THE CASE FOR UNIVERSAL DPYD TESTING PRIOR TO 5-FU/CAPECITABINE: A SCIENTIFIC WHITE PAPER

By Lucio Gordan, MD, Kiana Mehring, MBA, Austin Cox, PharmD, Paul Chadwick, Kristen Boykin, PharmD, RPh/CPh, BCOP, BCPS, Anjan Patel, MD, Alexander Glick, MD, David Wenk, MD, Jennifer Gass, PhD, & Nicole Radford, MS, MLS


Lucio Gordan


Kiana Mehring


Austin Cox


Paul Chadwick


Kristen Boykin


Anjan Patel


Alexander Glick


David Wenk


Jennifer Gass


Nicole Radford

Fluoropyrimidines (FPs) such as 5-fluorouracil (5-FU) and capecitabine remain cornerstones in the treatment of colorectal, breast, head and neck, and other malignancies.

However, they have a narrow therapeutic index: severe toxicity (often grade ≥3) occurs in up to ~30% of patients, and treatment-related mortality is commonly cited around ~0.5–1%, particularly when early-onset toxicity occurs.[1,2]

A major driver of early catastrophic toxicity is reduced activity of dihydropyrimidine dehydrogenase (DPD), the key enzyme in FP clearance encoded by DPYD. More than 80% of 5-FU is normally catabolized by DPD; patients with complete DPD deficiency are at high risk for rapid, life-threatening toxicity and death when exposed to standard FP doses.[1,3]

Clinically actionable DPYD variants cause partial DPD deficiency in a meaningful minority of patients (commonly cited ~3–8%), while complete deficiency is rare (often cited ~0.1–0.2%).[1,2]

Universal pretreatment DPD deficiency testing (genotyping ± phenotyping) is now widely supported internationally.

In April 2020, the European Medicines Agency recommended testing before FP treatment.[4] The United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) similarly advised in 2020 that all patients should be tested before FP therapy.[5] The Clinical Pharmacogenetics Implementation Consortium (CPIC) provides genotype-guided dosing recommendations using a standardized activity score approach.[6]

Clinical evidence supports genotype-guided dose reduction to reduce early severe toxicity without compromising effectiveness. In a large prospective Dutch multicenter study, prospective DPYD genotyping with prespecified dose reductions improved safety and was feasible in routine care.[7]

In U.S. real-world implementation work, DPYD-guided dosing in variant carriers was associated with materially fewer severe events and fewer hospitalizations (e.g., reported hospitalization reductions from 64% to 25% among carriers after implementation).[8]

From an economic standpoint, a U.S. cost-effectiveness analysis estimated an incremental cost-effectiveness ratio (ICER) of approximately $20,506 per QALY for pretreatment DPYD testing, well below common U.S. willingness-to-pay thresholds.[9] Testing can be cost-saving under plausible assumptions when it meaningfully reduces hospitalization and emergency utilization.[9]

Regulatory expectations in the U.S. have also intensified. The U.S. Food and Drug Administration (FDA) approved safety labeling changes for fluorouracil injection products in March 2024, addressing risks in patients with DPD deficiency.[10] Capecitabine labeling was updated (October 2025 approval letter) with prominent DPD-deficiency language, including an "evaluation and testing" section before initiating therapy.[11]

In February 2026, the FDA posted a safety labeling update emphasizing that DPYD testing is advised before initiating capecitabine or 5-FU unless immediate

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treatment is required, and that clinicians should avoid use in certain high-risk genotypes and individualize dosing for partial deficiency.[1,2]

Recommendation: All fluoropyrimidine-naïve patients should undergo pretreatment DPD deficiency evaluation, ideally with DPYD genotyping (core variants) with reflex/adjunct phenotyping (e.g., baseline uracil) when available. This aligns U.S. practice with international safety standards, reduces preventable harm, lowers avoidable utilization, and strengthens defensibility for payers and providers.

INTRODUCTION

Fluoropyrimidines are among the most widely used anticancer drugs globally. Severe FP toxicity remains common and clinically consequential, and early-cycle events can be catastrophic in patients with markedly reduced DPD activity.[1,2] Proactive identification of high-risk patients enables safer initial dosing and avoids preventable hospitalization and downstream costs.[9]

BIOLOGICAL BASIS AND EPIDEMIOLOGY

DPD is the rate-limiting enzyme responsible for catabolizing the majority of administered 5-FU (>80%).[1,3] Reduced DPD activity results in higher systemic exposure and a sharply increased risk of early severe toxicity, including mucositis, diarrhea, neutropenia, and neurotoxicity.[1,2,3]

Clinically important DPYD variants commonly included in testing panels include DPYD*2A (c.1905+1G>A), c.1679T>G, c.2846A>T, and c.1236G>A (HapB3).[2,7]

