SMART Approach

DPYD Genotype-guided Dose Optimization of 5-Fluorouracil in Individuals with Pancreatic Cancer

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1. Overview

Pharmacogenetic analysis such as *DPYD* gene variants for systemic fluoropyrimidines (FP) provides critical genetic information to optimize dose modification or omission of common therapies. FP including intravenous 5-fluorouracil (IV 5-FU) and its oral prodrug capecitabine are used to treat a variety of solid tumors such as pancreatic, colorectal, and breast cancer.[1-2] National Comprehensive Cancer Network (NCCN) guidelines recommend FOLFIRINOX (IV 5-FU + leucovorin + irinotecan + oxaliplatin) or modified FOLFIRINOX (mFOLFIRINOX) as a preferred first-line treatment for all stages of pancreatic cancer.[2-6] NALIRI (IV-FU, leucovorin and liposomal irinotecan) regimen is often considered as subsequent-line therapy for those who did not receive FOLFIRINOX as initial therapy.[7] In addition, capecitabine is used in combination with gemcitabine as adjuvant treatment.[3,8] Often, capecitabine is also used as a radiosensitizer for those considered candidates for radiation.[9] Common toxicities of systemic fluoropyrimidines include fatigue, neutropenia, diarrhea, and vomiting.[6] Severe NCI CTCAE grade 3+ toxicities arising from fluoropyrimidine therapy in patients with select *DPYD* variants are also hematological or gastrointestinal.[1,10]

- **The *DPYD* gene codes for the dihydropyrimidine dehydrogenase (DPD) enzyme that is the rate-limiting step in catabolizing 5-FU to inactive metabolites.**[10-11]
- A patient's *DPYD* genotype predicts their DPD activity score (AS). Each *DPYD* allele is assigned a score of normal (1.0), decreased (0.5), or no (0.0) activity. The sum of a patient's two alleles is used to determine their AS, which is then used to categorize the patient as a **normal (AS=2.0, NM), intermediate (AS=1-1.5, IM), or poor (AS=0-0.5, PM) metabolizer.** [12-13]
- Five *DPYD* variants have moderate or strong evidence that they result in decreased (c.2846A>T (p.D949V), c.1129-5923C>G, c.1236G>A (HapB3), c.557A>G (p.Y186C) or no (c.1905+1G>A (*2A), c.1679T>G (*13)) DPD activity. [14] Approximately 2% of Black/African patients carry the c.557A>G variant, and 6% of those with European descent carry one of the other validated variants.[13] Other variants primarily of ethnic minorities are known and may be actionable but are typically not included in testing due to a lack of evidence.[15] **(Table 1)**
- Severe NCI CTCAE grade 3+ toxicity occurs in about one third of patients undergoing 5-FU therapy regardless of genotype and this risk is approximately two times greater[12-13] in patients carrying *DPYD* variants that decrease DPD activity.[13, 16-17] **Risk of fatal toxicity is about 25x higher in *DPYD* variant carriers.**[18]It should be noted that a patient can carry two variants with diminished or null DPD activity, which further increases their risk of severe and fatal toxicity.

Abbreviations used in this paper: AS, activity score; ; CPIC, Clinical Pharmacogenetics Implementation Consortium; DPD, dihydropyrimidine dehydrogenase; EMA, European Medicines Agency; ESMO, European Society of Medical Oncology; FDA, The Food and Drug Administration; FP, fluoropyrimidines: 5-FU, 5-fluorouracil, fluoropyrimidines; IM, intermediate metabolizer; NCCN, National Comprehensive Cancer Network; NM, normal metabolizer; PM, poor metabolizer.

Keywords: *DPYD,* DPD, 5-fluorouracil, 5-FU, pancreatic cancer

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Table 1. *DPYD* variant and resultant DPD AS.

