Universal DPYD Testing Prior to 5-FU and Capecitabine Therapy

A Scientific White Paper

Date: October 6, 2025
Authors: Lucio Gordan, Kiana Mehring, Ryan Ciarrocchi

Executive Brief

Fluoropyrimidines (FPs) such as 5-fluorouracil (5-FU) and capecitabine remain cornerstones in the treatment of colorectal, breast, head-and-neck, and other malignancies. Severe toxicities (grade ≥3) occur in 30–40% of patients, with mortality around 0.5–1%, largely due to dihydropyrimidine dehydrogenase (DPD) deficiency. Germline DPYD variants cause partial or complete DPD deficiency in 3–7% of patients. Universal pre-treatment DPYD testing—endorsed by EMA (2020), MHRA/NHS (2020), ESMO, CPIC, and others—enables genotype-guided dosing, dramatically reducing early severe toxicities, hospitalizations, and related costs.

Evidence demonstrates genotype-guided dosing in carriers reduces hospitalization rates (64%→25%) and avoids costly rescue therapies such as uridine triacetate (>$25,000–$75,000 per course). Economic models show ICER ≈$20,500/QALY, well below US willingness-to-pay thresholds. The FDA added strengthened DPD deficiency warnings to all FP labels in 2024, increasing the medico-legal impetus for testing, and again in October 2025 when it shifted to a boxed warning for capecitabine, requiring DYPD testing before treatment.

Recommendation: All FP-naïve patients should undergo DPYD genotyping (± phenotyping) before first dose of 5-FU/capecitabine. This aligns US practice with international safety standards, reduces preventable harm and healthcare expenditures, and preserves therapeutic efficacy.

Universal DPYD Testing Prior to 5-FU/Capecitabine: Scientific White Paper

Introduction

Fluoropyrimidines—5-FU and capecitabine—are administered to over 2 million patients worldwide each year. Despite decades of use, these agents retain a narrow therapeutic index, with 30–40% of patients developing grade ≥3 toxicity and 0.5–1% experiencing fatal events. Most early-cycle toxicities result from partial or complete DPD deficiency due to germline DPYD variants. From a payer perspective, early identification of at-risk patients through DPYD testing before therapy enables proactive dose adjustment that mitigates avoidable high-cost toxicity without compromising cancer control.

Biological Basis and Epidemiology

DPD, encoded by DPYD, catabolizes approximately 80% of administered 5-FU. Partial deficiency occurs in ~3–7% of patients of European ancestry; complete deficiency is rare (~0.1%). Clinically relevant alleles include DPYD*2A (c.1905+1G>A), c.1679T>G, c.2846A>T, and c.1236G>A/HapB3, among others. Phenotyping by baseline plasma uracil complements genotyping by capturing rare and non-genetic deficiencies.

Clinical Consequences of Early Toxicity

Severe early FP toxicity drives hospitalizations, treatment interruptions, and increases mortality. Hospitalization rates for severe toxicity range from 10–20%, with grade ≥3 events occurring in up to one-third of patients. Cardiotoxicity incidence is 1–18% depending on regimen. These preventable adverse events also burden health systems and diminish survival outcomes.

Guideline and Regulatory Landscape

Coverage of DPYD testing demonstrates alignment with national and international standards while also supporting payer quality metrics and value-based care models.

- European Medicines Agency (EMA, 2020) and the UK's MHRA/NHS England (2020): mandate or recommend DPYD testing prior to FP therapy.
- ESMO colon cancer guidelines: endorse testing before adjuvant therapy.
- CPIC guideline provides a standardized dosing algorithm: 50% starting dose reduction for intermediate metabolizers, FP avoidance for poor metabolizers.

- US FDA updated all 5-FU product labels in 2024 to highlight risk in DPD deficiency, reinforcing medico-legal expectations for testing.
- US FDA updated capecitabine labels in October 2025 to a boxed warning, requiring DYPD testing before treatment.

Effectiveness of Genotype-Guided Dosing

Prospective studies confirm significant reductions in grade ≥3 toxicity and hospitalizations among variant carriers when treated with reduced doses. A multicenter implementation report showed hospitalization in carriers fell from 64% to 25% with genotype-guided dosing, with no compromise in antitumor efficacy.

Health-Economic Impact & Payer Cost Modeling

Severe FP toxicities drive emergency visits, inpatient admissions, and expensive rescue therapy with uridine triacetate (Vistogard), costing $25,000–$75,000 per course. Cost-effectiveness analyses in the US demonstrate DPYD testing has an incremental cost-effectiveness ratio ≈$20,500 per QALY—well below conventional thresholds—and can be cost-saving through avoidance of hospitalization and emergency visits and high-cost rescue care. This is supportive of value-based payment programs and risk-sharing arrangements. At a 5% DPYD variant prevalence and a Medicare reimbursement rate of $174.81 per each test, universal pre-treatment DPYD testing yields approximately $155,000 per 1,000 patients, demonstrating clear cost-saving. Savings are driven by reductions in hospitalizations and avoidance of high-cost rescue therapy. Even with conservative assumptions, pre-treatment testing would remain cost neutral or cost-saving, making it a financially prudent strategy for payers.

