Ontario Health
Cancer Care Ontario

Fluoropyrimidine Treatment in Patients with Dihydropyrimidine Dehydrogenase (DPD) Deficiency

GUIDANCE FOR CLINICIANS

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Background

Fluoropyrimidines, including 5-fluorouracil (5-FU) and capecitabine, have been widely used for decades in the treatment of solid tumours including colorectal, gastric, head and neck and breast cancers, and remain the backbone of many combination chemotherapy regimens. Although the benefits of fluoropyrimidine treatment are well established, toxicities such as diarrhea, mucositis, myelosuppression and hand-foot syndrome can develop and often lead to treatment interruption or discontinuation, and occasionally hospitalization. While treatment with fluoropyrimidines is generally well tolerated, some studies have reported that up to one third of patients develop severe treatment-related toxicities, which can occur as early as the first cycle, and can be fatal in up to 1% of patients.[1–7] Severe treatment-related adverse effects can be attributed to genetic differences between individuals in metabolism of 5-FU, and this inter-patient variability can cause considerable challenges in the treatment with fluoropyrimidines.[1,2,8] This guidance was developed to support clinicians in optimizing fluoropyrimidine treatment for patients with these genetic variations. Recommendations were developed based on literature reviewed between December 2021 and February 2022 as well as expert consultations. The final content was reviewed and validated by a multidisciplinary group of oncology clinicians in Ontario.

Role of DPD in Fluoropyrimidine Metabolism

5-FU undergoes complex metabolism that plays a pivotal role in both its antitumor activity and toxicity (Figure 1). The cytotoxic effects of 5-FU rely on its intracellular conversion to active metabolites at the tumour site, which interfere with RNA and DNA synthesis, leading to cell death. Approximately 80% of a 5-FU dose is metabolized by dihydropyrimidine dehydrogenase (DPD), the rate-limiting enzyme of pyrimidine catabolism found mostly in the liver, which converts 5-FU to its inactive form.[6,9] Reduced DPD enzyme activity leads to decreased clearance of 5-FU, accumulation of active metabolites and, thus, enhanced toxicity. In cases of severe 5-FU toxicity, reduced DPD activity was detected in 20-61% of patients.[2,8,10–12] This finding highlights the important role of the DPD enzyme in predicting fluoropyrimidine toxicity.

