Fluoropyrimidine Treatment in Patients with Dihydropyrimidine Dehydrogenase (DPD) Deficiency

GUIDANCE FOR CLINICIANS

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Ontario Health
Cancer Care Ontario

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Introduction

Objective

Ontario Health (Cancer Care Ontario) initiated provincial reimbursement for *DPYD* genotyping in cancer patients with planned fluoropyrimidine treatment in April 2023. This guideline was developed to support the implementation and interpretation of routine *DPYD* testing across Ontario and optimize fluoropyrimidine (FP) treatment in patients with these genetic variants.

A review and potential update of the guideline was requested by regional stakeholders as they gained experience with *DPYD* testing in Ontario, and as new literature became available. In 2024, a literature review was undertaken, and consensus-based, evidence-informed revisions were incorporated into the recommendations in early 2025, in collaboration with the *DPYD* Expert Panel. This updated guideline provides information on expanding *DPYD* testing to advance the scope and better support the delivery of high-quality care to all patients in Ontario.

Background

Fluoropyrimidines (FPs), 5-fluorouracil (5-FU) and capecitabine, have been widely used for decades in the treatment of a variety solid tumours (such as colorectal, gastric, head and neck and breast cancers), and remain the backbone of many combination chemotherapy regimens. The benefits of FP treatment are well established, however, toxicities such as diarrhea, mucositis, myelosuppression and hand-foot syndrome are common and can lead to treatment interruption, discontinuation, or hospitalization. Despite treatment with fluoropyrimidines being generally well tolerated, it has been 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 FP-related toxicity can be attributed in part to inter-patient variability in the activity of dihydropyrimidine dehydrogenase (DPD), the enzyme primarily responsible for FP catabolism. Genetic variations in the encoding gene, *DPYD*, are the most studied and recognized cause of reduced DPD activity (DPD deficiency). Inter-patient variability can cause considerable challenges when treating patients with FPs.[1,2,8] Identifying patients with causative genetic variants in *DPYD* can serve as one of the predictive markers of FP toxicity and help guide initial dosing of FP to reduce toxicity in patients with DPD deficiency.

Guideline Development and Recommendations

Methods

This guidance for clinicians was developed in collaboration with a multi-disciplinary group consisting of medical oncologists, pharmacists, nurses, a pathologist, molecular geneticist and clinical pharmacologist with knowledge and experience in pharmacogenomics and FP treatment. A review of relevant guidelines and available literature was conducted between December 2021 and February 2022. Foundational documents included the Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline[7] and the Ontario Health – Health Technology Assessment report.[9] Recommendations were developed based on best available evidence and expert consultations. The final content was reviewed and validated by clinical experts in Ontario.

A second literature review was conducted between June and September 2024. In February 2025, the multi-disciplinary panel of expert clinicians reviewed current guidelines and relevant literature based on the updated literature search, with a focus on additional clinically relevant *DPYD* variants by race, ethnicity and ancestry. Recommendations were updated based on best available evidence and consensus, and final content was reviewed by the expert panel.

Literature Search Strategy

The updated literature search was conducted using Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to May 20, 2024>. Results were limited to publications between January 2021 and May 2024. No methodological filters were applied to limit retrieval by publication type. A grey literature search was conducted on May 29, 2024, through a targeted internet search (site search, hand search, Google advanced search, Google Scholar) and included previously identified Canadian and international organizations and sources. Results were limited to resources from December 2021 to May 29, 2024. After preliminary review of the search results, additional searches were performed using PubMed, Google Scholar and sources referenced within other publications. New publications since the primary literature search in December 2021 and publications that investigated additional clinically relevant *DPYD* variants were the primary focus of the searches. Appendix 5 outlines the details of the search strategy.

Recommendations

Recommendation 1: Education

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.* With universal access to *DPYD* testing, the risks should be markedly reduced, however no current test can detect all variants.

*Patient education materials on DPD deficiency and testing are available on the Ontario Health (Cancer Care Ontario) website.
Refer to the DPD Deficiency Section for more information.

Recommendation 2: Planning

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

Refer to the Incorporating DPYD Testing into Clinical Practice section for more information.

Recommendation 3: Screening

Prior to initiating fluoropyrimidine-based therapies, patients should be screened for the following clinically relevant *DPYD* variants (as more evidence becomes available, the list of clinically relevant variants may be subject to revision):

- c.1905+1G>A
- c.2846A>T
- c.1679T>G
- c.1129-5923C>G (required)/
  c.1236G>A (optional) (HapB3 when identified together)
- c.557A>G
- c.2779C>T **
- c.868A>G**

**Clinical judgement should be exercised when interpreting test results for these variants as clinical evidence is limited. Consult with experts as necessary.
Refer to the DPD Deficiency and Testing for DPD Deficiency sections for more information.

Recommendation 4: Genotype-guided Treatment

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.

Refer to the Genotype-guided Fluoropyrimidine Dosing section for more information.

Overview

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 (FUMP and FUDR) at the tumour site, which leads to interference with RNA and DNA synthesis, and ultimately cell death. This only accounts for 1 to 5% of 5-FU. 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.[5,10] Changes in DPD enzyme activity therefore have a significant effect on the metabolism of 5-FU. Reduced DPD activity leads to decreased clearance of 5-FU, and accumulation of active metabolites, which enhances toxicity. In cases of severe 5-FU toxicity, reduced DPD activity was detected in 20 to 61% of patients.[2,8,9,11,12] This finding highlights the important role of the DPD enzyme in predicting fluoropyrimidine toxicity.

