Guideline Resource Unit
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Adaptation of Ontario Health (Cancer Care Ontario) Guidance Material

Fluoropyrimidine Treatment in Patients with Dihydropyrimidine Dehydrogenase (DPD) Deficiency

Effective Date: May 2025

Cancer Care Alberta

Clinical Practice Guideline SPEC-002 – Version 1 – DRAFT
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Background

Dihydropyrimidine dehydrogenase (DPD) is a key enzyme involved in the metabolism of fluoropyrimidines, such as 5-fluorouracil (5-FU) and capecitabine. These agents are widely used in cancer therapy. In 2023 alone, 1,635 patients in Alberta received their first dose of intravenous fluorouracil or oral capecitabine (unpublished internal data from Cancer Surveillance & Reporting). Genetic variation in the *DPYD* gene, can lead to severe and potentially life-threatening toxicities in patients receiving fluoropyrimidine-based therapy. Screening for DPD deficiency is essential for identifying patients at risk of adverse drug reactions, allowing personalized dose adjustments or selection of alternative therapies.

Recognizing this critical need, the 2023 guidance material from Ontario Health (Cancer Care Ontario [CCO]) on Fluoropyrimidine Treatment in Patients with Dihydropyrimidine Dehydrogenase (DPD) Deficiency provides comprehensive recommendations for clinicians. It is the most detailed Canadian guidance available, outlining essential discussions, necessary screenings, and potential dose adjustments for fluoropyrimidine treatment. The guidance material includes input from experts in medical oncology, pharmacy, laboratory services, pathology and patient education.

This adaptation aims to contextualize the guideline for the Alberta population, leveraging the extensive work done by Ontario Health (CCO) to minimize duplication of efforts.

Guideline Questions

1. Which patients would benefit from DPD deficiency testing?
2. What type of testing should be done?
3. Which *DPYD* variants should patients be screened for?
4. Should fluoropyrimidine doses be adjusted according to *DPYD* genotype results?

Search Strategy

For the 2025 guideline adaptation, the PubMed database was searched for relevant studies, guidelines and consensus documents published between 2021-2024. The specific search strategy, search terms, and search results, are presented in Appendix A. Online resources from oncology-based health organizations and guideline developers were also systematically searched, and relevant guidelines were considered in the development of our recommendations.

Target Population

The following recommendations apply to adult patients (≥18 years of age) with planned fluoropyrimidine-based therapies.

Endorsement Methodology

The Guideline Working Group adapted the Ontario Health (CCO) guidance material, *Fluoropyrimidine Treatment in Patients with Dihydropyrimidine Dehydrogenase (DPD) Deficiency*[1], using the process

outlined in Ontario Health (CCO)'s Guideline Endorsement Protocol[2]. This process included selecting a guideline, assessing the recommendations, drafting the endorsement document by the Guideline Working Group, conducting an internal review by content and methodology experts, and an external review by the Alberta Provincial Gastrointestinal, Breast, Endocrine and Lung Tumour Teams.

The Guideline Working Group assessed the quality of the Ontario Health (CCO) guideline using the AGREE II tool[3]. AGREE II is a validated tool designed to assess the methodological rigor and transparency of guideline development. Detailed results of the AGREE II assessment are available in Appendix B. The overall quality of the guidance material was rated a 5 on a scale from 1 to 7 by both appraisers. The AGREE II average quality ratings for the individual domains were as follows: scope and purpose scored 58%, stakeholder involvement 86%, rigor of development 42%, clarity of presentation 94%, applicability 66%, and editorial independence 0%.

The Guideline Working Group assessed each recommendation from the 2023 Ontario Health (CCO) guidance material, *Fluoropyrimidine Treatment in Patients with Dihydropyrimidine Dehydrogenase (DPD) Deficiency*[1], to determine if it should be endorsed verbatim, adapted with modifications, or rejected. This assessment was conducted using a SurveyMonkey survey. Respondents were asked whether they agreed with Ontario Health (CCO)'s interpretation of the available evidence, its applicability and acceptability in the Alberta context, its feasibility for implementation, and whether any new evidence published since Ontario Health (CCO) completed its literature review in 2021 might alter the recommendations.

The survey was distributed by the Guideline Resource Unit (GURU) to the DPD Deficiency Working Group members. It remained open from September 27, 2024, to October 21, 2024. To ensure a response rate greater than 50%, two reminders were sent. Four of the five potential respondents, completed the survey, resulting in an 80% response rate. The respondents comprised three medical oncologists, and one laboratory representative. The results of the survey are available in Appendix C.

As part of the external review, the revised guideline was sent to medical oncologists and pharmacists of the Provincial Gastrointestinal, Breast, Endocrine, and Lung Tumour Teams, for review and feedback. The review period ran from January 6 to January 20th 2025, with a reminder sent midway. Nine people responded.

Recommendations

Of the four Ontario Health (CCO)[1] recommendations, one was endorsed, two were adapted with major modifications, and one was adapted with a minor modification. None were rejected.

