U.S. Department of Veterans Affairs
Veterans Health Administration
PBM Academic Detailing Services

CLINICIAN GUIDE

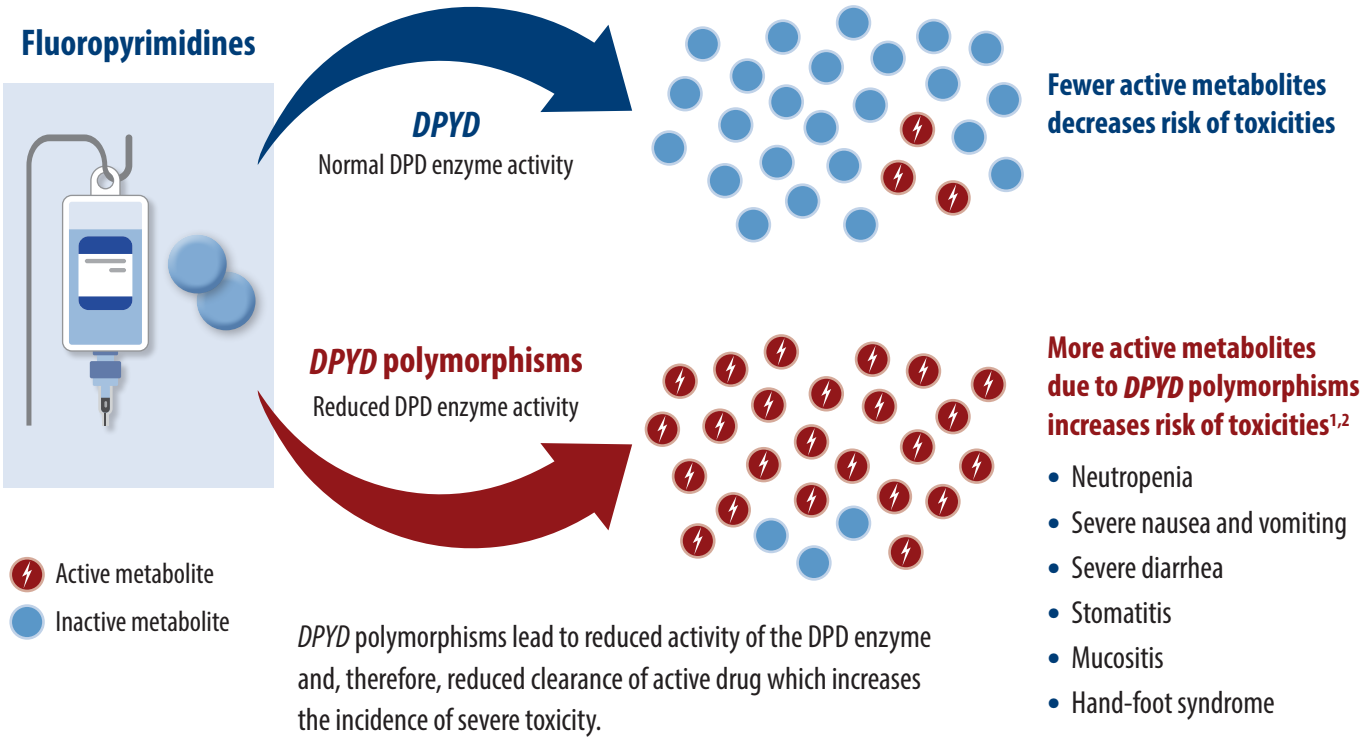
Applying Pharmacogenomics (PGx) to Fluoropyrimidine Therapy

PGx testing can help prevent life-threatening fluoropyrimidine toxicity.

The fluoropyrimidines 5-fluorouracil (intravenous) and capecitabine (oral) are widely used in the treatment of colorectal, pancreatic, gastric, anal, breast, and biliary tract cancers as well as head and neck squamous cell carcinoma.[1]

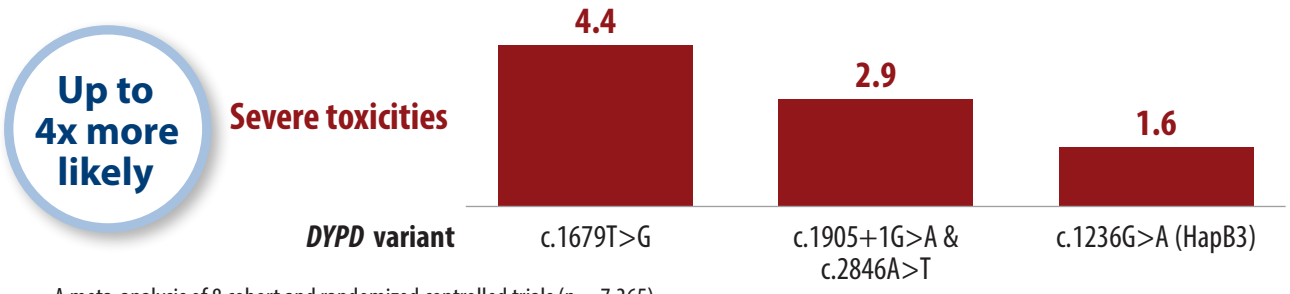
- **Severe toxicities develop in up to 30% of patients** prescribed a systemic fluoropyrimidine, with treatment related mortality as high as 5% in elderly patients.[2]
- Variation in the **dihydropyridine dehydrogenase gene *(DPYD)*** resulting in reduced activity of the dihydropyrimidine dehydrogenase (DPD) enzyme is detected in 39-61% of patients with severe toxicities.[2]
- Patients with *DPYD* gene variants have a **25 times increased risk of treatment-related death** with standard dosing of fluoropyrimidines compared to those with normal DPD function.[3]