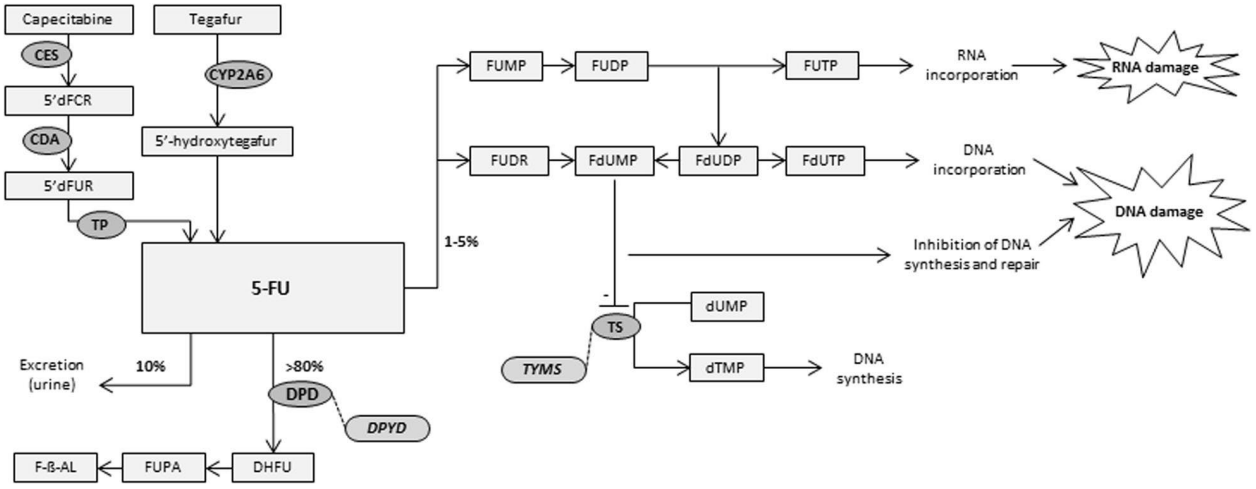

Figure 1 – Overview of fluoropyrimidine metabolism. Capecitabine, a pro-drug of 5-FU, is converted to 5-FU, then undergoes the same metabolism as 5-FU. The anabolism and catabolism of 5-FU are shown to the right and bottom left, respectively; the remaining 5-FU is excreted renally. Tegafur is not available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

DPD Deficiency

DPD deficiency refers to the partial or complete loss of DPD enzymatic function, often the result of genetic variants in the *DPYD* gene, which encodes the DPD enzyme. Numerous variants in the *DPYD* gene have been identified, however not all of them alter the enzymatic activity of DPD or increase the risk of FP toxicity. Several studies and meta-analyses have investigated the association between

specific *DPYD* variants, and DPD activity or fluoropyrimidine toxicity. From this, clinically actionable *DPYD* variants have been identified with the most established risk (moderate to strong evidence).[7] These include: c.1905+1G>A (*2A), c.1679T>G (*13), c.2846A>T, c.[1236G>A; 1129-5923C>G] (HapB3) and c.557A>G.[7,8,13,14] Of these variants, c.1905+1G>A and c.1679T>G have the most deleterious effect on DPD activity. Variants c.2846A>T, c.1129–5923C>G and c.557A>G result in moderately reduced DPD activity (Table 1).[7] Additional variants, including c.2279C>T and c.868A>G have also been linked to moderate reductions in DPD activity. Although clinical evidence for these two variants remains limited, in vitro studies have demonstrated reduced DPD activity, and both have been recognized as clinically relevant by the Association for Molecular Pathology (AMP).[15,16] Other *DPYD* variants continue to be investigated to address their potential clinical relevance or impact on FP-associated toxicity.

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

DPYD Variant	Activity Score[a]	Functional Status[b,7]	Reduction in DPD Activity	
			Heterozygous State[7,9,16,17]	Homozygous State[9]
Wild type e.g. c.1627A>G (*5) c.85T>C (*9A)	1	Normal activity	None	None
c.2846A>T	0.5	Decreased activity	30%	50%
c.1236G>A, c.1129-5923C>G[c] haplotype B3 (HapB3)	0.5	Decreased activity	35%	20-70%
c.557A>G	0.5	Decreased activity	46%	N/A
c.2279C>T	0.5	Decreased activity	45%[d]	N/A
c.868A>G	0.5	Decreased activity	45%[d]	N/A
c.1905+1G>A (*2A)	0	No activity	50%	100%
c.1679T>G (*13)	0	No activity	68%	75%

N/A Not available

a Individual variant allele activity score (distinct from gene activity score); see Appendix 2 for definitions

b Variant allele definitions and assignment of allele function can be found in the CPIC *DPYD* Allele Functionality Table[18]

c Recent evidence suggests that these 2 variants are not in complete linkage disequilibrium (one may exist without the other); c.1129-5923C>G is likely the causal variant leading to decreased function.

d Heterozygous expression in vitro. There is currently no clinical data available for *DPYD* variants c.2279C>T and c.868A>G.

Prevalence of *DPYD* Variants

The combined carrier frequency of the variants c.1905+1G>A (*2A), c.2846A>T, c.1679T>G (*13), c.1129-5923C>G, c.1236G>A and c.557A>G is approximately 5 – 7% of the general population.[7,19] The majority of clinical studies which provide evidence for the clinical utility of *DPYD* testing were conducted in European populations, where the variants c.1905+1G>A (*2A), c.2846A>T, c.1679T>G(*13), c.1129-5923C>G, c.1236G>A are most prevalent. However, there are biogeographical differences in variant frequency that have been noted.[7,12,20,21] Due to heterogenous definitions of "race", "ethnicity" and "ancestry" in genetic research, these terms are often used interchangeably to describe biological constructs, however, "race" and "ethnicity" are generally recognized as social constructs. Consequently, the terms employed in this report reflect those used in the referenced studies and databases. The most studied variant c.1905+1G>A, which has been reported to have a carrier frequency of 1.6% in European populations, has a multiethnic allele frequency of 0 to 0.5%. Similarly, the most common "European" variant c.1129-5923C>G (4.7% carrier frequency) has an allele frequency that ranges from 0.06 to 2.4% when taking into account other populations/ancestral groups.[7,15] The variant c.2846A>T has a carrier frequency of 0.7% in the European population and the rare, no function variant c.1679T>G is also primarily observed in this group (0.08%).[15] These "European" variants are much less prevalent in those of African ancestry and are rare or absent in individuals of East Asian ancestry.[7,9,12,15] The variant c.557A>G (Y186C), by contrast, is more prevalent among those with African genetic ancestry (3 to 5% carrier frequency) and is virtually non-existent in European, East Asian and South Asian populations.[7,21,22] Similarly, the rare c.868A>G variant has not been found in those of European, East Asian or South Asian populations but is observed in the African ancestry population at an overall frequency of 0.2%.[15] The decreased function variant c.2279C>T is different from the others in that it is mostly present in individuals of South Asian ancestry (0.5 to 1%), and has not been observed in those of African or European ancestry.[15,22,23] The geographic and ancestral variation among *DPYD* variants is described in Table 2.

