

CADTH Reference List

Dihydropyrimidine Dehydrogenase Testing for Fluoropyrimidine Toxicity

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Key Message

- One evidence-based guideline was identified regarding the use of dihydropyrimidine dehydrogenase testing before treatment with fluoropyrimidine (i.e., 5-fluorouracil and capecitabine) in patients being treated for cancer.

Research Question

What are the evidence-based guidelines regarding the use of dihydropyrimidine dehydrogenase testing before treatment with fluoropyrimidine (i.e., 5-fluorouracil and capecitabine) in patients being treated for cancer?

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were treatment with fluoropyrimidine (i.e., 5-fluorouracil and capecitabine) in patients with cancer and dihydropyrimidine dehydrogenase (DPD) testing. No filters were applied to limit the retrieval by study type, with the exception of DPD testing only, which was limited to guidelines. Comments, newspaper articles, editorials, and letters were excluded. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents published between January 1, 2011 and January 23, 2021. Internet links were provided, where available.

Selection Criteria and Summary Methods

One reviewer screened literature search results (titles and abstracts) and selected publications according to the inclusion criteria presented in Table 1. Full texts of study publications were not reviewed. The Overall Summary of Findings section was based on information available in the abstracts of selected publications. Open-access, full-text versions of evidence-based guidelines were reviewed when abstracts were not available and relevant recommendations were summarized.

Results

One evidence-based guideline was identified regarding the use of dihydropyrimidine dehydrogenase testing before treatment with fluoropyrimidine (i.e., 5-fluorouracil and capecitabine) in patients being treated for cancer.¹

Table 1: Selection Criteria

Criteria	Description
Population	Patients with cancer who are being considered for treatment with fluoropyrimidines
Intervention	DPD testing – based on either the enzyme activity of DPD or the DPYD genotype – before treatment with fluoropyrimidines (i.e., 5-fluorouracil and capecitabine)
Comparator	No comparator
Outcomes	Recommendations regarding DPD testing before treatment with fluoropyrimidines for patient with cancer
Study designs	Evidence-based guidelines

DPD = dihydropyrimidine dehydrogenase.

Additional references of potential interest that did not meet the inclusion criteria are provided in Appendix 1.

Overall Summary of Findings

One relevant guideline was identified for this report.¹ The German Guideline Program in Oncology's guidelines for treating colorectal cancer recommends testing for dihydropyrimidine dehydrogenase (DPD) deficiency before initiating fluoropyrimidine treatment, and states that genotype testing of the *DPYD* gene, specifically testing for the *DPYD*2A* polymorphism, can be performed.¹

Reference

Guidelines and Recommendations

1. S3-Guideline Colorectal Cancer, long version 2.1. AWMF registration number: 021-0070L. Berlin (DE): German Guideline Program in Oncology (German Cancer Society, German Cancer Aid, AWMF); 2019: https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Kolorektales_Karzinom/Version_2/GGPO_Guideline_Colorectal_Cancer_2.1.pdf. Accessed 2021 Jan 25.
See 9.3.2. Dihydropyrimidine Dehydrogenase (p.184-185)

Appendix 1: References of Potential Interest

Systematic Reviews and Meta-analyses

- Conti V, De Bellis E, Manzo V, et al. A Genotyping/Phenotyping Approach with Careful Clinical Monitoring to Manage the Fluoropyrimidines-Based Therapy: Clinical Cases and Systematic Review of the Literature. *J Pers Med*. 2020 Sep 03;10(3):03. [Medline](#)

Non-Randomized Studies

Alternative Outcome – Screening Tests for Dihydropyrimidine Dehydrogenase Genetic Variants or Activity Deficiency