Figure 1. *DPYD* polymorphisms result in life-threatening toxicities.[1,4]



DPYD polymorphisms lead to reduced activity of the DPD enzyme and, therefore, reduced clearance of active drug which increases the incidence of severe toxicity.

Figure 2. Severe toxicities are up to 4 times more likely in patients with *DPYD* variants receiving standard fluoropyrimidine therapy.[2,5]



A meta-analysis of 8 cohort and randomized controlled trials (n = 7,365).

Figure 3. Genotype-guided dosing results in fewer adverse outcomes from fluoropyrimidines.[6,7]

Order PGx testing prior to initiating systemic fluoropyrimidine therapy to reduce toxicity.

Applying PGx test results

PGx test results will appear in the electronic health record, and the patient will receive a copy in the mail. The report will indicate the patient's **phenotype** and **activity score (AS), which represents the degree of DPD enzyme function.** Both should be used to guide dosing strategy. For help interpreting results, see *An Introduction to Pharmacogenomics Clinician Guide* or consult your PGx Clinical Pharmacist Practitioner (CPP).

The Federal Drug Administration (FDA) and *Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines* recommend **therapeutic management adjustments** for patients with *DPYD* variants.[1,8-9]

Figure 4. CPIC dosing recommendations are based on frequently occurring allele variants.†

***DYPD* Phenotype and DPD activity**	**Normal metabolizer** *Normal function*	**Intermediate metabolizer** *Decreased function*	**Poor metabolizer** *No function*
Select allele variants	No variants detected	c.2846A>T c.1129-5923C>G (HapB3)/ c.1236G>A	c.1905+1G>A c.1679T>G

†The incidence of these alleles varies widely among ancestral groups.[1] Refer to the National Pharmacogenomics Program SharePoint for the most up-to-date information regarding genes and alleles included on available PGx test panels.

Table 1. CPIC systemic fluoropyrimidine dosing recommendations based on *DPYD* phenotype and AS[1]

DYPD phenotype[§]	Implications	AS	Strength of recommendation	Dosing recommendations
Normal metabolizer	Use label-recommended dosing	**AS 2**	Strong	Use label recommended dosage and administration
Intermediate metabolizer	Decreased *DPYD* activity (at **30% to 70%** of normal metabolizers) and increased risk for severe or even fatal drug toxicity	**AS 1 or 1.5:** Reduce dose by 50%	**AS 1:** Strong	**Reduce starting dose** based on AS followed by titration of dose based on toxicity and therapeutic drug monitoring[±]
			AS 1.5: Moderate	
Poor metabolizer	Complete *DPYD* deficiency and increased risk for severe or even fatal drug toxicity	**AS 0.5:** Avoid or start at a strongly reduced dose[+]	Strong	**Avoid use** of fluorouracil or fluorouracil prodrug-based regimens. If alternative agents are not possible, administer at a strongly reduced dose[+] with early therapeutic drug monitoring
		AS 0: Avoid		**Avoid use** of fluorouracil or fluorouracil prodrug-based regimens

[§]Variation in the *DPYD* gene leads to varying function of the DPD enzyme responsible for metabolism. Nomenclature reflected to match *DPYD* metabolizer status as displayed in the lab report. [+]Refer to CPIC Guidelines or reach out to your PGx Clinical Pharmacist Practitioner (CPP) for more information. [±]Evaluate the patient for a dose increase in those experiencing no or clinically tolerable toxicity in the first two cycles to maintain efficacy.

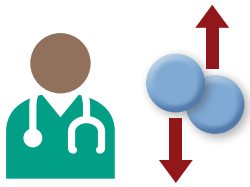
If I reduce the dose, what about efficacy?[1]

Pharmacokinetic analyses show exposure to fluoropyrimidine metabolites to be similar between patients with *DPYD* variants receiving adjusted dosing and those with normal DPD function receiving standard dosing.[6] A prospective, multicenter match pair analysis of 931 patients demonstrated **no negative impact on progression-free survival or overall survival with *DPYD*-guided fluoropyrimidine dosing** in those with common *DPYD* variants compared to patients without variants receiving standard dosing.[10]

PGx testing should be applied as an additional tool in the overall shared clinical decision-making process between providers and their patients.

