

Positive Quality Intervention: DPYD Testing Prior to Fluoropyrimidine Treatment

Description: The purpose of this PQI is to review recommendations for *DPYD* testing prior to initiation of treatment with fluoropyrimidine based chemotherapy and increase awareness of the clinical benefit of pre-treatment *DPYD* testing.

Background: Fluoropyrimidine (5-fluorouracil or capecitabine) chemotherapy is highly effective for several solid tumor types, including colorectal and breast cancer. FP treatment is associated with substantial risk of severe toxicities including neutropenia, diarrhea, mucositis, and hand-foot syndrome that can cause hospitalization and death. Approximately 7% of patients carry pathogenic germline variants in *DPYD*, the gene encoding the DPD enzyme. These pathogenic variants reduce DPD activity and substantially increase risk of severe (>50%)^{1,2} and sometimes fatal (2%-4%)³ toxicity. This increased toxicity risk is acknowledged in the FDA-approved drug labeling as well as in clinical practice guidelines published by the National Comprehensive Cancer Network (NCCN).⁴ The Clinical Pharmacogenetics Implementation Consortium (CPIC) assigned *DPYD*/fluoropyrimidines as Level A, indicating that “[*DPYD*] information should be used to change prescribing of [fluoropyrimidines],” and published consensus dosing recommendations based on *DPYD* genotype.⁵ Briefly, patients are assigned a DPD activity score (AS) based on their *DPYD* genotype, and the AS is used to determine whether the patient should receive standard or reduced dosing or should avoid FP treatment, if possible. Two prospective single-arm clinical trials have demonstrated that pre-treatment testing and *DPYD*-guided FP dose-reduction significantly reduces severe toxicity and overall healthcare costs.^{6,7} The NCCN Guidelines for Colon Cancer acknowledge that pre-treatment *DPYD* testing has been demonstrated to reduce toxicity and be cost effective.⁴ Pre-treatment *DPYD*/DPD testing is recommended by the European Society of Medical Oncology (ESMO)⁸ and is standard of care throughout Europe. However, in the United States, pre-treatment testing has not been recommended by the FDA or by the NCCN⁴, and pre-treatment testing is not the prevailing standard of care. Nevertheless, based on the demonstrated clinical benefit, NCODA supports pre-treatment *DPYD* testing.

PQI Process:

- Identify patient scheduled to initiate systemic FP (5-fluorouracil or capecitabine) treatment
- Order CLIA-approved *DPYD* genotype test (<https://www.ncbi.nlm.nih.gov/gtr/>)
- Follow CPIC guideline to recommend appropriate dosing. Table in the supplemental section is up-to-date as of 11/22/2021 but the CPIC website should be consulted for the current dosing recommendations <https://cpicpgx.org/guidelines/guideline-for-fluoropyrimidines-and-dpyd/>
- Monitor patient for toxicity to guide dose escalation or further dose reduction

Patient Centered Activities: The patient should be informed that:

- Testing may take 5-10 days and may not be appropriate when there is an urgent need to start treatment as soon as possible
- A positive *DPYD* test does not guarantee they will experience toxicity from standard FP dosing (risk of toxicity 50%-90%) and a negative test does not guarantee they will not experience toxicity (risk of toxicity ~30%)
- The best available studies suggest that reduced dose chemotherapy in *DPYD* carriers should achieve treatment effectiveness similar to standard dosing in *DPYD* non-carriers; however, definitive studies have not been conducted
- The dose may need to be re-adjusted after the first or second treatment based on whether they are

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tolerating treatment

- Insurance coverage of pre-treatment *DPYD* testing varies by insurance provider and geographic region, and testing may have out of pocket costs of up to \$300

Supplemental Section:

Recommended dosing of fluoropyrimidines (5-fluorouracil or capecitabine) by DPD phenotype

Phenotype	Implications for Phenotypic measures	Dosing recommendations	Classification of recommendation
DPYD normal metabolizer	Normal DPD activity and “normal” risk for fluoropyrimidine toxicity.	Based on genotype, there is no indication to change dose or therapy. Use label-recommended dosage and administration.	Strong
DPYD intermediate metabolizer	Decreased DPD activity (leukocyte DPD activity at 30% to 70% that of the normal population) and increased risk for severe or even fatal drug toxicity when treated with fluoropyrimidine drugs.	Reduce starting dose based on activity score followed by titration of dose based on toxicity or therapeutic drug monitoring (if available). Activity score 1 or 1.5: Reduce dose by 50%	Activity score 1: Strong Activity score 1.5: Moderate
DPYD poor metabolizer	Complete DPD deficiency and increased risk for severe or even fatal drug toxicity when treated with fluoropyrimidine drugs.	Activity score 0.5: Avoid use of 5-fluorouracil or 5-fluorouracil prodrug-based regimens. In the event, based on clinical advice, where alternative agents are not considered a suitable therapeutic option, 5-fluorouracil should be administered at a strongly reduced dose with early therapeutic drug monitoring. Activity score 0: Avoid use of 5-fluorouracil or 5-fluorouracil prodrug-based regimens.	Strong

References:

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3. Sharma BB, Rai K, Blunt H, Zhao W, Tosteson TD, Brooks GA. Pathogenic *DPYD* variants and treatment-related mortality in patients receiving fluoropyrimidine chemotherapy: A systematic review and meta-analysis. *Oncologist.* 2021;10:13967.
4. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Colon Cancer.
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7. Henricks LM, Lunenburg C, de Man FM, et al. *DPYD* genotype-guided dose individualisation of fluoropyrimidine therapy in patients with cancer: a prospective safety analysis. *Lancet Oncol.* 2018;19:1459-1467.
8. Argilés G, Taberero J, Labianca R, et al. Localised colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2020;31:1291-1305. doi: 1210.1016/j.annonc.2020.1206.1022. Epub 2020 Jul 1220.

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