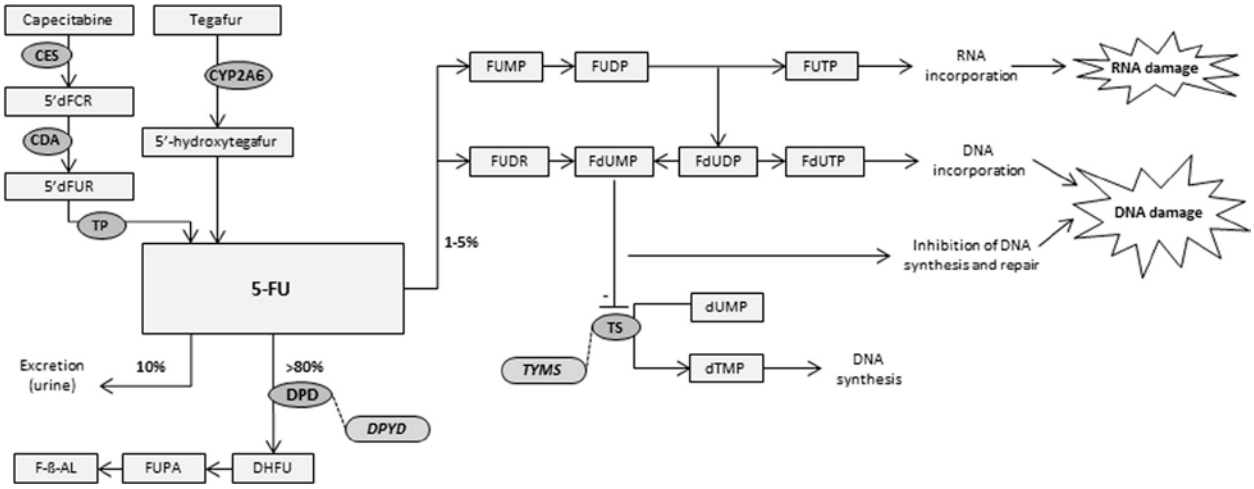

Figure 1. Overview of fluoropyrimidine metabolism. Capecitabine, a pro-drug of 5-FU, is converted to 5-FU, then undergoes the same metabolism as 5-FU. The anabolism and catabolism of 5-FU are shown to the right and bottom left, respectively; the remaining 5-FU is excreted renally. Tegafur is not available in Canada. Eur J Hum Genet. 2020 Apr;28(4):508-517

DPD Deficiency

DPD deficiency is the partial or complete loss of DPD enzymatic function, which is often the result of genetic polymorphisms in *DPYD*, the gene that encodes the DPD enzyme. Numerous genetic variants in *DPYD* have been identified, however not all variants alter the enzymatic activity of DPD, or lead to worse toxicity. Several studies and meta-analyses have analyzed the link between specific variants and predicting fluoropyrimidine toxicity, and have identified four main variants with the most established risk: c.1905+1G>A (*DPYD**2A), c.1679T>G (*DPYD**13), c.2846A>T, and c.[1236G>A; 1129-5923C>G] (HapB3). [3,8,13,14] Of these variants, *DPYD**2A and *DPYD**13 have the most deleterious effect on DPD activity (Table 1). The c.2846A>T and c.1129–5923C>G variants result in moderately reduced DPD activity. [3]

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/)

The incidence of reduced DPD activity among the general population has been estimated to be 3-5% overall. [15,16] However, distinctions among different racial and ethnic groups have been noted.[3,12,15] In Caucasians, the prevalence of the aforementioned variants has been estimated to be approximately 7%.

The most common variant in Europeans is c.1129-5923C>G (4.7% carrier frequency), followed by c.1905+1G>A (*DPYD**2A) (1.6% carrier frequency) and c.2846A>T (0.7% carrier frequency).[3] The occurrence of these variants in other populations, such as people with African or Asian ancestry, is much less (estimated prevalence of *DPYD**2A and c.2846A>T is 0.1% in people of African ancestry).[11,12] The less studied variant c.557A>G (Y186C), however, is much more common in those with African ancestry with an incidence of 3 – 5%.[3]

Complete DPD deficiency is much more rare than partial deficiency, with an estimated incidence of 0.1% in the general population.[13,17] The complete absence of DPD activity is listed as a contraindication in the product monographs of both capecitabine and 5-FU.[18,19] Manufacturers also recommend consideration of DPD deficiency testing prior to starting treatment with either agent.

Recommendation 1:

Patients with planned fluoropyrimidine-based therapies should be informed about DPD deficiency, available tests to detect deficiency, and the potential risks associated with fluoropyrimidine treatment if a deficiency is detected. It is important to note that with universal access to DPD testing, the risks should be minimal.

Patient education materials on DPD deficiency and testing can be found here.

Testing for DPD Deficiency

Phenotyping vs. Genotyping

There are two main types of testing for DPD deficiency: DPD phenotyping, which looks at the direct or indirect measurement of DPD enzyme activity and *DPYD* genotyping, which predicts DPD activity based on the presence of variants in the gene that encodes DPD.

Phenotype tests, such as those that measure uracil concentration or the dihydrouracil:uracil (UH2:U) ratio, have been investigated as a measure of DPD deficiency (DPD enzyme converts uracil into dihydrouracil) with varying results. Although there is some clinical validity to measuring plasma uracil concentrations, the association between UH2:U and fluoropyrimidine toxicity is poorly established and threshold values for partial or complete deficiency vary, making interpretation of results difficult.[3,10,12] These tests are not widely available and use is limited due to unclear clinical validity and lack of testing standardization.[11] In addition, measuring DPD activity upfront on a routine basis would be technically and logistically challenging, labour intensive, and costly.[10] Genotyping is generally easier, faster and less expensive to implement than phenotype tests, and although there are limited prospective studies, clinical validity for *DPYD* genotyping has been extensively demonstrated.[1,3,8,13,20,21] It should be noted that mutations in other genes, such as *TYMS*, also have potential to predict fluoropyrimidine response but the clinical utility of testing these genes to date is unclear.[3,8]

Screening Prior to Initiation of Fluoropyrimidines

Despite the potential implications on treatment toxicity and outcomes, the use of *DPYD* genotyping in Ontario has been limited, and a patient's genotype is often unknown when fluoropyrimidines are being prescribed. Prospective genotyping can help prevent severe toxicities, treatment discontinuation, hospitalization and mortality in patients receiving these treatments.

