Dihydropyrimidine Dehydrogenase (*DPYD*) Genetic Testing

A Position Statement of the Hematology/Oncology Pharmacy Association

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Statement of Official Position:

The Hematology/Oncology Pharmacy Association (HOPA) supports and strongly recommends pre-treatment dihydropyrimidine dehydrogenase (*DPYD*) genetic testing for patients with cancer being considered for fluoropyrimidine-based chemotherapy, including 5-fluorouracil (5-FU) and capecitabine, consistent with guidance from the U.S. Food and Drug Administration (FDA),[1,2] the National Comprehensive Cancer Network (NCCN),[3] and the American Society of Clinical Oncology (ASCO).[4] We further affirm that oncology pharmacists play a central role in the safe administration of chemotherapy, including implementation of *DPYD* genetic testing. HOPA emphasizes that successful and sustainable implementation of *DPYD* testing requires multidisciplinary institution-specific policies and procedures to streamline test ordering and application of results. Below is a set of recommendations to facilitate the adoption and application of evidence-based *DPYD* testing.

Testing

The identification of *DPYD* gene variants that reduce DPD enzyme activity prior to commencing fluoropyrimidine-based chemotherapy is a critical measure to enhance patient safety and reduce the risk of severe, and potentially fatal, adverse drug reactions.[5,6,7]

It is the position of HOPA that:

- *DPYD* genetic testing should be ordered as soon as a patient is diagnosed with any cancer for which fluoropyrimidine-based chemotherapy is standard of care or as soon as the chemotherapy plan is finalized.

[1] Food & Drug Administration. Safety labeling update for capecitabine and fluorouracil (5-FU) on risks associated with dihydropyrimidine dehydrogenase (DPD) deficiency [Internet]. Silver Spring (MD): Food & Drug Administration; 2026 Feb 5 [cited 2026 Mar 5]. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/safety-labeling-update-capecitabine-and-fluorouracil-5-fu-risks-associated-dihydropyrimidine

[2] Food & Drug Administration. Safety announcement: FDA highlights importance of DPD deficiency discussions with patients prior to capecitabine or 5FU treatment [Internet]. Silver Spring (MD): Food & Drug Administration; 2025 Jan 24 [cited 2026 Mar 5]. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/safety-announcement-fda-highlights-importance-dpd-deficiency-discussions-patients-prior-capecitabine?utm_source=chatgpt.com

[3] National Comprehensive Cancer Network. NCCN Guidelines [Internet]. Plymouth Meeting (PA): National Comprehensive Cancer Network; n.d. [cited 2026 Mar 5]. Available from: https://www.nccn.org/guidelines/guidelines-detail?id=1428

[4] American Society of Clinical Oncology. ASCO Clinical Notice: Reaffirming the Necessity for DPYD Genotyping in Fluoropyrimidine Therapy [Internet]. Alexandria (VA): American Society of Clinical Oncology; 2026 Jan 22 [cited 2026 Mar 5]. Available from: https://connection.asco.org/do/asco-clinical-notice-reaffirming-necessity-dpyd-x00a0-genotyping-fluoropyrimidine

[5] Kratz, J, Merritt K, Jorgensen, J, et al. Importance of and Strategies for Implementing DPYD Testing to Prevent Severe Fluoropyrimidine Chemotherapy Toxicity in Health Care Systems. ASCO Publications. 2026; doi: 10.1200/EDBK-26-521184

[6] Hertz DL, Venook AP. Ending the Controversy Around Pretreatment Dihydropyrimidine Dehydrogenase (DPD/ DPYD) Testing Heightens the Controversy Over Appropriate Fluoropyrimidine Dosing. J Clin Oncol. 2026; doi: 10.1200/JCO-25-02629.