Table 2 - Allele frequencies of *DPYD* variants by ancestry

***DPYD* Variant**	**Allele Frequency, %**				
	African	**Admixed American (AMR)/ Latino**	**East Asian**	**European**	**South Asian**
c.1905+1G>A	0.08	0.14	0	0.5	0.82
c.1679T>G	0	0	0	0.1	0
c.2846A>T	0.08	0.29	0	0.7	0.1
c.1129–5923C>G, c.1236G>A	0.08	0.58	0	2.39	1.94
c.557A>G	2.27	0.29	0	0	0
c.2279C>T	0	0	0	0	0.61
c.868A>G	0.15	0.14	0	0	0

Data derived from 1000 Genomes project phase III, pharmgkb.org [23]

Partial DPD deficiency can occur at a frequency of 3 to 8%, which varies among populations, however, complete DPD deficiency is rare, with an estimated incidence of 0.1% in the general population [14,15,24] Complete DPD deficiency is a rare, autosomal recessive disorder that shows a wide variability in clinical presentations and is associated with a higher risk of toxicity to FP. The complete absence of DPD activity is listed as a contraindication in the product monographs of both capecitabine and 5-FU.[25,26] Product manufacturers also recommend consideration of DPD deficiency testing prior to starting treatment with either agent.

Clinical Considerations

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.[7,11,12] These tests are not widely available and use is limited due to unclear clinical validity and lack of testing standardization.[9] In addition, measuring DPD activity upfront on a routine basis would be technically and logistically challenging, labour intensive, and costly.[11] 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.[1,7,8,14,27,28] 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.[7,8]

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.[29,30] 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.[12,31–33] Studies conducted in Quebec and Ontario illustrate the impact of pre-treatment *DPYD* genotyping in the Canadian landscape.[3,33] 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).[3] 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).[33]

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.[29,34] 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.[35]

Limitations

While *DPYD* genotyping has demonstrated value in guiding therapy for patients with DPD deficiency, it is important to recognize and consider the limitations of current genotyping tests.

The clinical actionability of *DPYD* variants through genotyping depends largely on the available evidence supporting their clinical utility. Ongoing research is exploring other *DPYD* variants to determine their potential clinical relevance and impact on FP-associated toxicity. It remains possible that other clinically relevant variants have not yet been identified. In addition, not all identified variants have clear or validated functional consequences on the DPD enzyme, particularly rare variants. As a result, there is no clear clinical guidance on how to interpret these variants.

When two different *DPYD* variants are identified in the same patient, most current genotyping methods do not indicate whether these variant alleles are carried on the same chromosome (cis) or different chromosomes (trans).[12] This makes interpretation of the test challenging as compound heterozygous poor metabolizers may not be flagged. Therefore, there is a potential risk for under detecting DPD deficiency.

EQUITY CONSIDERATIONS

For some variants, the evidence supporting their clinical utility in predicting FP toxicity remains limited or inconclusive. This is especially true for variants more commonly found in people of certain races, ethnicities and ancestries, which have often been understudied and lack validation in clinical settings. Diverse populations are also often under-represented in reference genomic databases and research. Given this, there is a higher chance of receiving a variant of unknown clinical significance (VUS) result from genetic testing in populations of certain races, ethnicities and ancestries. As a result, there are currently no clear recommendations on the use of FP in carriers of certain variants more

commonly found in diverse populations. The stronger body of evidence for variants primarily found in populations described as “European” or “Caucasian” in the literature, meaning white people, underscores existing inequities in pharmacogenetic testing, which disproportionately favour this group.

Genotype-guided Fluoropyrimidine Dosing

Summary of Evidence & Discussion

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).[29] Similar results were observed by Henricks et al. for prospectively screened heterozygous carriers of *DPYD* variants *DPYD**2A, c.2846A>T, c.1679T>G, and c.1236G>A 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%.[36]

The impact of genotype-guided dose reductions on treatment efficacy was evaluated in a 2019 study by Henricks et al. In this study, 40 prospectively identified heterozygous *DPYD**2A carriers who received a 50% dose reduction were compared to matched non-carrier controls who received full doses. The results showed no statistically significant difference in overall survival (OS) between the two groups (27 months for carriers vs. 24 months for non-carriers, p=0.47), nor in progression-free survival (PFS) (14 months vs. 10 months, p=0.54), suggesting that dose reduction in patients that carried the variant did not compromise treatment efficacy.[37]

Recommendations

International expert groups including the Dutch Pharmacogenetics Working Group (DPWG) and the Clinical Pharmacogenetics Implementation Consortium (CPIC) have provided guidance for the clinical interpretation of *DPYD* genotype tests to optimize FP treatment.[7,38] These guidelines utilize a gene activity score to standardize the reporting of predicted overall DPD activity. Based on this score, an individual’s genotype is assigned a likely phenotype – normal, intermediate or poor metabolizer – with prescribing recommendations for FPs prior to the start of treatment.

