

March 8, 2023

Re: Provincial Roll-out of *DPYD* testing

Dear colleagues,

It is with pleasure that we write this memo to inform you that the Cancer Genetics & Genomics Laboratory (CGL) at BC Cancer will be offering *DPYD* testing for the entire province effective March 1, 2023. *DPYD* testing has been available as part of a pilot project since August 2022 for patients being treated by VCC oncologists prior to treatment with 5-fluorouracil (5FU)/capecitabine, as well as for patients outside the VCC catchment that have had a known or suspected adverse reaction to 5FU/capecitabine.

The *DPYD* test is designed to detect six common variants in the *DPYD* gene that are known to result in reduced dihydropyrimidine dehydrogenase (DPD) enzymatic activity. The DPD enzyme is responsible for the metabolism and inactivation of more than 80% of administered 5-fluorouracil. It is known that patients with reduced DPD enzyme activity are at risk of early, severe, and life-threatening toxicity if treated with routine standard of care doses of these agents.^{1,2} It is therefore recommended by the Clinical Pharmacogenetics Implementation Consortium (CPIC) that the initial dose of 5-fluorouracil or capecitabine is reduced for patients with *DPYD* genotypes associated with reduced DPD activity.^{3,4}



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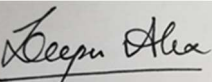
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What patients/indications qualify for *DPYD* testing?

DPYD testing is approved and funded at CGL for all patients in the Province that either:

- Are expected to initiate treatment with 5FU/capecitabine (prospective testing)
- Are known or suspected to have had an unexpected adverse reaction to 5FU/capecitabine (retrospective testing).

Note: Testing is not indicated for patients that have declared themselves to be tolerant of 5FU/capecitabine by virtue of successfully transiting through initial treatment cycles without an unanticipated adverse reaction.

How is the test ordered?

For CST-Cerner sites

- Order the test through CERNER. Select “LAB-Miscellaneous Test (Blood)” in the search window → write “DPYD test” in the ‘Name of the Lab test’ field.
- Print the test requisition. Currently this resides outside of the Cerner environment and can be found at <http://cancergeneticslab.ca/requisitions/> and select “**PDF – Pharmogenomics (including DPYD)**”.
- Test results will be received through the CERNER message center, posted to the patient’s electronic medical record (only Cerner and CAIS) and mailed (paper copy via Canada Post).

For non CST-Cerner sites:

- Print the test requisition. This can be found at <http://cancergeneticslab.ca/requisitions/> and select “**PDF – Pharmogenomics (including DPYD)**”. Give the patient the physical copy of the requisition and instruct them to take it to any phlebotomy lab for sample collection.
- Test results will be posted to the patient’s electronic medical record (only Cerner and CAIS) and mailed (paper copy via Canada Post).

How and where can patients have their blood drawn?

- The patient can be given a physical copy of the requisition that can be taken to any phlebotomy lab for sample collection.
- Alternatively the completed requisition can be either e-mailed (a PDF copy) to LifeLabs at: PatientREQSBC@lifelabs.com or faxed to 1-888-674-0370. Note that the patients should be instructed to wait 24 hours after the requisition is submitted before going to any LifeLabs to ensure that the requisition has been processed. Additional information and instructions regarding this process can be found on LifeLabs website:
<https://www.lifelabs.com/healthcare-providers/requisitions/>

What variants are detected by the *DPYD* test?

Testing is performed by a real-time quantitative PCR (qPCR) assay that has been designed to determine a patient’s genotype for the following six common *DPYD* variants known to be associated with reduced activity of the DPD enzyme:

- *DPYD* c.557A>G: Reduced function allele
- *DPYD* c.1236G>A: Reduced function allele
- *DPYD* c.1679T>G (*DPYD**13): Non-functional allele
- *DPYD* c.1905+1G>A (*DPYD**2A): Non-functional allele
- *DPYD* c.2279C>T: Reduced function allele
- *DPYD* c.2846A>T: Reduced function allele

What will the common results be and how should these be interpreted?

- **No variants identified:** As the vast majority of patients do not harbour a deleterious *DPYD* variant, this is the most common result. It should be noted that this assay does not detect all genetic variation associated with 5FU toxicity. An adverse reaction remains possible. *Predicted CPIC activity score = 2.0*

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- **Heterozygous for reduced function allele:** This patient was found to be a simple carrier of a reduced function *DPYD* allele. This result predicts for reduced DPD activity; suggesting a reduced initial dose of 5FU/capecitabine may be warranted. *Predicted CPIC activity score = 1.5*
- **Heterozygous for null allele:** This patient was found to be a simple carrier of a null or zero function *DPYD* allele. This result predicts for reduced DPD activity; suggesting a reduced initial dose of 5FU/capecitabine may be warranted. *Predicted CPIC activity score = 1.0*
- **Less common (rare) results:** Patient may be found to be compound heterozygotes or homozygotes for some combination of a reduced function or null allele. This result predicts for severely reduced DPD activity. Initial dose of 5FU/capecitabine will be dependent on the genotype identified. *Predicted CPIC activity score = 0 to 1.0*

Note: The *DPYD* test does not detect all variation associated with 5FU toxicity. The presence of other allele(s) associated with reduced DPD function can, therefore, not be excluded.

How should the initial dose of 5FU/capecitabine be altered based on the findings?

The *DPYD* genotype is converted to a predictive CPIC activity score; ranging from 0.0 (no activity) to 2.0 (predicted full activity).^{3,4} The CPIC activity score will be provided in the genetics report. Guidelines for dosing based on CPIC activity score can be found on the BC Cancer website using the following links:

[http://www.bccancer.bc.ca/drug-database-site/Drug Index/Capecitabine Ordering \(Dosing Table for DPYD Genotyping Study\).pdf](http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Capecitabine%20Ordering%20(Dosing%20Table%20for%20DPYD%20Genotyping%20Study).pdf)

or

[http://www.bccancer.bc.ca/drug-database-site/Drug Index/Fluorouracil Ordering \(Dosing Table for DPYD Genotyping Study\).pdf](http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Fluorouracil%20Ordering%20(Dosing%20Table%20for%20DPYD%20Genotyping%20Study).pdf)

What is the expected turn-around time (TAT) for DPYD?

- *DPYD* testing is performed weekly. The expected TAT is routinely ≤10 days. Actual TAT will be dependent on the day the specimen is received at CGL.

References:

- 1 Wörmann 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. doi:10.1159/000510258
- 2 Negarandeh R, Salehifar E, Saghafi F, et al. Evaluation of adverse effects of chemotherapy regimens of 5-fluoropyrimidines derivatives and their association with DPYD polymorphisms in colorectal cancer patients. *BMC Cancer.* 2020;20(1). doi:10.1186/s12885-020-06904-3
- 3 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. Also, November 2018 update. <https://doi.org/10.1002/cpt.911>
- 4 CPIC® Guideline for Fluoropyrimidines and DPYD <https://cpicpgx.org/guidelines/guideline-for-fluoropyrimidines-and-dpyd/>