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Food and Drug Administration
Oncology Center of Excellence
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Re: Docket No. FDA-2025-N-1110, "**Dihydropyrimidine Dehydrogenase Deficiency and the Use of Fluoropyrimidine Chemotherapy Drugs; Establishment of a Public Docket; Request for Comments**"

To Whom It May Concern:

On behalf of the American Association for Cancer Research (AACR), the world's oldest and largest scientific organization dedicated to cancer research, education, and collaboration, we express our sincere appreciation for the opportunity to provide FDA with information from thought leaders in clinical oncology and pharmacology regarding dihydropyrimidine dehydrogenase (DPD) deficiency. We commend the agency's commitment to listening to patient, researcher, and clinician voices on this important topic.

AACR recently held a workshop in collaboration with the FDA titled *To Test or Not to Test – That is the Question: DPD Deficiency and Weighing Potential Harms* (1). The purpose of this workshop was to provide an interdisciplinary forum to examine the existing evidence on DPD deficiency testing, consider the clinical implications of requiring testing, including potential unintended consequences, and to discuss the regulatory considerations for modifying FDA product labeling to require testing. We believe this workshop addressed many of the questions raised in this Request for Comments.

There is scientific consensus that DPD testing greatly benefits patients who are completely DPD deficient, for whom fluoropyrimidine chemotherapy is contraindicated. This condition cannot be reliably identified without appropriate DPD testing, and lack of upfront testing has led to severe adverse events, including death, in individuals with complete deficiency. As a consortium of cancer researchers, clinical investigators, industry professionals, and patient advocates committed to innovative cancer research and care, we share many of the concerns raised during this workshop regarding the potential challenges of universal DPD testing prior to fluoropyrimidine treatment. Chief among these concerns are outcomes for patients with partial deficiency, for whom some uncertainties remain regarding the benefit/risk ratio due to limited high-quality data on toxicity and efficacy following dose adjustments.

However, a key theme echoed throughout the FDA-AACR workshop was that "we should not let perfect be the enemy of the good." Reflecting on the data and patient stories shared throughout the workshop, the AACR supports including a mandate for DPD testing in the FDA labeling of systemic fluoropyrimidine chemotherapies. This mandate should apply to all patients who may receive these drugs and whose clinical status permits. We believe that encouraging DPD testing aligns with FDA's essential role in safeguarding public health by ensuring the safety of drugs. Moreover, we recommend an opt-out testing strategy, detailed below, as the approach likely to provide the most benefit. We respectfully offer the following comments and supporting

information to explain our rationale and inform future FDA decision-making on this critical topic. We have addressed the questions posed by FDA on a point-by-point basis below:

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?

Healthcare providers are bound by the Hippocratic Oath to "do no harm." Although it is not always possible to predict which patients may experience severe or life-threatening toxicities from many anticancer drugs, DPD testing stands out as a clear example where existing knowledge and technology enable the identification of at-risk patients, thereby helping to prevent avoidable harm.

However, FDA's current recommendation to *consider* testing has not led to widespread adoption. Similarly, FDA's statements in the updated labeling and recent safety announcement recommending providers to inform patients of DPD deficiency have not led to widespread patient counseling. Consequently, unnecessary severe adverse events and deaths continue to occur in DPD-deficient patients who were unaware of the existence of this deficiency because of infrequent testing and patient counseling (2). Lawsuits against doctors and medical centers have resulted from these unfortunate events.

Additionally, the current recommendation does not lend itself to spurring developments in testing. If testing were mandated, it would likely drive advancements in technology, incorporation into clinical guidelines, reduced costs, and broader insurance coverage. These are all key barriers limiting widespread testing uptake, awareness, and consideration. This lack of awareness and familiarity with testing contributes to significant variability across providers and institutions, potentially leading to disparate patient outcomes depending on treatment location. This is the result of the uneven application of current recommendations to counsel patients and consider testing.

2. What factors are considered by healthcare providers when deciding whether or not to test patients for DPD deficiency prior to initiating treatment with fluorouracil or capecitabine? Which, if any, of these factors may result in a healthcare provider's decision to initiate treatment with fluorouracil or capecitabine without prior testing for DPD deficiency?

There are many factors that healthcare providers may consider when deciding whether or not to test patients for DPD deficiency. Among these, improved safety for patients with DPD deficiency is a compelling factor in favor of testing. While complete deficiency is rare, the clinical benefits of avoiding fluoropyrimidine administration in this population are well-established. Partial deficiency, by contrast, is more common, affecting an estimated 2 to 8 percent of the general population. Studies have shown safety benefits for testing and subsequent dosing modifications in patients with partial deficiency (3,4). The most comprehensive study to date of variant carriers reported that patients with partial deficiency without dose modification have a 2.3 percent chance of treatment related mortality, which is 25.6 times higher than populations without identified DPD variants (5). Considering the vital and broadly accepted role that predictive biomarkers of efficacy have played in the era of precision oncology, ensuring 'right patient gets the right drug,' DPD testing should be considered with the same evidence-based lens. While imperfect, it is a validated predictive biomarker of toxicity that can identify patients at risk of severe or even life-threatening toxicity, to avoid a 'patient getting the wrong drug." A growing number of U.S. institutions now employ universal testing as a result.