Two large prospective studies evaluated the effects of prospective genotyping on safety outcomes and found that grade ≥3 toxicity was significantly reduced from 73% to 28% (p<0.001) and 77% to 18% ((p<0.001), respectively, when patients were genotyped before start of therapy, and received genotype-guided doses. Drug-induced mortality was reduced to zero in both studies, from 10% and 8%, respectively.[22,23] Screening for DPD deficiency has been recommended by several regulatory agencies including the European Medicines Agency (EMA) and Institut National D'excellence en Santé et en Services Sociaux (INESSS), and has been adopted as standard of care in Quebec, the Netherlands, France, Italy and Belgium.[12,24–26] Studies conducted in Quebec and Ontario illustrate the impact of pre-treatment *DPYD* genotyping in the Canadian landscape.[4,24] Wigle et al. demonstrated no significant difference in grade ≥3 toxicity between prospectively identified carriers of *DPYD* variants (c.1905+1G>A, c.2846A>T, c.1679T>G, and c.1236G>A) treated with dose reductions and non-carriers treated with standard dose (23% vs. 31%, respectively, p = 0.265).[4] Jolivet et al. evaluated the implementation of *DPYD**2A genotyping in clinical practice in Quebec; in addition to observing no grade ≥3 toxicities, they noted no significant delays in treatment initiation due to testing (average of 6 days).[24]

Upfront testing not only improves patient safety and potentially outcomes, but also reduces healthcare costs associated with treatment-related adverse effects. Studies in the Netherlands have illustrated the cost savings associated with testing for *DPYD* variants (DPYD*2A, c.2846A>T, c.1679T>G and c.1236G>A) prior to starting therapy, and concluded that the costs of treating severe adverse effects and hospitalization outweigh the cost of screening the entire population.[22,27] A recent report assessing the cost effectiveness of implementing pre-emptive testing in Ontario mirrored these results, with an estimated savings of $714,963 over the next 5 years if *DPYD* genotyping is implemented for patients with planned fluoropyrimidine treatment.[11]

Limitations

Although *DPYD* genotyping has been demonstrated to be beneficial for guiding therapy in DPD deficiency, it is important to understand the limitations of current genotype tests. It is very likely that other clinically relevant variants of the *DPYD* gene have yet to be identified, or that evidence for validity in predicting toxicity is still insufficient for some of the existing variants. Also, in the event that 2 different variants are identified in the same patient, current *DPYD* genotyping does not confirm if these variant alleles are carried on the same or different chromosomes.[12] This means there is potential for incorrect prediction of DPD enzyme function. Lastly, the higher prevalence of clinically significant variants in the Caucasian population and lack of robust evidence around variants more prone in racial/ethnic groups has resulted in genetic tests that largely favour a Caucasian population.

Recommendation 2:

Prospective *DPYD* genotyping should be included in the planning of fluoropyrimidine-based therapies.

Recommendation 3:

Prior to initiating fluoropyrimidine-based therapies, patients should be screened for clinically relevant *DPYD* variants (c.1905+1G>A, c.2846A>T, c.1679T>G, and c.1236G>A).