Implementation in Community Oncology

Testing should be performed once in all FP-naïve patients prior to first dose. Recommended workflow: genotype core alleles plus phenotyping as available; apply CPIC dosing algorithms; titrate based on cycle-1 tolerability; use therapeutic drug monitoring where feasible. Turnaround times are typically 24–72 hours, minimizing treatment delays.

From a payer perspective, adoption of recommended workflow reduces variation in care and ensures equitable application of precision medicine. This supports claim transparency for risk adjusted outcomes.

Policy and Equity Considerations

Given ethnic variability in allele frequencies, broad panels or reflex phenotyping should be used to ensure equitable protection. Testing improves patient safety, reduces litigation risk, and aligns with international guidelines, making it a patient-safety and policy imperative.

Conclusion

Universal pre-treatment DPYD testing for all patients initiating 5-FU or capecitabine is supported by strong biologic plausibility, predictive validity, and clinical effectiveness. DPYD testing offers measurable clinical and economic benefits that are highly relevant to payers. It reduces preventable toxicity, lowers healthcare utilization and costs, preserves treatment efficacy, and aligns US practice with international standards. From a system level perspective, implementation of standardized DPYD testing based on evidence-based guidelines reduces variability in care delivery and aligns with professional society and regulatory recommendations. This approach promotes equitable patient safety through identification of at-risk individuals across diverse populations. This approach is representative of a precision medicine strategy and in alignment with value-based care objectives, making it a justified intervention for coverage consideration.
Testing should be adopted immediately as the standard of care.

References

1. EMA. Recommendations on DPD testing prior to fluorouracil/capecitabine/tegafur. 2020.

2. MHRA/NHS England. Drug Safety Update on DPD testing before fluoropyrimidines. 2020.

3. ESMO. Clinical Practice Guidelines on Localized Colon Cancer – DPD testing recommendations. Ann Oncol. 2020.

4. CPIC. Guideline for Fluoropyrimidines & DPYD: activity-score dosing algorithm. Updated 2024.

5. FDA. Safety-labeling changes for fluorouracil products highlighting DPD deficiency risk. 2024.

6. Gmeiner WH, Miller CR. Genetic factors affecting fluoropyrimidine therapy; severe toxicity and mortality. Precis Cancer Med. 2021.

7. Deac AL, et al. Fluoropyrimidine-induced cardiotoxicity: incidence and spectrum. World J Clin Oncol. 2020.

8. Le Teuff G, et al. FUSAFE IPD meta-analysis: prevalence and impact of DPD deficiency. Eur J Cancer. 2024.

9. De With M, et al. Implementation of DPD testing across Europe—post-EMA 2020 status. Eur J Cancer. 2023.

10. Shaunak N, et al. NHS England national commissioning of DPYD testing. Br J Clin Pharmacol. 2024.

11. Pratt VM, et al. AMP/JMD recommendations for clinical DPYD genotyping. J Mol Diagn. 2024.

12. Roncato R, et al. Prospective DPYD/UGT1A1 PGx-informed therapy improves safety with preserved efficacy. JAMA Netw Open. 2024.

13. Dweib M, et al. Oncology specialists' perspectives and need for national guidance. Front Pharmacol. 2025.

14. Brooks GA, et al. Cost-effectiveness of DPYD genotyping prior to FP chemotherapy—US model. JCO Oncol Pract. 2022.

15. Fariman SA, et al. Cost-effectiveness of preemptive DPYD genotyping in metastatic CRC. J Pers Med. 2023.

16. Nguyen DG, et al. Real-world impact of in-house DPYD testing on dosing, toxicities, hospitalizations. JCO Oncol Pract. 2024.

17. CAP Today. Hospitalization reduction with pretreatment testing in carriers (64%→25%). 2024.

18. De Mattia E, et al. Rare/novel DPYD variants and clinical implementation. Pharmacogenomics J. 2024.

19. Tentoni N, et al. Early 5-FU toxicity and adverse survival impact in first-cycle FOLFOX/FOLFIRINOX. Cancers (Basel). 2024.

20. Ma WW, et al. Uridine triacetate emergency rescue—96% survival ≤96 h. J Clin Oncol. 2017.

21. The Medical Letter. Vistogard—US wholesale acquisition cost per full course. 2016.

22. García JJ, et al. Economic model: uridine triacetate vs supportive care—incremental cost and offset. J Oncol Pharm Pract. 2025.

23. Keen J, et al. Clinical Oncology update on DPYD testing and toxicity prevention. Clin Oncol (R Coll Radiol). 2025.

24. ARUP Laboratories. 2025 implementation guide summarizing ESMO strong recommendation and US positions. 2025.