[7] Nguyen, DG, Morris SA, Hamilton A, et al. Real-World Impact of an In-House Dihydropyrimidine Dehydrogenase (DPYD) Genotype Test on Fluoropyrimidine Dosing, Toxicities, and Hospitalizations at a Multisite Cancer Center. JCO Precis Oncol. 2024; doi: 1200/EDBK-26-521184

- Prior to the administration of the first fluoropyrimidine dose, *DPYD* test results should be available and reviewed as part of the pre-treatment workup.
- There should be a checkpoint within pharmacy operations to verify that *DPYD* testing has been completed during chemotherapy order verification for 5-FU regimens or by specialty pharmacy prior to dispensing capecitabine.
- *DPYD* test results or documentation should form part of the chemotherapy treatment parameters verified by pharmacy before dispensing any fluoropyrimidine agent.
- In patients who have been previously tested, clinicians should review the test's comprehensiveness to ensure, at a minimum, the Association for Molecular Pathology (AMP) list of Tier 1 *DPYD* variants were included.[8]
- Consider re-testing in patients who have previously been genotyped using a test that does not include the AMP Tier 1 variants. The patient's insurance status may be a barrier to re-testing.
- If testing has not been completed or results are still pending at the time of treatment initiation, clear documentation of the reason for initiating treatment without *DPYD* results should be included in the patient record. Patients should be part of shared decision making, including discussion of risks versus benefits of testing or not testing, or delaying treatment.

Additionally, health-systems and laboratories are urged to implement efficient workflows for comprehensive *DPYD* genotyping. Special attention should be given to the unique needs of rural and resource-limited settings, where access and laboratory capacity may differ from larger academic institutions. Maintaining a current, comprehensive reference document that lists laboratories performing *DPYD* genetic testing is recommended. Resources such as the Genetic Testing Registry may be utilized, noting that completeness depends on laboratory participation and reporting.[9] The absence of FDA-approved *DPYD* genotyping assays highlights the need for ongoing collaboration among clinical laboratories, regulatory agencies, and professional organizations to establish robust standards for test quality and oversight.

HOPA further supports the following laboratory considerations:

- Maintain turnaround-times less than one week to ensure timely return of results prior to initiating fluoropyrimidine-based treatment.

[8] Pratt VM, Cavallari LH, Fulmer ML, et al. DPYD Genotyping Recommendations: A Joint Consensus Recommendation of the Association for Molecular Pathology, American College of Medical Genetics and Genomics, Clinical Pharmacogenetics Implementation Consortium, College of American Pathologists, Dutch Pharmacogenetics Working Group of the Royal Dutch Pharmacists Association, European Society for Pharmacogenomics and Personalized Therapy, Pharmacogenomics Knowledgebase, and Pharmacogene Variation Consortium. J Mol Diagn. 2024;26(10):851-863. doi: 10.1016/j.jmoldx.2024.05.015
[9] National Institutes of Health. Genetic Testing Registry (GTR). Retrieved from https://www.ncbi.nlm.nih.gov/gtr/. Accessed on April 14, 2026

- Comply, at minimum, with the AMP guidelines for Tier 1 alleles (preferably including both Tier 1 and 2 alleles) to ensure comprehensive detection of clinically significant *DPYD* variants.[8]
- Ensure transparent communication regarding variant coverage of the assay, performance, and turnaround time with the ordering clinician/health system.
- Laboratories performing next generation sequencing of the tumor for the detection of somatic mutations should also perform *DPYD* genotyping when a normal germline sample is available. Clinicians should incorporate results into the patient's record for downstream use, if and when applicable.

Timely *DPYD* genetic testing, combined with rigorous laboratory standards and integrated clinical verification within pharmacy, promotes safe and effective chemotherapy delivery. Clinicians and laboratory partners are encouraged to continuously enhance testing procedures, capacity, and interdisciplinary communication to uphold patient care excellence.

Documentation

Current electronic health record (EHR) workflows frequently document *DPYD* testing results in an episodic or encounter-based manner. At many institutions, *DPYD* test results are stored as scanned laboratory reports or PDF documents, significantly limiting searchability, clinical visibility, and usability. This documentation is often inconsistent within an individual institution, and consistency is almost completely lacking between institutions. This presents a particularly concerning issue when patients are seen at multiple institutions or have undergone testing years prior.

Moreover, integration with clinical decision support (CDS) is often limited or absent, resulting in missed opportunities for automated alerts, dosing guidance, and prescribing safeguards at the point of care. Documentation of pharmacogenomic results is further hindered by the need for EHR upgrades or additional, often costly, genomic modules to support standardized data capture and interpretation.

