Capecitabine (XELODA) Boxed Warning Update on *DPYD* Pretreatment Testing: Abbreviated Guide for Oncologists

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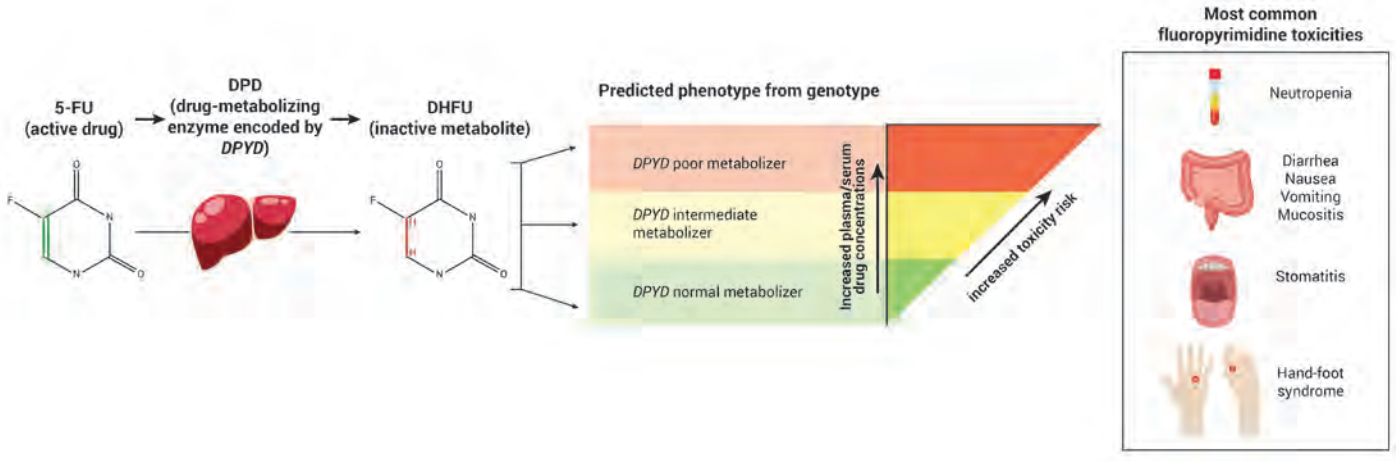
FDA Mandates *DPYD* Testing in XELODA Boxed Warning Update

In October 2025, the FDA strengthened the boxed warning for capecitabine (XELODA), **instructing clinicians to test for *DPYD* variants before starting treatment, unless immediate therapy is necessary, and to avoid prescribing capecitabine for patients with complete dihydropyrimidine dehydrogenase (DPD) deficiency**. The warning further states that serious adverse reactions or death may occur in patients with complete DPD deficiency.[1]

Additional details on the label instruct providers to:

- **Avoid capecitabine in complete DPD deficiency:** Patients with homozygous or compound heterozygous *DPYD* variants that result in complete or near-complete absence of DPD activity should not receive capecitabine. No safe dose is established.[1]
- **Withhold and monitor:** Serious toxicity can occur even if no variants are detected.[1] Clinicians should withhold or discontinue therapy based on the onset and severity of adverse reactions.
- **Recognize testing limitations:** No FDA-authorized test is currently available. Existing laboratory-developed tests vary in both the accuracy of results and in the specific variants they detect.[1]



NCCN Recommends *DPYD* Testing for Capecitabine and 5-Fluorouracil

The National Comprehensive Cancer Network (NCCN) updated its colon cancer guidelines (Version 5.2025, published October 30, 2025)[2] to align with the FDA's recommendations for *DPYD* testing before initiation of capecitabine treatment.

Additionally, the NCCN recommends *DPYD* testing for patients receiving 5-fluorouracil (5-FU), although the FDA has not updated the drug's label. The guidelines[2] include a disclaimer noting that no specific test is endorsed and that available data are insufficient to guide dose adjustments for many *DPYD* variants.

Considerations for *DPYD* Test Selection

Because the FDA label now requires pretreatment *DPYD* genotyping, oncologists must select a reliable assay. The National Institutes of Health's Genetic Testing Registry (GTR)[3] provides a searchable catalogue of available *DPYD* tests and lists laboratories that perform them.

When selecting a test, prioritize the following:

- **Variant coverage aligned with guidelines:** The Association for Molecular Pathology (AMP) Pharmacogenomics Working Group published a joint consensus recommendation[4] identifying key *DPYD* variants for pharmacogenetic testing. These variants are classified into two tiers based on clinical relevance:
    - **Tier 1 variants (should test):** Variants in this tier represent the minimum recommended set for routine testing, supported by well-characterized functional effects and appreciable allele frequencies.
    - **Tier 2 variants (can test):** Variants in this tier meet at least one criterion for tier 1 but currently lack sufficient evidence for routine testing. However, some tier 2 variants may be clinically relevant in individuals from specific ancestral backgrounds and could be considered in extended panels when appropriate.

