity. 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.

[e] May require > 50% dose reduction in starting dose for carriers of this genotype, based on case reports

Adapted from the 2017 CPIC Guidelines and Supplementary Tables. **CPIC guidelines and content are subject to updates and modifications, refer to cpicpgx.org for most current content**.

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Initial Genotype-guided Fluoropyrimidine Dosing Recommendations by Hetero/Homozygous State

Table 3 - Initial Fluoropyrimidine Dosing Recommendations for Heterozygous Carriers of a *DPYD* Variant Allele[a]:

***DPYD* Variant**	**Starting Dose Recommendation**[b]
c.1905+1G>A (*2A)	Reduce[c] starting dose by 50%
c.1679T>G (*13)	Reduce[c] starting dose by 50%
c.1129-5923C>G, c.1236G>A (HapB3)	Reduce[c] starting dose by 50%
c.2846A>T	Reduce[c] starting dose by 50%

Table 4 - Initial Fluoropyrimidine Dosing Recommendations for Homozygous Carriers of *DPYD* Variant Alleles:

***DPYD* Variant**	**Starting Dose Recommendation**[b]
c.1905+1G>A (*2A)	Avoid use of 5-FU or 5-FU prodrug-based regimens.
c.1679T>G (*13)	Avoid use of 5-FU or 5-FU prodrug-based regimens.
c.1129-5923C>G, c.1236G>A (HapB3)	Reduce[c] starting dose by 50%
c.2846A>T	Reduce[c] starting dose by 50%[d]

[a] Does not refer to carriers of compound or double heterozygous variant alleles.

[b] For standard dosing of 5-FU or capecitabine. Excludes low (metronomic) dosing as this was not represented in studies; dose adjustments in these patients should be based on clinical judgement.

[c] Followed by titration of dose based on toxicity. 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] May require > 50% dose reduction in starting dose for carriers of this genotype, based on case reports

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