Genotype-guided Fluoropyrimidine Dosing

To reduce the risk of severe, potentially fatal toxicity in carriers of *DPYD* variants, an individualized approach to fluoropyrimidine dosing should be considered standard of care. The feasibility of genotype-guided dosing has been demonstrated in the prospective clinical trial by Dineen et al., in which patients were screened for *DPYD**2A, and heterozygous carriers received a 50% dose reduction in the starting dose of capecitabine (90%) or 5-FU (10%). The rate of severe toxicity in carriers receiving reduced dose was comparable to non-carriers receiving standard doses (28% vs. 23%, respectively, p=0.64).[22] Similar results were observed by Henricks et al. for prospectively screened heterozygous carriers of all four clinically relevant variants receiving genotype-guided doses, compared to non-carriers on standard doses. The relative risk of severe toxicity was reduced in carriers of *DPYD**2A and c.1679T>G variants but not in c.2846A>T and c.1236G>A carriers who received a 25% dose reduction rather than 50%.[28]

The question of whether genotype-guided dose reductions impact treatment efficacy was assessed in a 2019 study by Henricks et al. Forty prospectively identified heterozygous *DPYD**2A carriers treated with a 50% dose reduction were compared to matched controls (non-carriers, full dose). The investigators found that reduced doses did not have a statistically significant effect on overall survival (27 months vs. 24 months, p=0.47) or progression-free survival (14 months vs. 10 months, p=0.54) of patients that carried the variant compared to non-carriers receiving full doses.[23]

In addition to guidelines published by European groups,[6,29] the Clinical Pharmacogenetics Implementation Consortium (CPIC) developed guidelines for recommended treatment modifications of 5-FU and capecitabine, before the start of therapy.[3] For heterozygous carriers of decreased or no-function *DPYD* variants (partial DPD deficiency) starting doses should be reduced by 50%, followed by titration based on tolerability or toxicity. The dose reduction for heterozygous carriers of decreased function variants (c.2846A>T and c.1236G>A) was changed in a 2018 update. Previously, dose reductions for this group started at 25% based on small retrospective or prospective trials that suggested higher doses might be tolerated. However, after an increased toxicity risk despite 25% dose reduction in a large prospective trial, a greater dose reduction of 50% was recommended.[28] For individuals that are homozygous for a no-function variant (complete DPD deficiency), fluoropyrimidines should be avoided altogether as no safe dose has been established. Pre-treatment dose recommendations based on genotype and likely phenotype, for standard dosing schedules (e.g. excluding metronomic low dosing), are summarized in Appendix 1.

It is important to consider that even if a patient is a carrier of a decreased or no function variant, they may still tolerate normal 5-FU or capecitabine doses. Conversely, patients may still experience severe toxicities despite a reduction in starting dose. Other factors can influence the risk of fluoropyrimidine toxicity including the chemotherapy regimen and patient characteristics such as age, gender, and performance status.[11,30] According to the CPIC guidelines, during the first 2 cycles of treatment, doses should be increased for patients who do not experience intolerable adverse effects, and further reduced in patients that do not tolerate starting doses despite an initial dose reduction.[3] There are no clear guidelines on how to adjust subsequent doses. Monitoring should be ongoing and doses readjusted if necessary in subsequent cycles to maintain effectiveness and tolerability.

Recommendation 4:

Initial dose adjustments for fluoropyrimidine treatments should be made according to the *DPYD* genotype identified, as part of an informed discussion with patients based on consideration of risks and benefits. During subsequent cycles, the dose should be re-adjusted according to the patient's tolerance to minimize toxicity and to optimize the treatment's effectiveness.

Incorporating *DPYD* Testing into Clinical Practice

As *DPYD* genotyping becomes more available, a standardized approach to dose individualization for initial fluoropyrimidine treatment becomes necessary for incorporating into routine clinical practices across Ontario. Based on the currently available evidence, genotype-guided screening for the four *DPYD* variants (.1905+1G>A, c.2846A>T, c.1679T>G, and c.[1236G>A; 1129-5923C>G]) should be conducted for every patient being considered for treatment with fluoropyrimidine therapy. The results of the genotype test should be integrated into electronic health records (EHR) and if possible, made available in computerized physician order entry (CPOE) systems in a way that is easily accessible for present and future clinical decision-making. Studies have shown that when protocols are in place, clinicians will more readily follow guideline recommendations,[31] and protocols for ordering and assessing genotype tests in patients with planned fluoropyrimidine therapy should be implemented on an institutional level. Figure 2 provides a schematic overview of a suggested implementation workflow.

