ASSOCIATION FOR MOLECULAR PATHOLOGY

Providing global expertise in molecular testing that drives patient care
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Dockets Management Staff
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2025-N-1110 for "Dihydropyrimidine Dehydrogenase Deficiency and the Use of Fluoropyrimidine Chemotherapy Drugs; Establishment of a Public Docket; Request for Comments."

Comments submitted electronically via www.regulations.gov

To Whom It May Concern:

Thank you for the opportunity to submit these comments in response to the request for information on "Dihydropyrimidine Dehydrogenase Deficiency and the Use of Fluoropyrimidine Chemotherapy Drugs". The Association for Molecular Pathology (AMP) is an international medical and professional association representing approximately 3,100 physicians, doctoral scientists, and medical technologists who perform or are involved with laboratory testing based on knowledge derived from molecular biology, genetics, and genomics. Membership includes professionals from the government, academic medicine, private and hospital-based clinical laboratories, and the in vitro diagnostic industry. Through the work of our subject matter experts, AMP continues to develop and update our evidence-based guidelines to foster and support innovation while establishing clinical best practice recommendations.

The AMP Pharmacogenomics (PGx) Working Group is comprised of subject matter experts from the American College of Medical Genetics and Genomics (ACMG), Centers for Disease Control and Prevention (CDC), Clinical Pharmacogenetics Implementation Consortium (CPIC), College of American Pathologists (CAP), Dutch Pharmacogenetics Working Group (DPWG), European Society for Pharmacogenomics and Personalized Therapy (ESPT), Pharmacogenomics Knowledgebase (PharmGKB), Pharmacogene Variation Consortium (PharmVar), and the PGx clinical testing and research communities and has provided recommendations for a minimum set of variants (alleles) that should be tested using a two-tier strategy for selection criteria in recommending PGx variants for clinical testing of *DPYD*.[1] Briefly, Tier 1 recommended variants are those that meet the following criteria: 1) have a well-characterized effect on the function of the protein and/or gene expression, 2) have an appreciable minor allele frequency in a population/ancestral group, 3) have publicly available reference material(s) (RMs), and (4) are technically feasible for clinical laboratories to interrogate using standard molecular testing methods. Tier 2 recommended variants meet at least one but not all the Tier 1 criteria. Tier 2 variants may be reclassified to Tier 1 if additional information or RM(s) become available. Variants with unknown effect

[1] https://pubmed.ncbi.nlm.nih.gov/39032821/

on protein function or gene expression are not included in these recommendations for clinical genotyping assays. The AMP PGx Working Group recommends *DPYD* variants for Tier 1 include NM_000110.4:c.1905+1G>A, c.1679T>G, c.1129-5923C>G, c.557A>G, c.868A>G, c.2279C>T, and c.2846A>T and for Tier 2 include NM_000110.4:c.299_302del, c.703C>T, c.1314T>G, c.1475C>T, c.1774C>T, and c.2639G>T.

Due to the large number of rare variants and potentially severe toxicities, clinical laboratories may choose to conduct full gene sequencing rather than targeted genotyping to identify variants in the *DPYD* gene. However, laboratories performing sequencing should be aware that the current ACMG/AMP guidelines for interpretation of sequence variants are not designed for interpreting pharmacogenomic variants. As such, many rare variants encountered during clinical sequencing may ultimately be classified as variants of uncertain significance. While sequencing may allow for detection of both common and rare variants, use of Sanger sequencing or short-read NGS will not resolve the phase of variants when more than one variant is detected.

As tumor sequencing is becoming more routine in cancer care, the AMP PGx Working Group supports consideration of *DPYD* testing in the setting of tumor diagnostic testing; however, if tumor tissue is sequenced, germline confirmation may be required. The AMP PGx Working Group recognizes that either targeted genotyping or sequencing approaches may be used by laboratories and does not recommend a particular methodology for testing.

1. What, if any, challenges have healthcare providers and patients encountered based on the current recommendation to consider testing for genetic variants of DPYD prior to initiating treatment with fluorouracil or capecitabine to reduce the risk of serious adverse reactions if the patient's clinical status permits and based on clinical judgment?

Prior to the change in the FDA labeling, AMP members have, with some frequency, encountered instances where coverage of *DPYD* testing has been denied for patients. As the labeling information recently changed, there has not been enough time to determine whether it will have any effect on patient access to testing and/or barriers to coverage.

Thank you again for providing the opportunity to comment on the use of fluoropyrimidine chemotherapy drugs in patients with Dihydropyrimidine Dehydrogenase deficiency. If AMP may be of further assistance, please contact Annie Scrimenti, AMP Director of Public Policy and Advocacy at ascrimenti@amp.org.

Sincerely,

Jane S. Gibson, PhD
President, Association for Molecular Pathology