DPYD Variants Recommended for Testing by the AMP Pharmacogenomics Working Group					
Variant (NM_000110.4)	Legacy Name	CPIC-Defined DPD Function	Activity Score	rsID	Multiethnic Allele Frequency (%)
Tier 1 *DPYD* Variants					
c.1905+1G>A	*2A	No function	0	rs3918290	0–0.5
c.1679T>G	*13	No function	0	rs55886062	0–0.08
c.1129-5923C>G, c.1236G>A	HapB3	Decreased function	0.5	rs75017182, rs56038477	0.06–2.4
c.557A>G	–	Decreased function	0.5	rs115232898	0–2.1
c.868A>G	–	Decreased function	0.5	rs146356975	0–0.2
c.2279C>T	–	Decreased function	0.5	rs112766203	0–0.5
c.2846A>T	–	Decreased function	0.5	rs67376798	0–0.6
Tier 2 *DPYD* Variants					
c.299_302del	*7	No function	0	rs72549309	0–0.01
c.703C>T	*8	No function	0	rs1801266	0–0.03
c.1314T>G	–	Decreased function	0.5	rs186169810	0–0.05
c.1475C>T	–	No function	0	rs72549304	0–0.02
c.1774C>T	–	No function	0	rs59086055	0–0.08
c.2639G>T	–	No function	0	rs55674432	0–0.08

CPIC, Clinical Pharmacogenetics Implementation Consortium
Source: Pratt, 2024[4]

- **Accreditation and quality:** Use laboratories accredited by the College of American Pathologists (CAP), certified under the Clinical Laboratory Improvement Amendments (CLIA), and, ideally, accredited to International Organization for Standardization (ISO) 15189 standards. These accreditations indicate adherence to rigorous quality systems and competency.[5]
- **Consult the GTR and test-specific information:** Review each test's variant coverage, methodology, specimen requirements, and turnaround time.
    - For example, ARUP Laboratories' Dihydropyrimidine Dehydrogenase (DPYD) test is CAP- and ISO-accredited and detects nine clinically actionable variants, including all AMP tier 1 variants as well as c.1024G>A and c.1774C>T. The test uses polymerase chain reaction (PCR) with fluorescence monitoring, has a turnaround time of five to 10 days, and accepts ethylenediaminetetraacetic acid (EDTA) or acid-citrate-dextrose (ACD) whole blood specimens.[5,6]

Genotype-Guided Dosing Recommendations for Fluoropyrimidines

The CPIC provides publicly accessible recommendations for genotype-guided therapeutic dosing. The CPIC guideline for fluoropyrimidines and *DPYD* can be accessed here.[7] Each *DPYD* allele is assigned an activity score (1 for normal function, 0.5 for decreased function, and 0 for no function). The sum of activity scores from both alleles yields the total activity score, which informs the dosing recommendation:

Fluoropyrimidine Dosing Recommendations Based on *DPYD* Genotype[a]			
Phenotype	**Activity Score**	**Genotype Examples**	**Interpretation and Dosing Guidance**
Poor metabolizer	0	2 no-function alleles (e.g., c.1905+1G>A/2A or compound heterozygous for 2 no-function variants)	Predicts complete DPD deficiency Avoid 5-FU and capecitabine; select an alternative therapy if possible
	0.5	1 no-function allele plus 1 decreased-function allele or 2 decreased-function alleles (e.g., c.1679T>G/c.2846A>T)	Predicts near-complete DPD deficiency An alternative to fluoropyrimidines is preferred; if no alternative exists, start at a strongly reduced dose (<25% of the standard dose) with early TDM
Intermediate metabolizer	1 or 1.5	1 no-function allele (e.g., c.1905+1G>A, c.1679T>G) or 2 decreased-function alleles (activity score 1.0), **or** 1 normal allele plus 1 decreased-function allele (e.g., c.2846A>T or HapB3, activity score 1.5)	Predicts partial DPD deficiency Start fluoropyrimidine therapy at 50% of the standard dose, with early TDM and titration based on toxicity (increase if tolerated, reduce if not)
Normal metabolizer	≥2.0	2 normal alleles (e.g., wild type/wild type)	Predicts normal or mildly reduced DPD activity Use the standard starting dose and titrate upward if toxicity is absent or tolerable; decrease the dose if not tolerated

[a]Table adapted from the CPIC guideline for fluoropyrimidine dosing based on *DPYD* genotype.[7,8]
TDM, therapeutic drug monitoring
Sources: CPIC, 2025[7]; Amstutz, 2018[8]

Clinical Workflow

1. **Order *DPYD* testing before initiating therapy (unless immediate treatment is necessary)** through a CAP-accredited laboratory; the testing should include all AMP tier 1 variants and any tier 2 variants deemed clinically relevant for the patient population. Review the test report for the genotype and the predicted phenotype.[4]
2. **Apply CPIC dosing recommendations based on the patient's activity score.**
3. **Educate and monitor patients:** Counsel patients on the potential for early-onset toxicity and emphasize the importance of promptly reporting symptoms. Regardless of genotype, monitor blood counts and organ function throughout treatment. Adjust or withhold therapy as needed based on clinical findings.[1]

Summary

The updated capecitabine (XELODA) boxed warning underscores the importance of pretreatment *DPYD* genotyping to reduce the risk of severe toxicity. Choose a high-quality test from a laboratory accredited by CAP (and ideally, by ISO) that at a minimum includes all AMP tier 1 variants. Use CPIC guidelines to interpret results and guide dosing; that is: Avoid fluoropyrimidines in poor metabolizers, reduce initial doses by at least 50% for intermediate metabolizers, and use standard dosing for normal metabolizers with careful monitoring. Following these steps will help minimize life-threatening toxicity and support personalized, genotype-guided therapy for your patients.