Heterozygous carriers of decreased or no-function *DPYD* variants (partial DPD deficiency) are classified as intermediate metabolizers with an activity score of 1 or 1.5. In these patients, CPIC recommends that starting doses of 5-FU and capecitabine should be reduced by 50%, followed by titration based on tolerability or toxicity. In a 2018 update, the initial dose reduction for heterozygous carriers of decreased function variants (e.g. c.2846A>T and c.1236G>A) was revised.[18] Previously, a 25% to 50% dose reduction was recommended, based on small retrospective or prospective trials suggesting that higher doses might be tolerated. However, findings from a large, prospective trial

indicated an increased toxicity risk despite 25% dose reduction, and the recommended starting dose reduction was increased to 50%.[36] Individuals that are homozygous for a no-function variant (complete DPD deficiency) are categorized as poor metabolizers with an activity score of 0. FPs should be avoided altogether in these patients as no safe dose has been established. Rarely, individuals may carry one decreased function allele and one no-function allele. These patients are also considered poor metabolizers, but with an activity score of 0.5. FP treatment in these patients should also be avoided in most cases; if deemed necessary, careful consideration should be taken. Markedly reduced doses may be appropriate in certain cases (Appendix 1).

Ontario Health (Cancer Care Ontario) has largely adopted the pharmacogenomic-guided dosing recommendations provided by CPIC, with minor modifications. The pre-treatment dose recommendations – based on genotype and likely phenotype – for standard dosing schedules (excluding metronomic low-dose protocols), are outlined in Appendix 1.

The *DPYD* variants outlined in these recommendations were included based on their established association with toxicity risk, strength of supporting evidence, guidance from other pharmacogenetics groups, and expert consensus. For the two variants, c.2279C>T and c.868A>G, in vitro data suggests that they result in reduced DPD activity comparable to other variants assigned an activity score of 1.5. However, unlike other variants in this category, the clinical evidence supporting their impact is limited.[16,18,23] Despite this, both variants are classified as Tier 1 (recommended for testing) by AMP, which considers the effect on protein function, allele frequency in certain populations/ancestral groups, available reference materials and feasibility to test in a laboratory.[15] Dosing recommendations for these variants differ: a starting dose reduction of 25 to 50% should be considered, with particular emphasis on careful dose titration based on individual tolerability. Given the limited clinical evidence, it is important to use best clinical judgement and consult with experts in this area if needed.

It is important to recognize that carriers of a decreased or no function *DPYD* variant may still tolerate standard doses of 5-FU or capecitabine, while some patients may experience severe toxicities even with reduced starting doses. Fluoropyrimidine toxicity risk is influenced by multiple factors beyond *DPYD* genotype, including the chemotherapy regimen and patient characteristics such as age, sex, and performance status.[7,39] According to CPIC guidelines, dose escalation should be considered after the first two treatment cycles for patients who do not experience intolerable adverse effects, while further dose reductions are recommended for patients that do not tolerate initially reduced doses.[7] However, clear guidelines on how to adjust subsequent doses is lacking. Ongoing monitoring is essential, and doses should be re-evaluated and adjusted if necessary in subsequent cycles to maintain treatment effectiveness and patient tolerability.

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 available evidence, genotype-guided screening for the recommended *DPYD* variants 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, guideline recommendations will be followed more readily,[40] 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.

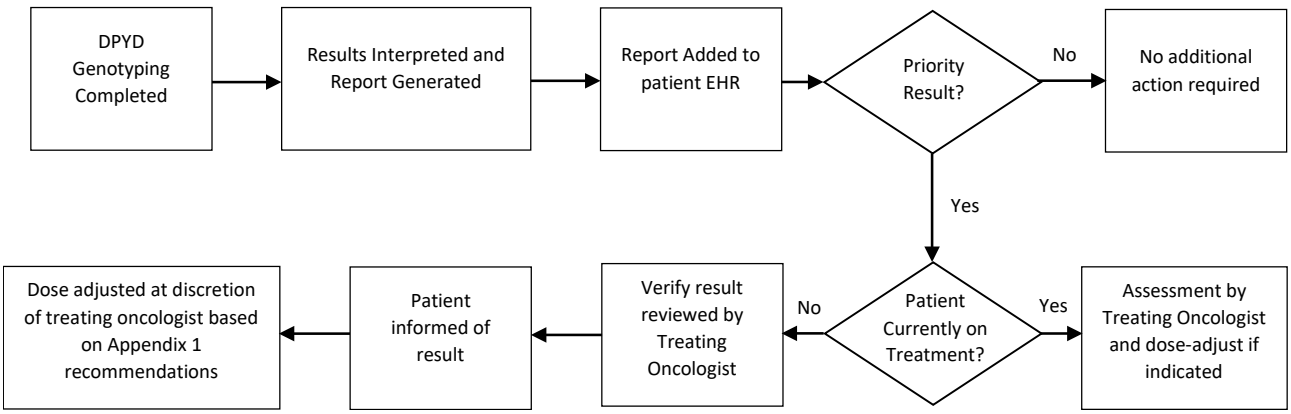

Figure 2. Suggested Implementation Workflow for *DPYD* Testing. EHR = Electronic Health Record. Priority result = a genetic test result that necessitates a change in drug, drug dose, or drug monitoring. Adapted from: Clin Pharmacol Ther. 2018;103(2):210-216

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).[40]

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 systems. 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 about treatment efficacy will ultimately be driven by the strength and availability of supporting evidence. Henricks et al. reported no statistically significant difference in OS or PFS between variant carriers that received reduced doses and non-carriers receiving full dose.[37] 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)[41]. 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.

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.

Management of Toxicities in DPD-deficient Patients

The integration of genetic pre-screening into routine clinical practice is expected to lower the risk of toxicity associated with DPD deficiency. However, not all cases of FP-related toxicity can be explained by *DPYD* variants or solely attributed to reduced DPD activity. Even patients who receive reduced starting doses may still experience toxicities. Several non-genetic factors can 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 the use of concomitant medications (e.g. cimetidine or metronidazole).[9,42,43]

Close monitoring for *severe* fluoropyrimidine-related toxicities is essential, especially during the first two cycles of treatment.[7] Patients should be provided with adequate education about potential side effects and encouraged to seek immediate medical attention at the first sign of toxicity, as symptoms may progress quickly.[44]

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 Ontario Health (Cancer Care Ontario) Drug Formulary website.

