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Including *DPYD* on Cancer Genetic Panels to Prevent Fatal Fluoropyrimidine Toxicity

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5-fluorouracil (5-FU) and its oral prodrug capecitabine are fluoropyrimidine agents recommended within NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for many solid tumors, including colon,¹ rectal,² pancreatic,³ biliary tract,⁴ gastric,⁵ head and neck,⁶ ovarian,⁷ and breast cancer.⁸ These agents have generally acceptable toxicity profiles, but a subset of patients experience severe, sometimes fatal toxicity, including myelosuppression, gastrointestinal toxicity, mucositis, and hand-foot syndrome. Severe toxicity is due in part to inherited polymorphisms in dihydropyrimidine dehydrogenase, encoded by the *DPYD* gene, which is the enzyme responsible for fluoropyrimidine elimination. A meta-analysis of >5,000 patients validated 4 decreased-activity *DPYD* polymorphisms (*DPYD**2A [rs3918290], *DPYD**13 [rs55886062], *DPYD* D949V [rs67376798], and *DPYD* HapB3 [rs56038477]) that increase severe toxicity (adjusted relative risk for carrying a variant: 1.59–4.30).⁹ Approximately 7% of Caucasian patients carry 1 of these 4 *DPYD* variants,¹⁰ which confer >50% risk of severe toxicity⁹ and approximately 3% risk of fatal toxicity¹¹ in patients receiving standard fluoropyrimidine dosing. The NCCN Guidelines for Colon Cancer state that carriers of certain *DPYD* variants “have a significantly elevated risk for severe, life-threatening toxicity after a standard dose of fluoropyrimidine”¹¹; however, NCCN Guidelines that recommend fluoropyrimidine agents for other tumor types do not include such a statement.^{2–8}

The increased risk of life-threatening toxicity for variant carriers, so-called clinical validity, is necessary but not sufficient for recommending preemptive *DPYD* genetic testing. The recommendation to test requires clinical utility or evidence that genotyping improves clinical outcomes, which is most directly demonstrated in prospective clinical trials that randomize patients to *DPYD*-guided treatment or non-*DPYD*-guided standard of care.¹² The ideal prospective randomized controlled trial has not been conducted, but the NCCN Guidelines for Colon Cancer acknowledge that, “Two prospective studies have shown *DPYD* genotyping and fluoropyrimidine dose individualization to be feasible in clinical practice, improve patient safety, and be cost-effective.”¹

Deenen et al¹³ genotyped *DPYD**2A in 1,631 fluoropyrimidine-treated patients and dose-reduced *DPYD**2A carriers by 50%, followed by dose escalation as tolerated. The rate of grade ≥3 toxicity was significantly reduced in *DPYD**2A carriers receiving dose reduction (5 of 18; 28%) compared with historical controls receiving standard doses (35 of 48; 73%; *P* < .001).¹³ In another study, 1,181 patients were screened for the 4 validated *DPYD* variants, followed by a 25% or 50% dose reduction, depending on which variant was present.¹⁴ Similar to the findings from Deenen et al, 50% dose reduction in *DPYD**2A carriers normalized the rates of grade ≥3 toxicity (31%), but 25% dose reductions did not sufficiently reduce toxicity in carriers of D949V (47%) or HapB3 (39%), suggesting larger dose reductions are necessary. Across the 2 trials, 0 of 98 (0%) *DPYD* variant carriers who received reduced doses experienced fatal toxicity compared with 1 of 4 (25%) variant carriers who were inadvertently treated with standard doses. Based on these prospective studies, dosing guidelines from the Clinical Pharmacogenetics Implementation Consortium recommend carriers of these 4 *DPYD*

polymorphisms receive an initial 50% dose reduction followed by dose escalation as tolerated.¹⁰