There are significant barriers that currently prevent both the consideration and application of testing. One major barrier highlighted by the FDA-AACR workshop was an education gap: many healthcare providers are not aware of DPD deficiency or testing. The FDA-AACR workshop and two additional surveys (6, 7) provide the most comprehensive list of reasons that healthcare providers who are aware of testing may not test. These reasons include, but are not limited to:

- Testing turn-around time and potential treatment delays. If patients require immediate treatment, testing is not possible as it is reported to take ~7 days to receive test results.
- A lack of coverage for testing by insurance, leading to financial toxicity for patients or hospital systems.
- A lack of certainty regarding what to do upon receiving test results:
    - There may be few remaining guideline-recommended treatment options for certain patient populations if fluoropyrimidines are contraindicated. However, we respectfully challenge this reasoning. A treatment that carries significantly increased risk of death is also not a viable option. In such cases, the option is effectively lost regardless of whether testing occurs. Therefore, DPD testing does not reduce treatment options. It clarifies which options are truly safe and appropriate.
    - U.S. national practice guidelines do not yet recommend DPD testing and do not indicate how to treat patients with DPD deficiency, although other guidelines do exist (8,9,10).

We also emphasize that the decision to test for DPD deficiency should not rest solely with the healthcare provider. AACR supports an opt-out testing strategy, whereby testing is the default and patients must actively decline testing if they choose not to undergo it. This approach promotes shared decision-making, ensuring that both physicians and patients are engaged in the process, and has already been successfully employed in the United States (11).

3. What factors are considered by healthcare providers in deciding whether or not to use a fluorouracil or capecitabine product in a patient with a complete DPD deficiency (*e.g.*, using a markedly reduced dosage regimen) based on currently available data and information?

No dose of capecitabine or 5FU has been proven safe in patients with complete DPD deficiency. However, there are certain patient populations which may not have other guideline-recommended treatment options. In this case, alternative treatment options should be explored in consultation with experts and the patient.

4. What factors are considered by healthcare providers for determining dosing and monitoring approaches when using a fluorouracil or capecitabine product in patients with purported partial DPD deficiency based on currently available data and information?

Multiple guidelines exist which recommend dosing modifications for patients with purported partial DPD deficiency. Most are based on or are similar to Clinical Pharmacogenomics Implementation Consortium (CPIC) guidelines (8) and recommend initial 50 percent dose reduction with subsequent increases in dose if tolerable.

The major concern with such a dosing reduction, which has been shown to improve safety for patients with partial deficiencies as highlighted above, is a potential decrease in efficacy. This was debated during the FDA-AACR workshop. Notably, the same study (12) was cited by participants to support opposing interpretations: that there is no clear evidence for inferior efficacy, and

conversely, that it is unclear whether there is inferior efficacy when treatment is initiated at reduced doses in this population. However, both parties also cited this study's use of improper comparators, limiting its interpretability and speaking to the need for more definitive work in this area. Since uncertainty remains, it is key to integrate shared decision-making with patients who are partially deficient. During patient counseling, providers should clearly communicate that a dose reduction may help prevent severe and potentially fatal toxicities but could lead to decreased treatment efficacy. Different patients will have different values, priorities, and tolerance for risk, leading to different and equally valid choices in this context of clinical uncertainty.

Summary

We believe the FDA's recent labeling changes, safety communications, and the FDA-AACR workshop on DPD deficiency represent significant progress in addressing this timely issue. To continue this forward progress, we urge the FDA to exercise regulatory flexibility to mandate DPD testing for all patients being considered for treatment with systemic fluoropyrimidine chemotherapies, with the exception of patients whose clinical status does not permit. An opt-out testing strategy is likely the best approach, ensuring both physician and patient involvement in testing decisions and providing necessary flexibility.

While current testing paradigms are not without limitations, the benefit of testing is clear for patients with homozygous or compound heterozygous deleterious *DPYD* mutations, where the risk of severe toxicity is highest. Conversely, uncertainties remain regarding the interpretation and clinical actionability of testing for patients with partial deficiency, who carry a heterozygous mutation. However, we do not think this should preclude testing from being implemented. A particular concern discussed at the workshop was how best to approach dose reduction for patients with partial deficiency, and whether dose reduction would reduce treatment benefits. Although robust clinical data are lacking, existing models for dose adjustment offer a foundation. One pragmatic path forward may be to follow the European Medicines Agency's approach, which recommends testing and dose reduction for patients with partial deficiency, without prescribing a specific dose. This allows for individualized treatment planning based on clinical judgement and patient context. In such cases, it is essential that patients are fully informed, and that treatment decisions are made collaboratively between themselves and their healthcare team.

Thank you for your unwavering commitment to advancing cancer research and regulatory science. We look forward to ongoing collaboration with the FDA on this and other critical topics in oncology drug development and treatment.

Sincerely,

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Co-Chair of FDA-AACR Workshop:
DPD Deficiency and Weighing Potential Harms

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