DPYD Variant, cDNA	Historic Name	rsID	Allele Clinical Functional Status	**DPD AS** (activity score)	Reference
c.1129-5923C>G, c.1236G>A	HapB3	rs75017182, rs56038477	Decreased function	**0.5**	30, 31
c.557A>G	p.Y186C	rs115232898	Decreased function	**0.5**	32
c.2846A>T	p.D949V	rs67376798	Decreased function	**0.5**	32
c.1905+1G>A	*2A	rs3918290	No function	**0.0**	33
c.1679T>G	*13	rs55886062	No function	**0.0**	34

- Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines recommend a 50% dose reduction for patients with AS=1.0-1.5, and avoidance of fluoropyrimidine treatment for patients with AS=0-0.5. Patients with normal activity (AS=2.0) should proceed with the standard starting dose.
- Prospective clinical studies of *DPYD*-guided dosing have demonstrated that **patients who carry *DPYD*-variants and receive reduced fluoropyrimidine doses have lower toxicity risk** and noninferior progression-free and overall survival compared to variant carriers receiving standard dose. Toxicity risk and survival is similar to patients with normal DPD activity receiving standard dosing.[14,19-20]
- Due to these clinical benefits, pre-treatment *DPYD* testing to inform fluoropyrimidine dosing is recommended by the European Medicines Agency (EMA) and European Society of Medical Oncology (ESMO) and commonly conducted in Europe.[21-22] The Food and Drug Administration (FDA) and NCCN have not yet recommended this strategy, though the FDA updated labeling for injectable 5-FU and capecitabine in early 2024 to advise clinicians to consider pre-treatment *DPYD* testing.[14]

2. Who should be tested:

Pre-treatment testing *should be considered* for any patient with unknown *DPYD* genotype preparing to receive their first dose of systemic fluoropyrimidine chemotherapy [25-26], unless treatment must be initiated before the result will be known (i.e., < 7 days). Testing for DPD deficiency may be performed by assessing *DPYD* genotype or by conducting a phenotypic DPD activity test, such as uracil measurement. Providers should determine which test is appropriate when considering their patient population, institutional workflow, and cost/reimbursement for testing. [27-28] *DPYD* testing is unlikely to be beneficial in patients who have already initiated systemic fluoropyrimidine chemotherapy or are initiating treatment with reduced doses (e.g., mFOLFIRINOX).[3,28]

3. How to manage dose:

CPIC Guidelines: Avoid 5-FU for patients with an AS 0-0.5. Reduce dose by 50% when AS=1-1.5. NM Patients with AS=2.0 receive standard dosing.[23]
PM: Fluoropyrimidine administration is not recommended for patients with complete DPD deficiency (AS= 0 or 0.5).[23-26]

Non-5-FU regimens that are recommended by NCCN include gemcitabine-based regimens or targeted therapy based on tumor biomarkers (e.g., olaparib for BRCA 1 or 2 mutations, or entrectinib, larotrectinib, and repotrectinib for *NTRK* gene fusion-positive pancreatic cancer).[29, 3]

IM: Patients with partial DPD deficiency (AS=1.0-1.5) should be initiated on a reduced dose according to CPIC guidelines.

Current Issues to Consider

- The EMA recommendation for testing and FDA guidance to consider testing do not specify which patients to test based on tumor type, fluoropyrimidine agent, or disease setting (i.e., adjuvant vs. metastatic).[14, 21-22]
- Additionally, dosing guidelines do not include specific recommendations based on agent or 5-FU infusion type (i.e., bolus vs. continuous), warranting further clarification.[23-24]
- **Recommendations for 5-FU (IV, capecitabine)/*DPYD* pharmacogenetic management in pancreatic cancer**
- To our knowledge, these are the first pancreatic cancer-specific pharmacogenetic-guided management recommendations for fluoropyrimidines/*DPYD*.

For IV 5-FU, both the bolus and the continuous infusion should be adjusted based on CPIC recommendations.[14, 23]

For **capecitabine**, the intended starting dose should be adjusted based on CPIC guidelines, recognizing there is variability between clinicians and institutions regarding standard capecitabine starting doses.[17, 23]

Patients who tolerate the reduced starting dose should be re-escalated for their next cycle as tolerated, perhaps in increments of 10% of the original starting dose per cycle. [23]

Table 2. Dose recommendations by *cumulative* DPD AS.

DPD AS	Recommended Dose
2.0	100% standard dose
1-1.5	50% standard dose
0-0.5	Avoid 5-FU therapy

To calculate the **cumulative DPD AS**, take the DPD AS for each of the patient's two alleles in Table 1 and add them.

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Author Contributions:

Dr. Javier Granados conducted literature search, compiled relevant studies, and drafted manuscript. Dr. Vaibhav Sahai provided medical review, edits, and additional studies. Dr. Dan Hertz supervised the project, provided guidance and revised the manuscript.

Conflicts of Interest:

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