Additional Resources

For more information on pharmacogenetic testing, refer to the ARUP Consult Germline Pharmacogenetics - PGx topic.

For technical information on ARUP Laboratories' dihydropyrimidine dehydrogenase (*DPYD*) test, refer to the Dihydropyrimidine Dehydrogenase (DPYD) Test Fact Sheet.

References

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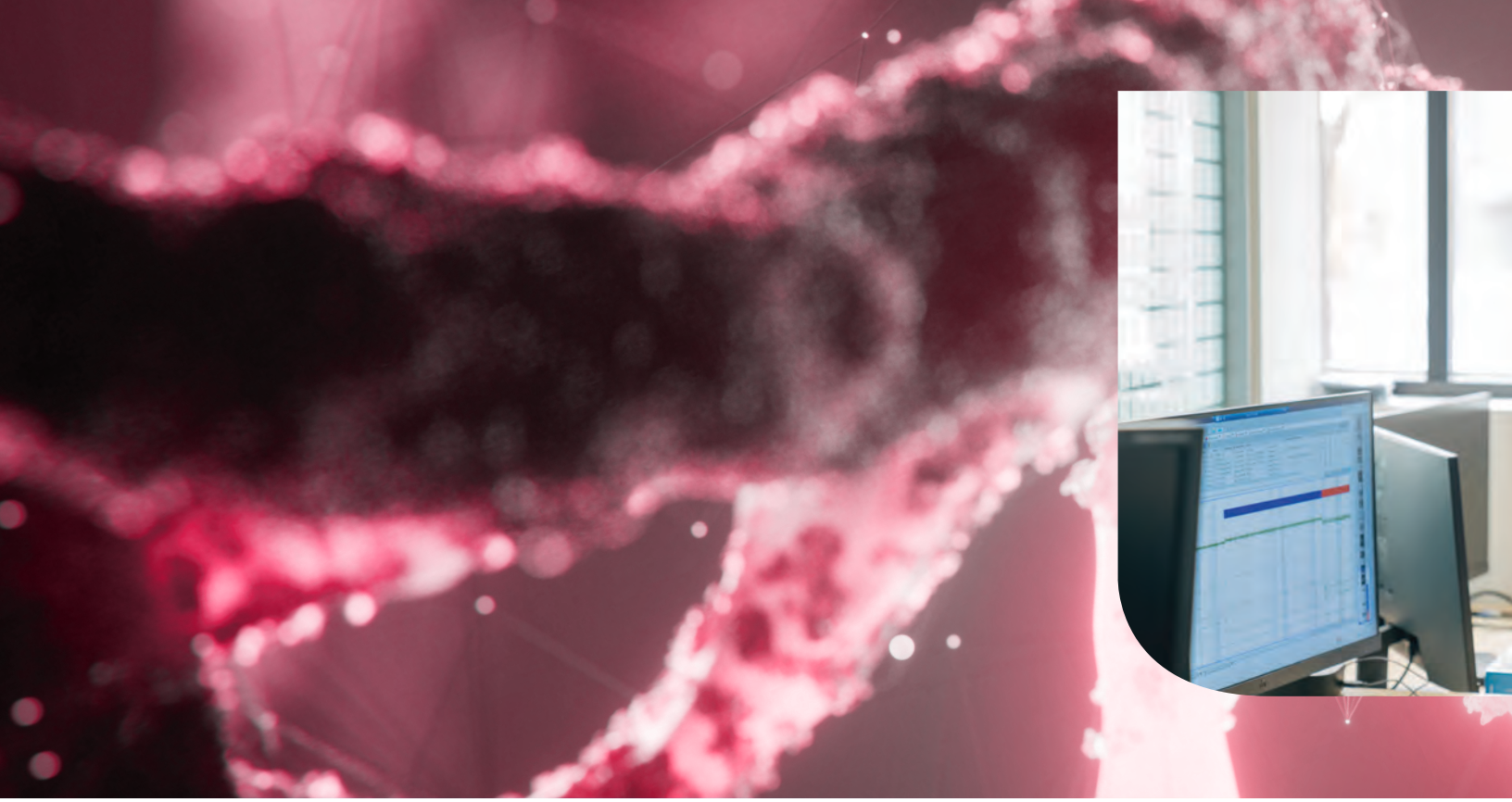

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