Despite these demonstrations of clinical benefit, clinical uptake of preemptive *DPYD* genotyping has been limited. One reason for the lack of clinical uptake is that the benefit in reducing rates of severe (from >50% to approximately 30%) and fatal (from approximately 3% to <1%) toxicity in *DPYD* carriers must be weighed against the potential risk for diminished efficacy, particularly in the up to 50% of *DPYD* carriers who would not have experienced severe toxicity and received unnecessary dose reduction. These concerns are somewhat attenuated by the similar toxicity rates and systemic drug concentrations in *DPYD**2A carriers receiving 50% dose reduction compared with noncarriers receiving standard doses¹³ and the recommendation to dose-escalate based on tolerability.¹⁰ However, noninferior efficacy has not been formally shown in a randomized prospective clinical trial, which could be the reason that the NCCN Guidelines for Colon Cancer state, “Universal pretreatment *DPYD* genotyping remains controversial, however, and the NCCN Panel does not support it at this time,”¹¹ and that oncology clinical practice guidelines from ASCO¹⁵ and ESMO¹⁶ do not recommend *DPYD* testing.

The primary intent of this commentary is not to advocate for preemptive *DPYD* genotyping, which has been extensively reviewed and debated elsewhere. Although *DPYD* genotyping reduces overall healthcare costs¹³ due to reductions in toxicity-related hospitalization and use of the expensive rescue medication uridine triacetate,¹⁷ one of the barriers to clinical uptake is likely to be the upfront cost and inconvenience of *DPYD* genetic testing. Rather, our intent with this commentary is to advocate for including *DPYD* within genetic testing that is otherwise being conducted in patients with cancer, as a highly efficient strategy to identify *DPYD* carriers without incurring the cost or inconvenience of additional testing in all patients. Clinicians can then decide whether their patients should be considered for initial dose reduction based on the established decrease in toxicity, or receive standard doses based on the potential concern for decreased efficacy.

Patients with cancer undergo genetic testing for several reasons. Testing of the tumor’s somatic genome for treatment selection or trial enrollment often includes matched germline genotyping to differentiate somatic mutations from germline polymorphisms and/or to identify inherited cancer susceptibility syndromes. *DPYD* should be included in matched germline testing conducted simultaneously with somatic tumor genetic testing.¹⁸ When matched germline testing is not conducted, *DPYD* should be included in somatic testing, followed by confirmatory germline testing in a CLIA-validated laboratory to exclude the unlikely possibility of a somatic mutation mimicking the germline polymorphism. Although this approach would incur the cost and inconvenience of *DPYD* testing for that patient, confirmatory testing of only the approximately 7% of suspected *DPYD* carriers is much more efficient than testing all patients before treatment.

The NCCN Guidelines recommend germline genetic testing for selected patients with colorectal, breast, and ovarian cancers, and all patients with pancreatic cancer.^{1,3,7,8} These are tumor types for which NCCN Guidelines include fluoropyrimidine regimens. Patients with these tumor types have a 5% to 10% prevalence of an actionable germline mutation, which is similar to the approximately 7% prevalence of carrying a potentially actionable *DPYD* allele. NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic recommend consideration of multigene panel testing for certain patients who meet testing criteria.¹⁹ Multigene panel testing may include intermediate penetrant genes without clinical actionability.

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DPYD should be included on all multigene germline panels for patients with tumor types that receive fluoropyrimidines, and is currently included on the Color panel (www.color.com).²⁰ Finally, patients suspected of carrying a *DPYD* variant based on nonclinical, direct-to-consumer genetic testing such as 23andMe, which includes *DPYD* variants, should also be sent for confirmatory germline *DPYD* testing in a CLIA-validated laboratory before fluoropyrimidine treatment.

Testing for 4 reduced-activity polymorphisms in *DPYD* decreases incidence of severe toxicity from fluoropyrimidine treatment but is not standard practice due to concerns about the potential for decreased efficacy, costs and inconvenience of testing, and lack of endorsement from

oncology guidelines. We advocate for inclusion of *DPYD* within genetic testing otherwise being conducted in patients with cancer types treated with fluoropyrimidine agents. We believe this represents a highly efficient strategy to identify *DPYD* carriers for whom fluoropyrimidine dose reduction should be considered to prevent severe, sometimes fatal, toxicity.

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