Major modifications include content rewrites, reorganization, the introduction of new concepts, or significant alterations, while minor modifications refer to typos, stylistic changes, formatting adjustments, and clarifying statements.

For the full evidence base and references supporting the recommendations, readers are encouraged to consult the original guideline. The references included in this adapted guideline focus on new or

modified content, while the underlying recommendations remain grounded in the evidence from the original source.

Recommendation 1

Patients with planned fluoropyrimidine-based therapies should be informed about the possibility of DPD deficiency, the available tests to detect it, and the potential risks associated with fluoropyrimidine treatment in patients with a deficiency. While universal access to DPD testing can significantly reduce risks, it is important to note that no current test can detect all variants. Consequently, a normal test suggests a low risk of DPD deficiency but does not entirely eliminate risk. ***[Adapted with minor modifications]***

Recommendation 2

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

Recommendation 3

Prior to initiating fluoropyrimidine-based therapies, patients should be screened for the following clinically relevant *DPYD* variants: c.557A>G, c.1129-5923C>G, c.1679T>G, c.1905+1G>A, c.2779C>T, c.2846A>T[4-12]. As additional data is collected in Alberta, the list of clinically relevant variants may be subject to revision. The turnaround time for this testing is two weeks. ***[Adapted with major modifications]***

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 that considers the associated risks and benefits. During subsequent cycles, dosing should be individualized with dose escalation or further dose reduction based upon patient tolerance. Please see Table 1. ***[Adapted with major modifications]***

Table 1. 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) **OR** 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) **OR** c.2846A>T **OR** c.557A>G **OR** 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)	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.
c.1679T>G (*13)	c.1129-5923C>G, c.1236G>A (HapB3) **OR** c.2846A>T **OR** c.557A>G **OR** 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.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) **OR** c.2846A>T **OR** c.557A>G **OR** c.2279C>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%
c.2846A>T	c.557A>G **OR** c.2279C>T	1	Intermediate	Reduce[d] starting dose by 50%
c.557A>G	any normal function variant	1.5	Intermediate	Reduce[d] starting dose by 50%
c.557A>G	c.557A>G **OR**	1	Intermediate	Reduce[d] starting dose by 50%

	c.2279C>T			
c.2279C>T	any normal function variant	1.5	Intermediate	Reduce[d] starting dose by 50%
c.2279C>T	c.2279C>T	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 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.
[*] 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 the most current content.

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Appendix A: Search Strategy

Database	Date	Search Terms	Limits	Results
PubMed	June 7, 2024	(((dihydropyrimidine dehydrogenase) OR (DPD)) AND (deficien*)) AND (test*)	Humans, English, 2021-present	35
PubMed	June 11, 2024	(("Fluorouracil"[Mesh] OR fluorouracil OR "Capecitabine"[Mesh] OR capecitabine OR fluoropyrimidines) AND ("Dihydrouracil Dehydrogenase (NADP)"[Mesh] OR "Dihydropyrimidine Dehydrogenase Deficiency"[Mesh] OR "Dihydropyrimidine Dehydrogenase Deficiency" OR "Dihydropyrimidine Dehydrogenase" OR DPYD OR DPD)) AND (test*)	Humans, English, 2021-present	76
PubMed	July 5, 2024	((((dihydropyrimidine dehydrogenase) OR (DPD)) AND (deficien*)) AND (test*)) AND (cost)	Humans, English, 2021-present	3
PubMed	November 27, 2024	((((dihydropyrimidine dehydrogenase) OR (DPD)) AND (deficien*)) AND (test*)) AND (allele OR DPYD)	English, 2019-present	52