In case of severe or life-threatening toxicity:

1. Stop treatment with fluoropyrimidines.
2. Provide supportive care (e.g. hemodynamic support, parenteral nutrition, antibiotic prophylaxis)[42]
3. 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.[43,44]
    - 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.[43]
4. 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 1: Pharmacogenomic-Guided Dosing Recommendations

Table 3 - Fluoropyrimidine Starting Dose Recommendations by *DPYD* Variant

Status	*DPYD* Variant 1	*DPYD* Variant 2	Activity Score[a]	*DPYD* Metabolizer[b]	Starting Dose Recommendation[c]
Homozygous	any normal function variant	any normal function variant	2	Normal	No dose adjustment
	c.1905+1G>A (*2A)	c.1905+1G>A (*2A)	0	Poor	Avoid use of 5-FU or 5-FU prodrug-based regimens.
	c.1679T>G (*13)	c.1679T>G (*13)	0	Poor	Avoid use of 5-FU or 5-FU prodrug-based regimens.
	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.2846A>T	c.2846A>T	1	Intermediate	Reduce[d] starting dose by 50%[e]
	c.557A>G	c.557A>G	1	Intermediate	Reduce[d] starting dose by at least 50%
	c.2279C>T	c.2279C>T	1	Intermediate	Reduce[d] starting dose by at least 50%
	c.868A>G	c.868A>G	1	Intermediate	Reduce[d] starting dose by at least 50%
Heterozygous	c.1905+1G>A (*2A)	any normal function variant	1	Intermediate	Reduce[d] starting dose by 50%
	c.1679T>G (*13)	any normal function variant	1	Intermediate	Reduce[d] starting dose by 50%
	c.1129-5923C>G, c.1236G>A (HapB3)	any normal function variant	1.5	Intermediate	Reduce[d] starting dose by 50%
	c.2846A>T	any normal function variant	1.5	Intermediate	Reduce[d] starting dose by 50%
	c.557A>G	any normal function variant	1.5	Intermediate	Reduce[d] starting dose by 50%
	c.2279C>T	any normal function variant	1.5	Intermediate	Reduce[d] starting dose by 25-50%
	c.868A>G	any normal function variant	1.5	Intermediate	Reduce[d] starting dose by 25-50%

Status	*DPYD* Variant 1	*DPYD* Variant 2	Activity Score[a]	*DPYD* Metabolizer[b]	Starting Dose Recommendation[c]
Compound Heterozygous	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.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.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.1905+1G>A (*2A)	c.557A>G	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.2279C>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.1905+1G>A (*2A)	c.868A>G	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

Status	*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.1679T>G (*13)	c.557A>G	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.2279C>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)	c.868A>G	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)	c.2846A>T	1	Intermediate	Reduce[d] starting dose by 50%

Status	*DPYD* Variant 1	*DPYD* Variant 2	Activity Score[a]	*DPYD* Metabolizer[b]	Starting Dose Recommendation[c]
	c.1129-5923C>G, c.1236G>A (HapB3)	c.557A>G	1	Intermediate	Reduce[d] starting dose by 50%
	c.1129-5923C>G, c.1236G>A (HapB3)	c.2279C>T	1	Intermediate	Reduce[d] starting dose by 50%
	c.1129-5923C>G, c.1236G>A (HapB3)	c.868A>G	1	Intermediate	Reduce[d] starting dose by 50%
	c.2846A>T	c.557A>G	1	Intermediate	Reduce[d] starting dose by 50%
	c.2846A>T	c.2279C>T	1	Intermediate	Reduce[d] starting dose by 50%
	c.2846A>T	c.868A>G	1	Intermediate	Reduce[d] starting dose by 50%
	c.557A>G	c.2279C>T	1	Intermediate	Reduce[d] starting dose by 50%
	c.557A>G	c.868A>G	1	Intermediate	Reduce[d] starting dose by 50%
	c.2279C>T	c.868A>G	1	Intermediate	Reduce[d] starting dose by 50%

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 tolerability. 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.

Table 4 & 5: Fluoropyrimidine Starting Dose Recommendations Summary [a]

Table 4 - Fluoropyrimidine Starting Dose Recommendations for *DPYD* Variants in the Heterozygous State[a]

***DPYD* Variant (Heterozygous[a])**	**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%
c.557A>G	Reduce[c] starting dose by 50%
c.2279C>T	Reduce[c] starting dose by 25-50%
c.868A>G	Reduce[c] starting dose by 25-50%

Table 5 - Fluoropyrimidine Starting Dose Recommendations for *DPYD* Variants in the Homozygous State:

***DPYD* Variant (Homozygous)**	**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]
c.557A>G	Reduce[c] starting dose by at least 50%
c.2279C>T	Reduce[c] starting dose by at least 50%
c.868A>G	Reduce[c] starting dose by at least 50%

a. Not including compound or double heterozygous.
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

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.

Appendix 2: Glossary

Term	Definition
Activity score	A score from 0 to 1 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 allele 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
Multiethnic allele frequency	The distribution of a specific genetic variant across multiple ethnic or ancestral populations. The terms “race” and “ethnicity” are often used in studies to refer to genetic ancestry.
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	Allele or genetic sequence that represents the standard, non-mutated form found most commonly in a given population and typically associated with normal biological function (i.e. not expected to alter drug metabolism).