Like adjusting for renal function, PGx testing **provides more information** for starting treatment

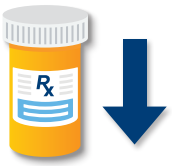
PGx testing can help with a more targeted and safe treatment strategy



Vigilant monitoring and dose adjustment is critical throughout treatment to maintain efficacy and avoid toxicity

Roughly 50% of decreased function *DPYD* variant carriers experience severe toxicities with standard dosing

with the other half tolerating standard fluoropyrimidine therapy.[1] **Consider a preemptive dose reduction** and increase with the next cycle if no toxicity occurs. Similarly, those without *DPYD* variation may still experience toxicity.



Consider an initial dose reduction to avoid severe toxicity

? DID YOU KNOW

PGx test results may reveal incidental findings related to other medication gene pairs on the available lab panel. A common example in the oncology setting is ondansetron. Variations in ***CYP2D6*** metabolism may impact the **efficacy** of ondansetron.[11-13] Ultrarapid *CYP2D6* metabolizers may have a decreased therapeutic response and benefit from an alternative anti-emetic therapy.[11]

Refer to *CPIC guidelines* (https://cpicpgx.org/guidelines/) or your PGx CPP for more information.

Clinical pharmacist practitioners (CPP)

PGx CPPs are Advanced Practice Providers who are highly trained members of the healthcare team with additional education or experience in pharmacogenomics.

Consult services are available in the electronic health record orders package for providers to request CPP assistance. CPPs can evaluate pharmacotherapy based on the PGx test results, make adjustments if needed, and contact patients for follow-up education.

For more information

RESOURCES:

Page 2: An Introduction to Pharmacogenomics Clinician Guide (http://tinyurl.com/2juazb6v); PGx Clinical Pharmacist Practitioner (CPP) (https://tinyurl.com/47zzsb8p)

Pages 2 and 4: Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines (https://cpicpgx.org/)

Pages 2 and 3: National Pharmacogenomics Program SharePoint (http://tinyurl.com/bdft5zd8)

REFERENCES: 1. Amstutz U, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing: 2017 Update. *Clin Pharmacol Ther.* Feb 2018;103(2):210-216. **2.** Meulendijks D, et al. Clinical relevance of DPYD variants c.1679T>G, c.1236G>A/HapB3, and c.1601G>A as predictors of severe fluoropyrimidine-associated toxicity: a systematic review and meta-analysis of individual patient data. *The Lancet Oncology.* Dec 2015;16(16):1639-50. **3.** Sharma BB, et al. Pathogenic DPYD Variants and Treatment-Related Mortality in Patients Receiving Fluoropyrimidine Chemotherapy: A Systematic Review and Meta-Analysis. *Oncologist.* Dec 2021;26(12):1008-1016. **4.** Launay M, et al. Beating the odds: efficacy and toxicity of dihydropyrimidine dehydrogenase-driven adaptive dosing of 5-FU in patients with digestive cancer. *Br J Clin Pharmacol.* 2016;81(1):124-130. **5.** Deenen MJ, et al. Upfront Genotyping of DPYD*2A to Individualize Fluoropyrimidine Therapy: A Safety and Cost Analysis. *J Clin Oncol.* Jan 20 2016;34(3):227-34. **6.** Henricks LM, et al. DPYD genotype-guided dose individualisation of fluoropyrimidine therapy in patients with cancer: a prospective safety analysis. *The Lancet Oncology.* Nov 2018;19(11):1459-1467. **7.** Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 Accessed Oct 2, 2023. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf. **8.** Table of Pharmacogenomic Biomarkers in Drug Labeling. Federal Drug Administration 2022. **9.** Table of Pharmacogenetic Associations. 2022. **10.** Knikman JE, et al. Survival of Patients With Cancer With DPYD Variant Alleles and Dose-Individualized Fluoropyrimidine Therapy-A Matched-Pair Analysis. *J Clin Oncol.* Aug 28 2023:Jco2202780. **11.** Bell GC, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 genotype and use of ondansetron and tropisetron. *Clin Pharmacol Ther.* Aug 2017;102(2):213-218. **12.** Candiotti KA, et al. The impact of pharmacogenomics on postoperative nausea and vomiting: do CYP2D6 allele copy number and polymorphisms affect the success or failure of ondansetron prophylaxis? *Anesthesiology.* Mar 2005;102(3):543-9. **13.** Kaiser R, et al. Patient-tailored antiemetic treatment with 5-hydroxytryptamine type 3 receptor antagonists according to cytochrome P-450 2D6 genotypes. *J Clin Oncol.* Jun 15 2002;20(12):2805-11.