- Capitain O, Seegers V, Metges JP, et al. Comparison of 4 Screening Methods for Detecting Fluoropyrimidine Toxicity Risk: Identification of the Most Effective, Cost-Efficient Method to Save Lives. *Dose Response*. 2020 Jul-Sep;18(3):1559325820951367. [Medline](#)
- Pallet N, Hamdane S, Garinet S, et al. A comprehensive population-based study comparing the phenotype and genotype in a pretherapeutic screen of dihydropyrimidine dehydrogenase deficiency. *Br J Cancer*. 2020 Sep;123(5):811-818. [Medline](#)
- Coenen MJH, Paulussen ADC, Breuer M, et al. Evolution of Dihydropyrimidine dehydrogenase Diagnostic Testing in a Single Center during an 8-Year Period of Time. *Curr Ther Res Clin Exp*. 2019;90:1-7. [Medline](#)
- Neto OV, Raymundo S, Franzoi MA, et al. DPD functional tests in plasma, fresh saliva and dried saliva samples as predictors of 5-Fluorouracil exposure and occurrence of drug-related severe toxicity. *Clin Biochem*. 2018 Jun;56:18-25. [Medline](#)
- Etienne-Grimaldi MC, Boyer JC, Beroud C, et al. New advances in DPYD genotype and risk of severe toxicity under capecitabine. *PLoS One*. 2017;12(5):e0175998. [Medline](#)

Guidelines and Recommendations

Unclear Methodology

- Casneuf V, Borbath I, Van den Eynde M, et al. Joint Belgian recommendation on screening for DPD-deficiency in patients treated with 5-FU, capecitabine (and tegafur). *Acta Clin Belg*. 2021 Jan 11:1-7. [Medline](#)
- 5-fluorouracil (intravenous), capecitabine, tegafur: DPD testing recommended before initiation to identify patients at increased risk of severe and fatal toxicity. London (UK): Medicines and Healthcare Products Regulatory Agency; 2020: <https://www.gov.uk/drug-safety-update/5-fluorouracil-intravenous-capecitabine-tegafur-dpd-testing-recommended-before-initiation-to-identify-patients-at-increased-risk-of-severe-and-fatal-toxicity>. Accessed 2021 Jan 25.
See: Advice for healthcare professionals
- Argilés G, Tabernero J, Labianca R, et al. Localised colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2020 Oct;31(10):1291-1305. [Medline](#)
See: Assessment of risk of complications from adjuvant treatment (p.1296)
- CPIC® Guideline for Fluoropyrimidines and DPYD. Stanford (CA): Clinical Pharmacogenetics Implementation Consortium (CPIC); 2020: <https://cpicpgx.org/guidelines/guideline-for-fluoropyrimidines-and-dpyd/>. Accessed 2021 Jan 25.
- Dihydropyrimidine dehydrogenase (DPD) testing and fluorouracil toxicity: diagnostic recommendation. Munich (DE): Munich Leukemia Laboratory; 2020: <https://www.mll.com/en/diagnostic-offer/pharmakogenetik/dihydropyrimidine-dehydrogenase-dpd-testing-and-fluorouracil-toxicity.html>. Accessed 2021 Jan 25.
See: Figure 1: Algorithm for diagnosis and dose modification before FU-containing therapy (modified according to DHGO position paper 2020)
- EMA recommendations on DPD testing prior to treatment with fluorouracil, capecitabine, tegafur and flucytosine. Amsterdam (NL): European Medicines Agency; 2020: https://www.ema.europa.eu/en/documents/referral/fluorouracil-fluorouracil-related-substances-article-31-referral-ema-recommendations-dpd-testing_en.pdf. Accessed 2021 Jan 25.
See: EMA recommendations on DPD testing prior to treatment with fluorouracil, capecitabine, tegafur and flucytosine (p.1)
- Pharmacovigilance Risk Assessment Committee (PRAC). Fluorouracil and fluorouracil related substances (capecitabine, tegafur and flucytosine) containing medicinal products. Amsterdam (NL): European Medicines Agency; 2020: https://www.ema.europa.eu/en/documents/referral/fluorouracil-fluorouracil-related-substances-article-31-referral-assessment-report_en.pdf. Accessed 2021 Jan 25.