To ensure that healthcare providers and patients who have had *DPYD* testing are able to find and appropriately utilize their results across their lifetime, HOPA supports enhanced genomic documentation capabilities in the EHR.

For these reasons, HOPA supports the following:

- Genomic results functionality in EHRs that does not require additional investment from the healthcare organization or participant.
- Discrete data entry for genomic results so that they are searchable in a patient's chart.
- Use of a time-independent page of the EHR specific to genomics.
- Drug / result interaction checking capabilities or interruptive alerts within the EHR.
- Inclusion of *DPYD* results in information that is shared between institutions to ensure that it can be used by all healthcare providers.
- Thorough investigation of a patient's chart by the medical team to determine if previous *DPYD* testing has been completed prior to starting fluoropyrimidines, and updating the chart accordingly, especially if testing will not be completed prior to treatment.
- Documentation that the patient has been informed about *DPYD* testing. If a patient decides to forego *DPYD* testing after discussion with their medical team, that decision should be documented in the EHR.

Dosing Considerations

Initial Dosing Considerations

The following dosing considerations will not be updated in real time and are intended to be an example only. Please refer to the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines (https://www.clinpgx.org/guideline/PA166251462) for the latest and most accurate dosing recommendations. Updates to CPIC guidelines available online may not be peer-reviewed or published in print.

Fluoropyrimidine dosing is a nuanced process determined by numerous variables and patient considerations. The following recommendations are based on CPIC guidelines and are based solely on *DPYD* genotype. Other patient and clinical factors should be considered, as applicable.

When verifying initial fluoropyrimidine dosing, pharmacists should:

- Confirm a laboratory report's Activity Score as older test results may not have been updated with evolving literature/evidence.
- Combine the Activity Values associated with identified alleles to calculate the combined Activity Score.
    - Verify current Activity Values using updated CPIC reference tables (https://www.clinpgx.org/guideline/PA166251462) online.

- Use the CPIC guidelines (https://www.clinpgx.org/guideline/PA166251462) for dosing recommendations associated with the calculated Activity Score.
- Discuss risks vs benefits of treating poor metabolizers with providers. CPIC guidelines currently do not recommend use of fluoropyrimidines in poor metabolizers, however, if no alternatives exist, providers may consider using fluoropyrimidines at extremely reduced doses.

Subsequent Dosing Considerations

Current guidelines recommend to titrate/dose escalate subsequent doses based on tolerability without giving specific dose escalation recommendations.[9] Doses should be slowly and gradually titrated to the maximum tolerated dose. General titration considerations beyond patient tolerance include but are not limited to: age, performance status, *DPYD* activity value/score, treatment intent (curative vs palliative), renal function, comorbid conditions, and patient's willingness to increase the dose. Refer to the CPIC guidelines for the most current considerations.

These considerations are not intended to be a substitute for the medical provider's knowledge, expertise, or professional judgment, or the patient's individual needs and preferences in directing his or her own medical care. This is intended to be an example for institutions only.

Insurance Coverage

Timely access to *DPYD* testing is essential to support safe fluoropyrimidine prescribing and reduce preventable treatment-related toxicity. Insurance coverage barriers, including prior authorization requirements, inconsistent medical necessity determinations, and delays in approval, may impede evidence-based care and disrupt treatment timelines. HOPA supports equitable and timely payer coverage policies that facilitate access to clinically appropriate *DPYD* testing.

It is the position of HOPA that:

- *DPYD* genetic testing should be covered by all payers when fluoropyrimidine-based therapy is being considered or when a patient is diagnosed with a cancer for which fluoropyrimidine-based therapy is standard of care.
- Coverage policies should recognize *DPYD* testing as medically necessary, supported by current evidence and regulatory and national guidelines.

- Prior authorization requirements for *DPYD* testing should be minimized, rapidly adjudicated, or waived when fluoropyrimidine treatment is planned.
- Additional documentation requirements, including repetitive letters of medical necessity, should not create unnecessary barriers to timely testing.
- Coverage determinations should support turnaround times that allow results to inform treatment decisions without delaying initiation of clinically indicated therapy.
- Repeat *DPYD* testing should be covered when prior results are unavailable, incomplete, outdated, or otherwise insufficient to guide current clinical decision-making.
- Coverage of multigene pharmacogenomic panels may be appropriate when *DPYD* is included and other actionable genes are relevant to the patient's planned therapy (for example, *UGT1A1* for irinotecan).