Appendix 3: Nomenclature for *DPYD* Variants

Variant	Legacy Name	rsID	*DPYD* RefSeqGene (LRG_722)	GRCh38.p13 chr 1	HGVS protein nomenclature
c.1905+1G>A	*2A	rs3918290	NG_008807.2: g.476002G>A	NC_000001.11: g.97450058C>T	N/A
c.1679T>G	*13	rs55886062	NG_008807.2: g.410273T>G	NC_000001.11: g.97515787A>C	NP_000101.2: p.Ile560Ser
c.2846A>T	N/A	rs67376798	NG_008807.2: g.843669A>T	NC_000001.11: g.97082391T>A	NP_000101.2: p.Asp949Val
c.1129–5923C>G, **c.1236G>A**	HapB3	rs75017182, rs56038477	NG_008807.2: g.346167C>G, NG_008807.2: g.352197G>A	NC_000001.10: g.97579893G>C, NC_000001.10: g.97573863C>T	N/A, NP_000101.2: p.Glu412Z
c.557A>G	N/A	rs115232898	NG_008807.2: g.226586A>G	NC_000001.11: g.97699474T>C	NP_000101.2: p.Tyr186Cys
c.2279C>T	N/A	rs112766203	NG_008807.2: g.620781C>T	NC_000001.11: g.97305279G>A	NP_000101.2: p.Thr760Ile
c.868A>G	N/A	rs146356975	NG_008807.2: g.330911A>G	NC_000001.11: g.97595149T>C	NP_000101.2: p.Lys290Glu

Adapted from the AMP Joint Consensus *DPYD* Genotyping Recommendations. Pratt et al. J Mol Diagn. 2024;26(10):851-863.

Appendix 4: Acknowledgements

DPYD Expert Panel Members

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Harriet Feilotter	Molecular Geneticist, Director, Molecular Genetics Laboratory, Kingston Health Sciences Centre Clinical Lead for Genetic Testing, Pathology and Laboratory Medicine Program, Ontario Health (Cancer Care Ontario)	1, 2
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Carlo De Angelis	Pharmacist, Clinician Scientist - Oncology Pharmacy, Sunnybrook Odette Cancer Centre	1, 2
Joseph Del Paggio	Medical Oncologist, Thunder Bay Regional Health Sciences Centre	1
Rachel Goodwin	Medical Oncologist, The Ottawa Hospital	1
Lori Hygaard	Registered Nurse, Manager for Systemic Therapy, Thunder Bay Regional Health Sciences Centre	2
Erin Kennedy	Surgical Oncologist, Sinai Health	2
Richard B. Kim	Clinical Pharmacologist, Wolfe Medical Research Chair in Pharmacogenomics, Chair Division of Clinical Pharmacology, London Health Sciences Centre	1, 2

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Special Mentions

- **Kathleen Bell**, Manager, Provincial Genetics Program, Ontario Health (Cancer Care Ontario)
- **Annie Cheung,** Senior Pharmacist, Systemic Treatment Program, Ontario Health (Cancer Care Ontario)
- **Kimberley Kerr**, Specialist, Medical Librarian (Research Office), Ontario Health
- **Sarah McBain**, Senior Advisor, Health Literacy and Patient Education, Ontario Health (Cancer Care Ontario)
- Patient and Family Advisor who reviewed the patient information sheet
- **Kylin Zhang**, Leslie Dan Faculty of Pharmacy, University of Toronto PharmD student

Appendix 5: Literature Search Strategy

Date: January 28, 2025
Date range: 2021 – present (May 2024)
Language: English
Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to May 20, 2024>

#	Query	Results
1	exp fluorouracil/ or exp capecitabine/ or exp tegafur/	51,830
2	(5-FU or 5FU or fluorouracil or 5-fluorouracil or 5Fluorouracil or fluoro uracil* or fluoruracil* or fluouracil* or fluracedyl* or floxuridin* or fluracil* or fluril* or fluro uracil* or fluroblastin* or adrucil* or onkofluor* or ribofluor* or flurablastin or fluracilium or ecansya or capecitabine* or fluorocytidine* or xeloda or tegafur* or florafur* or fluorofur* or futraful* or ftorafur* or sunfural* or uftoral* or utefos*).ti,ab,kf.	58,186
3	(Fluoropyrimidin* or (fluoro adj3 pyrimidinedion*)).ti,ab,kf.	4,102
4	exp Dihydropyrimidine Dehydrogenase Deficiency/ or exp "Dihydrouracil Dehydrogenase (NADP)"/	1,431
5	((pharmacogenetic* or pharmacogenomic* or pg guided or dpyd* or dpd or dhp or dhpdhase or dihydropyrimidine dehydrogenase or genotype-guided or genotype-based) adj5 (dosage or dosing or dose* or screen* or assessment* or genotyp* or check* or test* or status)).mp.	6,646
6	1 or 2 or 3	74,664
7	4 or 5	7,738
8	6 and 7	1,426
9	limit 8 to (english language and yr="2021-Current")	197
10	(exp infant/ or exp child/ or adolescent/) not exp adult/	2,201,068
11	9 not 10	195

