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%) and sometimes fatal (2%-4%) 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).

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. 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. The NCCN Guidelines for Colon Cancer acknowledge that pre-treatment DPYD testing has been demonstrated to reduce toxicity and be cost effective.

Pre-treatment DPYD/DPD testing is recommended by the European Society of Medical Oncology (ESMO) 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 NCCN, 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
- 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/](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%)

*Important notice:* NCODA has developed this Positive Quality Intervention platform. This platform represents a brief summary of medication uses and therapy options derived from information provided by the drug manufacturer and other resources. This platform is intended as an educational aid and does not provide individual medical advice and does not substitute for the advice of a qualified healthcare professional. This platform does not cover all existing information related to the possible uses, directions, doses, precautions, warning, interactions, adverse effects, or risks associated with the medication discussed in the platform and is not intended as a substitute for the advice of a qualified healthcare professional. The materials contained in this platform are for informational purposes only and do not constitute or imply endorsement, recommendation, or favoring of this medication by NCODA, which assumes no liability for and does not ensure the accuracy of the information presented. NCODA does not make any representations with respect to the medications whatever, and any and all decisions, with respect to such medications, are at the sole risk of the individual consuming the medication. All decisions related to taking this medication should be made with the guidance and under the direction of a qualified healthcare professional. Updated 12.13.21
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 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

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Implications for Phenotypic measures</th>
<th>Dosing recommendations</th>
<th>Classification of recommendation</th>
</tr>
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<tbody>
<tr>
<td>DPYD normal metabolizer</td>
<td>Normal DPD activity and “normal” risk for fluoropyrimidine toxicity.</td>
<td>Based on genotype, there is no indication to change dose or therapy. Use label-recommended dosage and administration.</td>
<td>Strong</td>
</tr>
<tr>
<td>DPYD intermediate metabolizer</td>
<td>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.</td>
<td>Reduce starting dose based on activity score followed by titration of dose based on toxicity or therapeutic drug monitoring (if available). <strong>Activity score 1 or 1.5:</strong> Reduce dose by 50%</td>
<td><strong>Activity score 1:</strong> Strong <strong>Activity score 1.5:</strong> Moderate</td>
</tr>
<tr>
<td>DPYD poor metabolizer</td>
<td>Complete DPD deficiency and increased risk for severe or even fatal drug toxicity when treated with fluoropyrimidine drugs.</td>
<td><strong>Activity score 0.5:</strong> 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. <strong>Activity score 0:</strong> Avoid use of 5-fluorouracil or 5-fluorouracil prodrug-based regimens.</td>
<td>Strong</td>
</tr>
</tbody>
</table>

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References:

4. Referenced from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Colon Cancer V.1.2015. © National Comprehensive Cancer Network, Inc 2014. All rights reserved. Accessed [August 22, 2014]. To view the most recent and complete version of the guideline, go online to www.nccn.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

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