Phenotyping approaches (e.g., baseline plasma uracil) are recommended/used in some jurisdictions to capture non-genetic contributors and rare variants not covered on limited genotyping panels.[4]

CLINICAL CONSEQUENCES OF EARLY TOXICITY

Across common regimens, severe toxicity is often cited up to ~30% with standard dosing; hospitalization for toxicity management is frequently reported in the ~10–20% range in some settings, and toxicity-related mortality is commonly cited ~0.5–1%.[1,2]

FP cardiotoxicity is also clinically important, with reported incidence varying widely across studies (roughly ~1% to as high as ~30%, depending on regimen, definition, and population).[13]

GUIDELINE AND REGULATORY LANDSCAPE

▲ **European Medicines Agency (2020):** recommended DPD testing before initiating FP therapy to reduce severe toxicity.[4]

▲ **UK MHRA (2020):** advised all patients should be tested for DPD deficiency before FP treatment.[5]

▲ **CPIC:** provides standardized DPYD activity score–based dosing guidance for intermediate and poor metabolizers.[6]

▲ **FDA (March 2024):** approved safety labeling changes for fluorouracil injection products regarding DPD deficiency risk.[10]

▲ **FDA (October 2025):** capecitabine labeling update/approval included prominent DPD-deficiency language and pretreatment evaluation/testing section.[11]

▲ **(FDA February 2026):** posted safety labeling update advising DPYD testing before capecitabine or 5-FU unless immediate therapy is required; avoid use in certain high-risk DPYD genotypes and individualize dosing for partial deficiency.[12]

EFFECTIVENESS OF GENOTYPE-GUIDED DOSING

Prospective and real-world data support DPYD genotype–guided dose modification:

▲ A large prospective multicenter study demonstrated feasibility of prospective DPYD testing and improved safety with genotype-guided dosing.[7]

▲ A U.S. implementation report described fewer severe toxicities and fewer hospitalizations after DPYD testing was embedded into routine workflows (including a reported hospitalization reduction among carriers from 64% to 25%).[8]

HEALTH ECONOMIC IMPACT & PAYER RELEVANCE

Avoidable FP toxicity drives emergency visits, inpatient admissions and use of rescue measures.

A U.S. cost-effectiveness model estimated DPYD testing at an ICER of ~$20,506/QALY and identified reasonable parameter ranges where testing becomes cost-saving.[9]

Separately, uridine triacetate is an emergency antidote for overdose or early-onset severe FP toxicity within 96 hours; outcomes are substantially better when administered promptly (e.g., early-onset cohort survival reported as 18/18 when treated within 96 hours in one key dataset).[14]

IMPLEMENTATION IN COMMUNITY ONCOLOGY

Recommended operational approach:

▲ Test once in all FP-naïve patients before first dose.

▲ Use DPYD genotyping (core variants) with reflex phenotyping when available and clinically appropriate.[4,6]

▲ Apply CPIC-informed initial dose reductions for intermediate metabolizers and avoid standard dosing in poor metabolizers, with cautious titration based on tolerability and clinical need.[6]

▲ Standardize documentation (test results, activity score, starting dose rationale) for transparency and quality reporting.

POLICY AND EQUITY CONSIDERATIONS

Because allele frequencies and variant spectra differ across ancestries, reliance on narrow "European-centric" panels can miss actionable risk in some populations; broader approaches and/or phenotyping can help mitigate inequities in protection.[1,4]

CONCLUSION

Universal pretreatment DPD deficiency evaluation (DPYD genotyping ± phenotyping) prior to 5-FU or capecitabine is supported by strong biologic rationale, clinical evidence for reduced severe toxicity with genotype-guided dosing, and payer-relevant economic modeling.[1,4,6,7,8,9]

In light of evolving international standards and strengthened U.S. labeling, universal DPYD testing should be adopted as a routine patient-safety standard in community oncology.

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▲ **Lucio Gordan**, MD, is President & Managing Physician; **Kiana Mehring**, MBA, is Vice President of Payer Strategy & Revenue Cycle, **Austin Cox**, PharmD, is Senior Director of Trade Relations, **Paul Chadwick**, is Chief Value & Procurement Officer; **Kristen Boykin**, PharmD, RPh/CPh, BCOP, BCPS, is Director of Pharmacy Operations; **Anjan Patel**, MD, is Director of Pharmacy & Therapeutics; **Alexander Glick**, MD, is Director of Pharmacy & Therapeutics; **David Wenk**, MD, is Assistant Managing Physician; **Jennifer Gass**, PhD, is a clinical laboratory geneticist and Associate Director Of Genetics; and **Nicole Radford**, MS, MLS, is Vice President of Laboratory Services; all 10 authors are employed at Florida Cancer Specialists & Research Institute.

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