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 DPYD 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 DPYD 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.
and LabCorp. Not all laboratories currently offer targeted genotyping for all four validated polymorphisms, however, an NCCN indication for preemptive 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.