Appendix 6: References

1. Lee AM, Shi Q, Pavey E, et al. DPYD variants as predictors of 5-fluorouracil toxicity in adjuvant colon cancer treatment (NCCTG N0147). *J Natl Cancer Inst*. 2014;106(12):1-12. doi:10.1093/jnci/dju298
2. Van Kuilenburg ABP. Dihydropyrimidine dehydrogenase and the efficacy and toxicity of 5-fluorouracil. *Eur J Cancer*. 2004;40(7):939-950. doi:10.1016/j.ejca.2003.12.004
3. Wigle TJ, Povitz BL, Medwid S, et al. Impact of pretreatment dihydropyrimidine dehydrogenase genotype-guided fluoropyrimidine dosing on chemotherapy associated adverse events. *Clin Transl Sci*. 2021;14(4):1338-1348. doi:10.1111/cts.12981
4. Froehlich TK, Amstutz U, Aebi S, Joerger M, Largiadèr CR. Clinical importance of risk variants in the dihydropyrimidine dehydrogenase gene for the prediction of early-onset fluoropyrimidine toxicity. *Int J Cancer*. 2015;136(3):730-739. doi:10.1002/ijc.29025
5. Lunenburg CATC, van der Wouden CH, Nijenhuis M, et al. Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene–drug interaction of DPYD and fluoropyrimidines. *European Journal of Human Genetics*. 2020;28(4):508-517. doi:10.1038/s41431-019-0540-0
6. Piedbois P. Toxicity of fluorouracil in patients with advanced colorectal cancer: Effect of administration schedule and prognostic factors. *Journal of Clinical Oncology*. 1998;16(11):3537-3541. doi:10.1200/JCO.1998.16.11.3537
7. 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. doi:10.1002/cpt.911
8. Terrazzino S, Cargnin S, Del Re M, Danesi R, Canonico PL, Genazzani AA. DPYD IVS14+1G>A and 2846A>T genotyping for the prediction of severe fluoropyrimidine-related toxicity: a meta-analysis. *Pharmacogenomics*. 2013;14(11):1255-1272. doi:10.2217/pgs.13.116
9. Ontario Health. DPYD Genotyping in Patients Who Have Planned Cancer Treatment With Fluoropyrimidines: A Health Technology Assessment. *Ont Health Technol Assess Ser*. 2021;21(14):1-186.
10. Diasio RB, Harris BE. Clinical pharmacology of 5-fluorouracil. *Clin Pharmacokinet*. 1989;16:215-237.
11. Meulendijks D, Henricks LM, Jacobs BAW, et al. Pretreatment serum uracil concentration as a predictor of severe and fatal fluoropyrimidine-associated toxicity. *Br J Cancer*. 2017;116(11):1415-1424. doi:10.1038/bjc.2017.94
12. Haute Autorité de Santé, Institut National du Cancer. Recherche de déficit en dihydropyrimidine déshydrogénase en vue de prévenir certaines toxicités sévères survenant sous traitement comportant des fluoropyrimidines. Recommandations et référentiels. 2018. Accessed February 4, 2022. https://www.has-sante.fr/portail/upload/docs/application/pdf/2018-12/recherche_dun_deficit_en_dihydropyrimidine_deshydrogenase_visant_a_prevenir_certaines_toxicites_severes_associees_aux_traite.pdf
13. Rosmarin D, Palles C, Church D, et al. Genetic markers of toxicity from capecitabine and other fluorouracil-based regimens: Investigation in the QUASAR2 study, systematic review, and meta-analysis. *Journal of Clinical Oncology*. 2014;32(10):1031-1039. doi:10.1200/JCO.2013.51.1857

14. Meulendijks D, Henricks LM, Sonke GS, et al. Clinical relevance of DPYD variants c.1679T>G, c.1236G>A/HapB3, and c.1601G>A as predictors of severe fluoropyrimidine-associated toxicity: A systematic review and meta-analysis of individual patient data. *Lancet Oncol*. 2015;16(16):1639-1650. doi:10.1016/S1470-2045(15)00286-7
15. Pratt VM, Cavallari LH, Fulmer ML, et al. DPYD Genotyping Recommendations: A Joint Consensus Recommendation of the Association for Molecular Pathology, American College of Medical Genetics and Genomics, Clinical Pharmacogenetics Implementation Consortium, College of American Pathologists, Dutch Pharmacogenetics Working Group of the Royal Dutch Pharmacists Association, European Society for Pharmacogenomics and Personalized Therapy, Pharmacogenomics Knowledgebase, and Pharmacogene Variation Consortium. *Journal of Molecular Diagnostics*. 2024;26(10):851-863. doi:10.1016/j.jmoldx.2024.05.015
16. Offer SM, Fossum CC, Wegner NJ, Stuflesser AJ, Butterfield GL, Diasio RB. Comparative functional analysis of dpyd variants of potential clinical relevance to dihydropyrimidine dehydrogenase activity. *Cancer Res*. 2014;74(9):2545-2554. doi:10.1158/0008-5472.CAN-13-2482
17. Offer SM, Lee AM, Mattison LK, Fossum C, Wegner NJ, Diasio RB. A DPYD variant (Y186C) in individuals of african ancestry is associated with reduced DPD enzyme activity. *Clin Pharmacol Ther*. 2013;94(1):158-166. doi:10.1038/clpt.2013.69
18. Clinical Pharmacogenetics Implementation Consortium (CPIC). Updates Since Publication. CPIC® Guideline for Fluoropyrimidines and DPYD. 2018. Accessed March 19, 2025. https://cpicpgx.org/guidelines/guideline-for-fluoropyrimidines-and-dpyd/
19. Nguyen DG, Morris SA, Hamilton A, et al. Real-World Impact of an In-House Dihydropyrimidine Dehydrogenase (DPYD) Genotype Test on Fluoropyrimidine Dosing, Toxicities, and Hospitalizations at a Multisite Cancer Center . *JCO Precis Oncol*. 2024;(8). doi:10.1200/po.23.00623
20. Liu XQ, Zhuang M, Wang Z, Huber RM. Correlation between dihydropyrimidine dehydrogenase and efficacy and toxicity of fluoropyrimidine drugs. *Eur Rev Med Pharmacol Sci*. 2014;18(18):2772-2776.
21. Chan TH, Zhang JE, Pirmohamed M. DPYD genetic polymorphisms in non-European patients with severe fluoropyrimidine-related toxicity: a systematic review. *Br J Cancer*. 2024;131(3):498-514. doi:10.1038/s41416-024-02754-z
22. Wu A, Anderson H, Hughesman C, et al. Implementation of pharmacogenetic testing in oncology: DPYD-guided dosing to prevent fluoropyrimidine toxicity in British Columbia. *Front Pharmacol*. 2023;14:1257745. doi:https://dx.doi.org/10.3389/fphar.2023.1257745
23. Whirl-Carrillo M, Huddart R, Gong L, et al. An Evidence-Based Framework for Evaluating Pharmacogenomics Knowledge for Personalized Medicine. *Clin Pharmacol Ther*. 2021;110(3):563-572. doi:10.1002/cpt.2350
24. Henricks LM, Opdam FL, Beijnen JH, Cats A, Schellens JHM. DPYD genotype-guided dose individualization to improve patient safety of fluoropyrimidine therapy: Call for a drug label update. *Annals of Oncology*. 2017;28(12):2915-2922. doi:10.1093/annonc/mdx411
25. Hoffmann-La Roche Ltd. *Xeloda Product Monograph*.; 2021.
26. Accord Healthcare Inc. *Fluorouracil Product Monograph*.; 2019.
27. Toffoli G, Giodini L, Buonadonna A, et al. Clinical validity of a DPYD-based pharmacogenetic test to predict severe toxicity to fluoropyrimidines. *Int J Cancer*. 2015;137(12):2971-2980. doi:10.1002/ijc.29654