- See: 2.2.3. Screening methods for detection of DPD deficiency (p.17-20); 2.2.5. Guidelines (p.21); 3. Expert Consultation (p.21-27); 7. Grounds for recommendation (p.32-33)
15. Hamzic S, Aebi S, Joerger M, et al. Fluoropyrimidine chemotherapy: recommendations for DPYD genotyping and therapeutic drug monitoring of the Swiss Group of Pharmacogenomics and Personalised Therapy. *Swiss Med Wkly*. 2020 Nov 16;150:w20375. [Medline](#)
 16. Innocenti F, Mills SC, Sanoff H, Ciccolini J, Lenz HJ, Milano G. All You Need to Know About DPYD Genetic Testing for Patients Treated With Fluorouracil and Capecitabine: A Practitioner-Friendly Guide. *JCO Oncol Pract*. 2020 Dec;16(12):793-798. [Medline](#)
 17. Lunenburg C, van der Wouden CH, Nijenhuis M, et al. Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene-drug interaction of DPYD and fluoropyrimidines. *Eur J Hum Genet*. 2020 04;28(4):508-517. [Medline](#)
 18. Machiels JP, René Leemans C, Golusinski W, Grau C, Licitra L, Gregoire V. Squamous cell carcinoma of the oral cavity, larynx, oropharynx and hypopharynx: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2020 Nov;31(11):1462-1475. [Medline](#)
See: Recommendations (p.1471)
 19. Ross P, Marinaki T. Personalised medicine approach for fluoropyrimidine-based therapies. London (UK): UK Chemotherapy Board; 2020: <https://www.theacp.org.uk/userfiles/file/resources/dpd-testing-ukcb-july-2020-final.pdf>. Accessed 2021 Jan 25.
See: Guidance (p.3)
 20. Wormann B, Bokemeyer C, Burmeister T, et al. Dihydropyrimidine dehydrogenase Testing prior to Treatment with 5-Fluorouracil, Capecitabine, and Tegafur: A Consensus Paper. *Oncol Res Treat*. 2020;43(11):628-636. [Medline](#)
 21. Haute Autorité de santé, Giraud C. Screening for dihydropyrimidine dehydrogenase deficiency to decrease the risk of severe toxicities related to fluoropyrimidines (5-fluorouracil or capecitabine). (*INAHTA brief: issue 2019/011*). Edmonton (AB): INAHTA; 2019: https://www.inahta.org/upload/2019/19011_Screening%20for%20dihydropyrimidine%20dehydrogenase%20deficiency.pdf. Accessed 2021 Jan 25.
 22. Quaranta S, Thomas F. Pharmacogenetics of anti-cancer drugs: State of the art and implementation - recommendations of the French National Network of Pharmacogenetics. *Therapie*. 2017 Apr;72(2):205-215. [Medline](#)

Alternative Methodology – Limited Literature Search

23. Clinical Commissioning Urgent Policy Statement Pharmacogenomic testing for DPYD polymorphisms with fluoropyrimidine therapies [URN 1869] (200603P). London (UK): NHS England; 2020: <https://www.england.nhs.uk/wp-content/uploads/2020/11/1869-dpyd-policy-statement.pdf>. Accessed 2021 Jan 25.
See: Commissioning position – Summary (p.1)

Review Articles

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24. Deac AL, Burz CC, Bocse HF, Bocsan IC, Buzoianu AD. A review on the importance of genotyping and phenotyping in fluoropyrimidine treatment. *Med Pharm Rep*. 2020 Jul;93(3):223-230. [Medline](#)
25. Knikman JE, Gelderblom H, Beijnen JH, Cats A, Guchelaar HJ, Henricks LM. Individualized Dosing of Fluoropyrimidine-Based Chemotherapy to Prevent Severe Fluoropyrimidine-Related Toxicity: What are the Options? *Clin Pharmacol Ther*. 2020 Oct 05;05:05. [Medline](#)
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