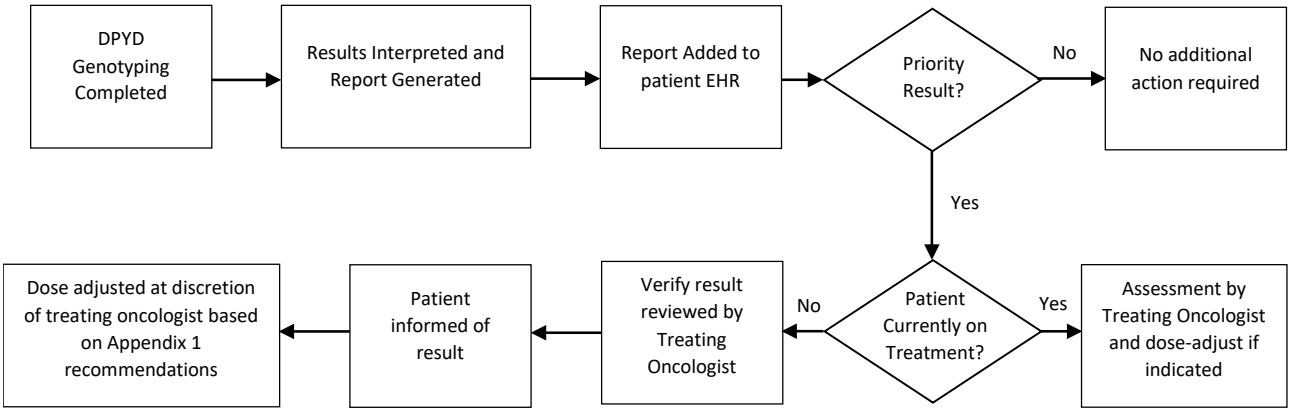

Figure 2. Suggested Implementation Workflow for *DPYD* Testing. EHR = Electronic Health Record. Priority result = a genetic test result that necessitates a change in drug, drug dose, or drug monitoring. Adapted from: Clin Pharmacol Ther. 2018;103(2):210-216

Barriers to Implementation

Barriers to implementing *DPYD* testing may include infrastructure challenges, including logistics and technology systems (e.g. cumbersome test ordering or issues linking results between multiple systems) or clinician perceptions or apprehensions (e.g. concerns around compromising efficacy with reduced doses or delays in starting treatment).[31]

Capecitabine can be dispensed in outpatient pharmacies outside of the cancer hospital system and pharmacogenetic tests may not be available or registered as a contraindication in the pharmacy system. Ensuring that *DPYD* test results are addressed at the clinic or hospital, when fluoropyrimidines are being prescribed, will help mitigate this risk. As more pharmacogenetic tests become available, pharmacy systems are likely to expand their databases to include these tests.

The cultural shift required to overcome concerns around treatment efficacy may be more challenging, but will ultimately depend on the availability of evidence. Henricks et al. reported no statistically significant difference in overall survival (OS) or progression-free survival (PFS) between variant carriers

that received reduced doses and non-carriers receiving full dose.[23] These results support the assumption that dose reductions in DPD-deficient patients do not result in inferior treatment outcomes. Launay et al. also investigated the effect of 5-FU dose individualization on treatment effectiveness. Of the 59 digestive cancer patients, 15 were identified as DPD deficient via dihydrouracil:uracil ratio and received an average dose reduction of 35%. Compared to non-deficient patients, there were no statistically significant differences in stable disease or progressive disease (p=0.893)[32]. The limitation of these studies is that they are small, and numerical differences could be clinically meaningful with a larger sample size. However, based on the available evidence, treatment response and cancer outcomes are not compromised by pre-emptively reducing doses in patients with DPD deficiencies. Dose reduction, along with individual dose titration are expected to result in usual responses to treatment.