28. Henricks LM, Lunenburg CATC, Meulendijks D, et al. Translating DPYD genotype into DPD phenotype: Using the DPYD gene activity score. *Pharmacogenomics*. 2015;16(11):1277-1286. doi:10.2217/PGS.15.70
29. Deenen MJ, Meulendijks D, Cats A, et al. Upfront genotyping of DPYD∗2A to individualize fluoropyrimidine therapy: A safety and cost analysis. *Journal of Clinical Oncology*. 2016;34(3):227-234. doi:10.1200/JCO.2015.63.1325
30. Henricks LM, van Merendonk LN, Meulendijks D, et al. Effectiveness and safety of reduced-dose fluoropyrimidine therapy in patients carrying the DPYD*2A variant: A matched pair analysis. *Int J Cancer*. 2019;144(9):2347-2354. doi:10.1002/ijc.32022
31. European Medicines Agency. *EMA Recommendations on DPD Testing Prior to Treatment with Fluorouracil, Capecitabine, Tegafur and Flucytosine*. Vol 31.; 2020.
32. Aubin F. Pre-emptive testing for dihydropyrimidine deshydrogenase (DPD) deficiency to improve patient safety with fluoropyrimidine therapy. In: *Ontario Gastrointestinal Cancers Advisory Committee Meeting*. ; 2020.
33. Jolivet C, Nassabein R, Soulières D, et al. Implementing DPYD*2A Genotyping in Clinical Practice: The Quebec, Canada, Experience. *Oncologist*. 2021;26(4):e597-e602. doi:10.1002/onco.13626
34. Henricks LM, Lunenburg CATC, Man FM de, et al. A cost analysis of upfront DPYD genotype–guided dose individualisation in fluoropyrimidine-based anticancer therapy. *Eur J Cancer*. 2018;107:60-67. doi:https://doi.org/10.1016/j.ejca.2018.11.010
35. Ontario Health. DPYD Genotyping in Patients Who Have Planned Cancer Treatment With Fluoropyrimidines: Recommendation. *Toronto (ON): Queen's Printer for Ontario*. Published online 2021:1-6.
36. Henricks LM, Lunenburg CATC, de Man FM, et al. DPYD genotype-guided dose individualisation of fluoropyrimidine therapy in patients with cancer: a prospective safety analysis. *Lancet Oncol*. 2018;19(11):1459-1467. doi:10.1016/S1470-2045(18)30686-7
37. Henricks LM, van Merendonk LN, Meulendijks D, et al. Effectiveness and safety of reduced-dose fluoropyrimidine therapy in patients carrying the DPYD*2A variant: A matched pair analysis. *Int J Cancer*. 2019;144(9):2347-2354. doi:10.1002/ijc.32022
38. Lunenburg CATC, van der Wouden CH, Nijenhuis M, et al. Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene–drug interaction of DPYD and fluoropyrimidines. *European Journal of Human Genetics*. 2020;28(4):508-517. doi:10.1038/s41431-019-0540-0
39. Schwab M, Zanger UM, Marx C, et al. Role of genetic and nongenetic factors for fluorouracil treatment-related severe toxicity: A prospective clinical trial by the German 5-FU toxicity study group. *Journal of Clinical Oncology*. 2008;26(13):2131-2138. doi:10.1200/JCO.2006.10.4182
40. Martens FK, Huntjens DW, Rigter T, Bartels M, Bet PM, Cornel MC. DPD testing before treatment with fluoropyrimidines in the Amsterdam UMCs: An evaluation of current pharmacogenetic practice. *Front Pharmacol*. 2020;10(January):1-10. doi:10.3389/fphar.2019.01609
41. Launay M, Dahan L, Duval M, et al. Beating the odds: Efficacy and toxicity of dihydropyrimidine dehydrogenase-driven adaptive dosing of 5-FU in patients with digestive cancer. *Br J Clin Pharmacol*. 2016;81(1):124-130. doi:10.1111/bcp.12790
42. Alberta Health Services. Management of 5-fluorouracil (5-Flourouracil, 5FU) infusion overdose guidelines. 2016;(February):1-5.
43. Ontario Health (Cancer Care Ontario). *Fluorouracil Drug Monograph*.; 2021. https://www.cancercareontario.ca/en/drugformulary/drugs/monograph/43831

44. Lipman B, Pasetka M. Dihydropyrimidine dehydrogenase (DPD) deficiency. *Hot Spot: The Newsletter of the Rapid Response Radiotherapy Program of the Odette Cancer Centre*. 2018;20(3).

Appendix 7: History

Date	Summary of Changes
July 2025	Version 2 • Recommendations 1 and 3 updated. *DPYD* Variants c.557A>G, c.2779C>T c.868A>G added to recommended testing panel with caveats for the latter two variants. • Allele frequencies of *DPYD* variants in certain populations/ancestral group added • Pharmacogenomic-guided starting dose recommendations for the variants c.557A>G, c.2779C>T c.868A>G added • Limitations section updated • Objective and Methods sections added. Reformatted.
April 2023	Version 1 First published as new clinical guidance.