Universal coverage and timely authorization of *DPYD* testing represents a critical step toward safer, more equitable, personalized, and cost-effective oncology care.

Education

Patient Education

Patients should be informed and educated about the availability, purpose, and potential implications of *DPYD* testing when fluoropyrimidine therapy is being considered. Effective patient education supports shared decision-making, improves understanding of treatment-related risks, and helps patients recognize symptoms of serious toxicity that require urgent evaluation. Education should be delivered in clear, patient-centered language and incorporated into routine treatment counseling workflows.

It is the position of HOPA that:

- Patients being considered for fluoropyrimidine therapy should be informed about *DPYD* testing and its role in identifying patients at increased risk for severe or life-threatening treatment toxicity.[5,6,7]
- Discussion of *DPYD* testing should occur at diagnosis, during treatment planning, or prior to initiation of fluoropyrimidine therapy whenever feasible.
- Patients should be educated that *DPYD* testing helps guide safer dosing and treatment selection but does not eliminate all risk of toxicity.
- Patients should be counseled on the signs and symptoms of potentially serious fluoropyrimidine toxicity and instructed to promptly contact their healthcare team if these

occur, including severe mucositis, diarrhea, hand-foot syndrome, neutropenia, fever, or neurologic symptoms.

- Patients should be informed that results indicating markedly reduced or absent DPD activity may require avoidance of fluoropyrimidines or substantial dose reduction.
- Patients should be informed that partial reductions in DPD activity may still allow fluoropyrimidine treatment using lower initial doses with close monitoring and subsequent dose escalation based on tolerability.
- Patients should be informed that treatment doses may be modified further after the first cycle based on adverse effects, clinical response, and ongoing safety assessment.
- Patients should be informed that a positive *DPYD* result indicates increased risk of toxicity but does not guarantee toxicity, and a negative result does not eliminate the possibility of treatment-related adverse effects with standard doses.
- Patients should be informed about testing logistics, including sample requirements, turnaround time, and costs.
- Patients should be informed that insurance coverage and out-of-pocket costs for *DPYD* testing may vary by payer and geographic region.
- *DPYD* education should be incorporated into standard chemotherapy teaching processes, with written or electronic educational materials available when possible.
- Institutions should define local workflows that identify when education occurs and which members of the care team are responsible for providing it.

Clear and consistent patient education is essential to support shared decision making, early toxicity recognition, and safe use of fluoropyrimidine therapy.

Provider Education

Successful implementation of *DPYD* testing requires that clinicians and frontline staff understand the clinical rationale for testing, interpretation of results, workflow responsibilities, and implications for treatment selection and dosing. Consistent provider education is necessary to support accurate result interpretation, coordinated patient counseling, and safe fluoropyrimidine prescribing across practice settings.

It is the position of HOPA that:

- Institutions implementing *DPYD* testing should provide structured interdisciplinary education for pharmacists, physicians, advanced practice providers, nurses, and other relevant staff.

- Educational initiatives should include the clinical significance of DPD deficiency, available testing strategies, result interpretation, and management implications for fluoropyrimidine therapy.
- Providers and staff involved in prescribing, verification, dispensing, or patient counseling should receive training on workflow responsibilities related to ordering, reviewing, documenting, and acting on *DPYD* results.
- Institutions should allocate appropriate time, staffing, funding, and operational resources to support implementation and ongoing education related to *DPYD* testing.
- Local implementation efforts should consider use of physician, pharmacist, and nursing champions to promote adoption, troubleshoot barriers, and reinforce best practices.
- Providers should have access to current evidence-based resources for genotype interpretation and dose modification, including CPIC guidelines.
- Educational content should be reviewed and updated regularly to reflect changes in national guidelines, prescribing information, laboratory standards, and emerging evidence.
- Institutions should provide practical training tailored to their specific workflows, including EHR documentation, clinical decision support tools, pharmacy verification processes, and patient communication strategies.
- HOPA supports development and dissemination of high-quality publicly available educational tools, reference materials, and implementation resources to assist clinicians and health systems.[10,11,12,13]

Effective provider education is fundamental to sustainable *DPYD* testing programs and helps ensure that patients receive accurate counseling, appropriate dose modifications, and safe, evidence-based care.