Guidelines for Implementing *DPYD* Testing

- Patients who may be candidates for fluoropyrimidine therapy should be identified at the earliest visit (e.g. first meeting with oncologist), and testing performed as early as possible
- Successful implementation will require embedding *DPYD* testing into a standard pre-chemotherapy check process. EHRs may be leveraged to ensure clear documentation and communication of test results and dose modification plans. These should be integrated as part of the multi-disciplinary clinical safety checks, prior to initiating 5-FU or capecitabine based treatments.
- The results of genetic testing should inform an initial treatment plan that includes other risk factors for toxicity, and patient characteristics and values; treatment plans should be adjusted to account for patient tolerance and treatment effectiveness, at the discretion of the treating oncologist. (Appendix 1)

Management of Toxicities in DPD-deficient Patients

With the adoption of genetic pre-screening into routine practice, a reduction in the risk of toxicity due to DPD deficiency is expected. However, not all toxicities can be attributed to genetic alterations in *DPYD* or entirely to DPD deficiency, and patients receiving reduced starting doses may still experience toxicities. Several non-genetic factors can also contribute to a patients' risk of toxicity including age, renal function, treatment regimen (e.g. combination therapy with cisplatin, oxaliplatin or irinotecan), type and duration of fluoropyrimidine administration and concomitant medications (e.g. cimetidine or metronidazole).[11,33,34]

It is imperative that patients are monitored for *severe* fluoropyrimidine-related toxicities, especially during the first 2 cycles of treatment. Patients should be provided with adequate education on the toxicities associated with treatment and encouraged to seek immediate medical care should toxicities arise, as symptoms may progress quickly.[35]

Mild toxicities can be managed according to local guidelines, based on treatment regimen and patient factors at the discretion of the treating physician. Decisions to further dose reduce or use alternative therapy will depend on clinician discretion. Suggested management of fluorouracil and capecitabine toxicities can be found on the OH-CCO Drug Formulary website.

In case of severe or life-threatening toxicity:

- Stop treatment with fluoropyrimidines.
- Provide supportive care (e.g. hemodynamic support, parenteral nutrition, antibiotic prophylaxis)[34]
- Provide an oral antidote to fluoropyrimidine, if available
    - Uridine triacetate (Vistogard®) is a prodrug of uridine and competes with 5-FU metabolites for incorporation into RNA and therefore reduces cellular damage.[33,35]
    - It is recommended to initiate uridine triacetate as soon as possible (within 96 hours of last fluoropyrimidine dose)
    - The recommended dose is 10 grams (1 packet of coated granules) orally every 6 hours for 20 doses in total
    - Uridine triacetate is not marketed in Canada but is available through the Health Canada Special Access Program for emergency treatment.[33]
- Permanent discontinuation for future 5-FU or capecitabine treatment may be required depending on the clinical scenario and clinician discretion. If treatment is permanently discontinued, this should be clearly documented in EHR to ensure patient is not re-treated.

Appendix

Appendix 1: 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[d] 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.

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**.

Tables 3 & 4 – 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

CPIC guidelines and content are subject to updates and modifications, refer to cpicpgx.org for most current content.

Appendix 2: Terminology

Activity score	A score assigned to alleles of a gene based on the extent to which they influence enzymatic activity; 1=fully functional, 0.5=reduced function, 0=non-functional. Gene activity score is the sum of the two lowest individual variant activity scores; represents the enzymatic phenotype of a patient, translated from *DPYD* genotype.
Allele	One of two or more versions of a gene at a given site (locus) on a chromosome. An individual inherits two alleles for each gene, one from each parent.
Carrier	An individual who carries one or more gene variants.
Genotype	The combination of alleles that an individual carries
Heterozygous	A variant is present in only one of the 2 alleles. Compound or double heterozygous refers to 2 different variants simultaneously present on each of the alleles.
Homozygous	An identical variant is present in both alleles.
Intermediate metabolizer	An individual carrying one normal function allele plus one no function or decreased function allele, *or* an individual carrying two decreased function alleles
Normal metabolizer	An individual carrying two normal function alleles
Phenotype	Expression of a trait e.g. DPD activity
Poor metabolizer	An individual carrying two no function alleles *or* an individual carrying one no function plus one decreased function allele
Wild-type	A gene in its natural, non-mutated form

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