Appendix B: AGREE II Score Sheet

	Domain		Item	Appraiser 1 Ratings[b] (RV)	Appraiser 2 Ratings[b] (XK)
1	**Scope and purpose**	1	Overall objective(s) of guideline specifically described.	**7**	**7**
		2	Health question(s) covered by guideline specifically described.	**1**	**1**
		3	Population to whom guideline meant to apply specifically described.	**7**	**4**
Domain score[a] = (27-6/42-6) x100 =21/36 x 100 =0.69 x 100= 58%				Score = 27	
2	**Stakeholder involvement**	4	Guideline development group includes individuals from all relevant professional groups.	**6**	**5**
		5	Views and preferences of target population have been sought.	**7**	**7**
		6	Target users of guideline clearly defined.	**7**	**5**
Domain score[a] = (37-6/42-6) x 100 = 31/36 x100 = 0.86 x 100= 86%				Score = 37	
3	**Rigor of Development**	7	Systematic methods used to search for evidence.	**1**	**1**
		8	Criteria for selecting evidence clearly described.	**1**	**1**
		9	Strengths and limitations of body of evidence clearly described.	**5**	**1**
		10	Methods for formulating recommendations clearly described.	**1**	**3**
		11	Health benefits, side effects, and risks considered in formulating recommendations.	**7**	**5**
		12	Explicit link b/n recommendations and supporting evidence.	**7**	**7**
		13	Guideline externally reviewed by experts prior to publication.	**6**	**7**
		14	Procedure for updating guideline provided.	**1**	**1**
Domain score[a] = (55-14/112-14) x 100 = 41/98 x 100 = 0.418 x 100= 42%				Score = 55	
4	**Clarity of presentation**	15	Recommendations specific and unambiguous	**7**	**7**
		16	Different options for mgmt. of condition or health issue clearly presented.	**5**	**7**
		17	Key recommendations easily identifiable.	**7**	**7**
Domain score[a] = (40-6/42-6) x 100 = 34/36 x 100 = 0.944 x 100= 94%				Score = 40	
5	**Applicability**	18	Guideline describes facilitators and barriers to application.	**7**	**7**
		19	Guideline provides advice and/or tools on how recommendations can be put into practice.	**7**	**7**
		20	Potential resource implications of applying recommendations considered.	**5**	**5**
		21	Guideline presents monitoring and/or auditing criteria.	**1**	**1**
Domain score[a] = (40-8/56-8) x 100 = 32/48 x 100 = 0.66 x 100= 66%				Score = 40	
6	**Editorial independence**	22	Views of the funding body have not influenced the content of the guideline.	**1**	**1**
		23	Competing interests of guideline development group members have been recorded and addressed.	**1**	**1**
Domain score[a] = (4-4 /28-4) x 100 = 0/24 x 100 = 0%				Score = 4	
Overall guideline assessment		1	Rate overall quality of guideline.	**5**	**5**
		2	I would recommend guideline for use.	**5**	**5**

[a]Domain score = (Obtained score – min. possible score) / (max. possible score – Min. possible score)
[b]Each AGREE II items and global rating items rated on 7-point scale (1, strongly disagree to 7–strongly agree).

Appendix C: Endorsement Results

CCO Recommendations	CCA Comments	Assessment
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.	-A caveat for physicians. Just because a person does not have one or more of the variants in the screen, does not mean that they are not DPD deficient -Whole or partial gene deletions would not be identified. -Patients should have ability to get tested for DPD deficiency and dose adjustments are required for safe treatments. -Clarification: Currently in Alberta screening is not routine and not funded.	Endorse unchanged 75%. Adapt with some modifications, 25%. Reject, 0%.
Recommendation 2 Prospective *DPYD* genotyping should be included in the planning of fluoropyrimidine-based therapies.		Endorse unchanged 100%. Adapt with some modifications, 0%. Reject, 0%.
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).	-Add 2 additional alleles (c.557A>G, c.2279C>T) for genotyping -I agree with the recommendations around the variants listed, but there are other known variants -Is there an enrichment of a particular variant in the Alberta population? i.e. founder effect.	Endorse unchanged 75%. Adapt with some modifications, 25%. Reject, 0%.
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.	-Not all pathogenic variants will be detected with this screen. Your risk is low but not zero if your result is negative in the screen. -Development of clear guidelines of how to interpret DPD deficiency testing results and how to adjust 5-FU/capecitabine dosing.	Endorse unchanged 75%. Adapt with some modifications, 25%. Reject, 0%.
General Comments		
-CCO recommendations are reasonable to be used in Alberta. -I have first-hand experience in application of CCO's *DPYD* testing recommendation in patients using 5FU based chemotherapy. I fully support the recommendations and practice. -The recommendations are evidence based, clear and outlines the required test, interpretation, and application of the results. -If and when adopting this guideline, communication and education to providers are key - Lab. requisition and how to interpret results and adjusting FP if needed.		

Development and Revision History

This guideline was developed by a multidisciplinary working group comprised of medical oncologists, a laboratory representative, and a methodologist from the Guideline Resource Unit. The draft guideline was externally reviewed and endorsed by members of the Alberta Provincial Gastrointestinal, Breast, Endocrine and Lung Tumour Teams who were not involved in the guideline's development, including medical oncologists, and pharmacists. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook and the Ontario Health Guideline Endorsement Protocol.

This guideline was originally developed in 2025.

Maintenance

A formal review of the guideline will be conducted in 2030. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

5-FU, 5-fluorouracil; AGREE, appraisal of guidelines for research and evaluation; CCO, Cancer Care Ontario; DPD, Dihydropyrimidine Dehydrogenase; *DPYD*, Dihydropyrimidine dehydrogenase allele; GURU, guideline resource unit.

Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial Gastrointestinal, Breast, Endocrine, and Lung Tumour Teams and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

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Conflict of Interest Statements

Dr. Dennis Bulman has nothing to disclose.
Dr. Navdeep Dehar has nothing to disclose.
Dr. Jan-Willem Henning has nothing to disclose.
Dr. Vanessa Krause has nothing to disclose.
Dr. David Maj reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or education events.
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***Dr. Dean Reuther** has nothing to disclose.
Rachel Vanderploeg has nothing to disclose.

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