[10] Strategies for DPYD testing prior to fluoropyrimidine chemotherapy in the US. https://doi.org/10.1007/s00520-024-08674-1
[11] El Rouby N, Aquilante CL, Bargal SA, Cavallari LH, Duarte JD, Gunderson K, Mazhindu T, Nagy M, Nie X, Nguyen DG, Patel JN, Skaar TC, Smith DM, Tuteja S, van Schaik RHN, Hicks JK; PGRN Implementation Working Group. Global Investigation of Clinical Implementation Strategies for DPYD Testing to Guide Fluoropyrimidine Therapy. Clin Transl Sci. 2026 Jan;19(1):e70466. doi: 10.1111/cts.70466. PMID: 41456101; PMCID: PMC12744196.
[12] Tuteja S, Hicks JK, Cavallari LH, El Rouby N, Smith DM, Patel JM, Hertz D; Leveraging implementation science to enhance the adoption of DPYD testing. Pharm and Gen. 2025 Dec;36(2). doi: 10.1097/FPC.0000000000000581
[13] Ho TT, Smith DM, Aquilante CL, Cicali EJ, El Rouby N, Hertz DL, Imanirad I, Patel JN, Scott SA, Swain SM, Tuteja S, Hicks JK; Pharmacogenomics Global Research Network Publication Committee. A Guide for Implementing DPYD Genotyping for Systemic Fluoropyrimidines into Clinical Practice. Clin Pharmacol Ther. 2025 May;117(5):1194-1208. doi: 10.1002/cpt.3567. Epub 2025 Jan 31. PMID: 39887719; PMCID: PMC11993294.

Call to Action

Pretreatment *DPYD* testing is an essential component of high-quality oncology care that can reduce preventable fluoropyrimidine-related severe toxicities, hospitalizations, and fatalities, improve treatment individualization, and support safer medication use. As evidence, national guidelines, and prescribing information continue to evolve, healthcare systems should prioritize timely implementation of standardized testing workflows that ensure appropriate ordering, result interpretation, documentation, and application to treatment decisions. HOPA strongly encourages meaningful involvement of oncology pharmacists in the design and execution of these processes, given their expertise in medication safety, dose optimization, patient counseling, and interdisciplinary care coordination. HOPA calls upon clinicians, institutions, laboratories, payers, and health information technology stakeholders to work collaboratively to expand access to *DPYD* testing, integrate it into routine cancer care, and conduct ongoing quality review of testing practices.

Available Resources

1. A Guide for Implementing DPYD Genotyping for Systemic Fluoropyrimidines into Clinical Practice: https://pubmed.ncbi.nlm.nih.gov/39887719/
2. A New Standard of Care Announced by the FDA on October 3, 2025: https://test4dpd.org/
3. Addressing barriers to increased adoption of DPYD genotyping at a large multisite cancer center: https://pubmed.ncbi.nlm.nih.gov/37235983/
4. All You Need to Know About DPYD Genetic Testing for Patients Treated With Fluorouracil and Capecitabine: A Practitioner-Friendly Guide: https://pmc.ncbi.nlm.nih.gov/articles/PMC8462561/
5. DPYD Genotyping Recommendations: https://pubmed.ncbi.nlm.nih.gov/39032821/
6. Global Investigation of Clinical Implementation Strategies for DPYD Testing to Guide Fluoropyrimidine Therapy: https://pmc.ncbi.nlm.nih.gov/articles/PMC12744196/
7. Importance of and Strategies for Implementing DPYD Testing to Prevent Severe Fluoropyrimidine Chemotherapy Toxicity in Health Care Systems: https://ascopubs.org/doi/10.1200/EDBK-26-521184
8. Strategies for DPYD testing prior to fluoropyrimidine chemotherapy in the US: https://pubmed.ncbi.nlm.nih.gov/38980476/

Disclaimer: This resource is intended for informational purposes only and does not encompass all recommendations relating to DPYD testing. The provision of this resource does not replace the need to conduct research on these issues. All medical decisions should be made in accordance with the healthcare professional's institutional policies.

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