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NCCN Guidelines Panel: Colon/Rectal/Anal Cancer Panel

On behalf of University of Michigan, I respectfully request the NCCN Colon/Rectal/Anal Cancer Panel to review the enclosed data for inclusion of *DPYD* genetic testing prior to initiation of treatment with 5-fluorouracil (5-FU) or capecitabine.

Specific Changes:

Colon Cancer Treatment Guidelines: Recommend targeted germline *DPYD* polymorphism testing (*DPYD*2A* (rs3918290), *DPYD*13* (rs55886062), *DPYD D949V* (rs67376798), and *DPYD HapB3* (rs56038477)) as a routine component of pre-treatment workup for all patients likely to receive 5-FU or capecitabine containing treatment, including patients with colon cancer appropriate for resection and patients with suspected or proven metastatic synchronous adenocarcinoma. Recommend dosing according to evidence-based CPIC dosing guidelines for carriers of *DPYD* variants.

Rectal Cancer Treatment Guidelines: Addition of information regarding the increased risk of severe toxicity from 5-FU or capecitabine treatment in carriers of *DYPD* variants, and the clinical benefit and cost-effectiveness of pre-treatment *DPYD* testing that is currently included in the NCCN Colon Guidelines (MS-36, *Severe Fluoropyrimidine-Associated Toxicity*). Also, recommend targeted germline *DPYD* polymorphism testing (*DPYD*2A* (rs3918290), *DPYD*13* (rs55886062), *DPYD D949V* (rs67376798), and *DPYD HapB3* (rs56038477)) as a routine component of pre-treatment workup for all patients likely to receive 5-FU or capecitabine containing treatment, including patients with rectal cancer appropriate for resection and patients with suspected or proven metastatic adenocarcinoma. Recommend dosing according to evidence-based CPIC dosing guidelines for carriers of *DPYD* variants.

Anal Carcinoma Treatment Guidelines: Addition of information regarding the increased risk of severe toxicity from 5-FU or capecitabine treatment in carriers of *DYPD* variants, and the clinical benefit and cost-effectiveness of pre-treatment *DPYD* testing that is currently included in the NCCN Colon Guidelines (MS-36, *Severe Fluoropyrimidine-Associated Toxicity*). Also, recommend targeted germline *DPYD* polymorphism testing (*DPYD*2A* (rs3918290), *DPYD*13* (rs55886062), *DPYD D949V* (rs67376798), and *DPYD HapB3* (rs56038477)) as a routine component of pre-treatment workup for all patients likely to receive 5-FU or capecitabine containing treatment, including patients with anal canal cancer and perianal cancer. Recommend dosing according to evidence-based CPIC dosing guidelines for carriers of *DPYD* variants.

FDA Clearance: Although not FDA cleared, the NCBI Genetic Testing Registry (https://www.ncbi.nlm.nih.gov/gtr/) lists more than a dozen CLIA-approved laboratories that provide *DPYD* targeted polymorphism genotyping and/or *DPYD* sequencing, including targeted genotyping from commonly used laboratories such as Quest Diagnostics

(https://www.questdiagnostics.com/dms/Documents/Other/pgx/PGx_med_guide.pdf) and LabCorp (https://www.labcorp.com/test-menu/24266/dpd-5-fluorouracil-toxicity). Not all laboratories currently offer targeted genotyping for all four validated polymorphisms, however, an NCCN indication for pre-emptive testing should provide sufficient justification for most laboratories to update their tests accordingly. It is also worth mentioning that there are multi-gene tumor sequencing panels and germline panels that either do or could include *DPYD*, which are currently not returning this clinically actionable information due to the lack of practice guidelines recommending *DPYD* information be used.

Rationale: Clinical utility that *DPYD*-genotype guided treatment is "equivalent to standard of care with some other advantage" (i.e., decreased toxicity) has been demonstrated in two prospective trials in which 50% dose reductions in cycles 1 and 2, followed by dose escalation as tolerated, in *DPYD* variant carriers (~7% of Caucasians) decreases severe toxicity risk from ~70% to ~30% (and treatment-induced death from ~3% to <<1%), and normalizes drug concentrations suggesting no concern for decreased efficacy from short-term dose reduction, while decreasing overall healthcare costs by $50-$60/patient.

The following articles that confirm clinical validity, clinical utility, and cost-effectiveness of pre-emptive *DPYD* genotyping in patients receiving 5-FU or capecitabine, and provide evidence-based consensus dosing recommendations for *DPYD* variant carriers, are submitted in support of these proposed changes.

1. Meulendijks D, Henricks LM, Sonke GS, et al: Clinical relevance of DPYD variants c.1679T>G, c.1236G>A/HapB3, and c.1601G>A as predictors of severe fluoropyrimidine-associated toxicity: a systematic review and meta-analysis of individual patient data. Lancet Oncol 16:1639-50, 2015

2. 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 34:227-34, 2016

3. 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 19:1459-1467, 2018

4. Henricks LM, Lunenburg C, de Man FM, et al: A cost analysis of upfront DPYD genotype-guided dose individualisation in fluoropyrimidine-based anticancer therapy. Eur J Cancer 107:60-67, 2019

5. 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 103:210-216, 2018