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On behalf of our cosignatories, we respectfully request that the NCCN Colon Cancer and Rectal Cancer Panels consider the enclosed data in support of amending the NCCN Colon and Rectal Cancer Guidelines.

Specific changes: We recommend the inclusion of a footnote in the Colon and Rectal Cancer Guidelines stating: “Germline polymorphisms of the *DPYD* gene are known to increase risk for grade 3-5 toxicity among patients receiving fluoropyrimidine chemotherapy. Consider pharmacogenomic or phenotypic testing to assess for risk of severe toxicity prior to initiation of fluoropyrimidine chemotherapy.”

FDA Clearance: The current FDA label for 5-fluorouracil states: *“Increased Risk of Serious or Fatal Adverse Reactions in Patients with Low or Absent Dipyrimidine Dehydrogenase Activity: Withhold or permanently discontinue fluorouracil in patients with evidence of acute early-onset or unusually severe toxicity, which may indicate near complete or total absence of dipyrimidine dehydrogenase (DPD) activity. No fluorouracil dose has been proven safe in patients with absent DPD activity. (5.1)”*

Rationale: Fluoropyrimidines, including 5-fluorouracil and capecitabine, are some of the most commonly prescribed anti-cancer medications. Fluoropyrimidines are metabolized into non-toxic metabolites by dihydropyrimidine dehydrogenase, the product of the *DPYD* gene. Among patients exposed to fluoropyrimidine chemotherapy, DPD deficiency is associated with significant toxicities including nausea, vomiting, diarrhea, mucositis, dehydration, leukopenia, neutropenia, thrombocytopenia, and treatment-related mortality.¹

Approximately 3-5% of the population has DPD deficiency, and most cases of DPD deficiency are caused by germline polymorphisms of the *DPYD* gene.² Fifty to 88% of patients with pathogenic polymorphisms of the *DPYD* gene will develop grade 3-5 toxicity upon treatment with fluoropyrimidine chemotherapy. While fluoropyrimidine-associated mortality is infrequent (estimated at 0.5-1%), the risk of treatment-related mortality increases to approximately 10% for heterozygous carriers of the *DPYD**2A allele (1-2% of the population).³ Fluoropyrimidine chemotherapy is fatal for most patients who are either homozygous for *DPYD**2A or who have compound heterozygosity including *DPYD**2A (estimated at 1 in 2500 individuals). Other *DPYD* variants are also associated with substantial risk of fatal toxicity, including the c.2846A>T and c.1679G>T alleles.²

Routine pretreatment screening for the *DPYD**2A allele was recently evaluated in a large, prospective study. Pharmacogenomic screening and fluoropyrimidine dose adjustment was found to decrease mortality among patients with germline polymorphisms from 10% to 0%, while decreasing grade 3 or higher toxicity from 73% to 28%.³ Screening was found to be cost-effective in this analysis, after accounting for costs of treatment-related toxicities, such as hospitalization.³ Importantly, per-protocol dose reductions for patients with heterozygous *DPYD* polymorphisms did not appear to result in reduction of fluoropyrimidine efficacy. Pharmacogenetic testing for pathogenic *DPYD* abnormalities is available from multiple commercial laboratories in the United States, with predictable turnaround times of 1 week or less. Guidelines for pharmacogenomically-guided dose modifications of fluoropyrimidines were published in 2017 by the Clinical Pharmacogenomics

Implementation Consortium (CPIC), and are readily available to guide treatment recommendations for patients with pathogenic *DPYD* polymorphisms.⁴ Based on available data regarding *DPYD* mutation prevalence and risk of toxicity, we estimate that the number needed to screen to prevent one fluoropyrimidine-related death is approximately 700, and the number needed to screen to prevent one hospitalization is approximately 70.

In summary, DPD deficiency is a significant cause of serious and sometimes fatal toxicity among patients treated with fluoropyrimidine chemotherapy. Readily identifiable polymorphisms of the *DPYD* gene are the most common causes of DPD deficiency, and pharmacogenomic and phenotypic tests are available to identify patients at risk for severe toxicity or treatment-related mortality. **A substantial proportion of deaths related to DPD deficiency could be prevented through pre-treatment pharmacogenomic or phenotypic screening**, and available evidence supports the cost-effectiveness of pharmacogenomic screening for DPD deficiency prior to treatment with fluoropyrimidine chemotherapy. The current low uptake of pre-treatment screening for DPD deficiency is related in part to a lack of awareness of screening and risk-mitigation strategies, and inclusion of the recommended footnote in the NCCN guidelines would serve as an important starting point for the U.S. oncology community to achieve greater familiarity with this important strategy for improving patient safety.

The following references have been submitted in support of this request:

1. Lee AM, Shi Q, Pavey E, et al. *DPYD* variants as predictors of 5-fluorouracil toxicity in adjuvant colon cancer treatment (NCCTG N0147). *J Natl Cancer Inst.* 2014;106(12).
2. Lunenburg C, Henricks LM, Guchelaar HJ, et al. Prospective *DPYD* genotyping to reduce the risk of fluoropyrimidine-induced severe toxicity: Ready for prime time. *Eur J Cancer.* 2016;54:40-48.
3. Deenen MJ, Meulendijks D, Cats A, et al. Upfront Genotyping of *DPYD**2A to Individualize Fluoropyrimidine Therapy: A Safety and Cost Analysis. *J Clin Oncol.* 2016;34(3):227-234.
4. 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.

Sincerely,


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*N.B. This petition is submitted in collaboration with Ken Surprenant, patient advocate. Ken's wife Kathryn died of treatment-related toxicity in 2012 after a single dose of FOLFOX chemotherapy. While she was not tested for DPYD polymorphisms prior to her death, each of her four children carries the DPYD*2A allele; Ken does not carry any known DPYD abnormalities.*