Open Access Letter to Editor

Closing the Safety Gap in Fluoropyrimidine Therapy Through DPD Testing in the United States

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Fluoropyrimidines and their hazards: Fluoropyrimidines, such as 5-fluorouracil (5-FU), capecitabine, and tegafur, are cornerstone chemotherapeutic agents used to treat various malignancies. Dihydropyrimidine dehydrogenase (DPD) is the first and rate-limiting enzyme in 5-FU catabolism. Genetic variants in DPYD can reduce or abolish enzyme activity, thereby impairing drug clearance and increasing systemic toxicity. Patients with partial or complete DPD deficiency are considered by the NCCN and FDA; however, this is not practiced in many US cancer centres. In contrast, DPYD testing is recommended and typically performed in European countries and the United Kingdom.

Barriers and Misconceptions: Resistance to preemptive DPD testing in the U.S. persists due to several misconceptions. Some believe that DPD deficiency is too rare; however, it affects 4–8% of patients. Others worry that testing delays treatment, although results are typically available within 48 hours, and reduced dosing can safely begin while awaiting results. Concerns about reduced efficacy are unfounded, as dose-adjusted therapy maintains survival while lowering toxicity and hospitalisations. Although payer coverage lags, guideline endorsement often drives policy change, and NCCN leadership could accelerate adoption. Ultimately, avoidable hospitalisations, ICU stays, and death exceed the effort of implementing routine testing.

Why a Phenotype-First, Genotype-Confirmatory Model Works: Phenotype testing is usually helpful for clinicians to determine whether a patient is an intermediate metaboliser with partial DPD deficiency; however, this nomenclature is still inconsistent. More than 1,000 deleterious DPYD variants have been identified, most of which are extremely rare and uncharacterized. No single testing strategy can detect all variants, making DPYD testing extremely complex. Hence, a stepwise approach, phenotype first, followed by confirmatory genotyping, offers optimal sensitivity and confidence. Already implemented in Europe, this model can be easily adapted to U.S. practice, with empiric dose reduction as a safer option for urgent cases while awaiting results.

Why the U.S. Still Lags on DPD Testing and How to Change It?

Despite strong evidence, DPD testing remains underused in the US. FDA drug labels for 5-FU and capecitabine only suggest that testing should be "considered," and NCCN guidelines have only recently begun to address the issue. Fewer than 5% of oncologists in the US routinely order DPYD testing, often citing the lack of guideline recommendation, uncertainty about insurance coverage, turnaround time concerns, and misconceptions regarding the rarity of deficiency or potential efficacy loss with dose reduction as described above. The 2025 NCCN update for colon cancer marks an important step forward by encouraging clinicians to discuss DPD testing before starting treatment. But simply discussing testing isn't enough. The NCCN can standardise pre-treatment testing by formally including it in the "Pre-Treatment Evaluation guidelines" for cancers where fluoropyrimidines are widely used, including but not limited to colon, gastric, breast, and head and neck cancers.

Simultaneously, progress will require coordinated efforts with CMS and private insurers to ensure reimbursement, standardised assays, and proper clinician education. Without a stronger, unified push, we risk continuing avoidable toxicity and even preventable deaths from a risk we already know how to identify.

From Consideration to Recommendation: Fluoropyrimidines remain a cornerstone of cancer therapy, and the severe toxicity they can cause is largely preventable. We already have the science, the tools, and testing at a reasonable cost. What we lack is consistent implementation.

The NCCN's cautious acknowledgement in 2025 is a meaningful start, but the next step is clear: we must move from simply *considering* DPD testing to actively *recommending* it. A phenotype-first strategy, followed by genotype confirmation, is practical, equitable, and cost-effective.

The science is settled, the technology exists, and the cost is modest. What is missing is the mandate and reinforcement.

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