Implementation of DPYD Pharmacogenomic Testing and Dose Adjustments

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Objectives

- Understand the role of *DPYD* in fluoropyrimidine metabolism and effects on toxicity
- Review fluoropyrimidine dose-adjustments for *DPYD* polymorphisms
- Describe methods to implement *DPYD* protocol at an academic institution

Poll Question

When is DPYD testing for fluoropyrimidines conducted at your institution?

A. Prior to fluoropyrimidine therapy for all patients

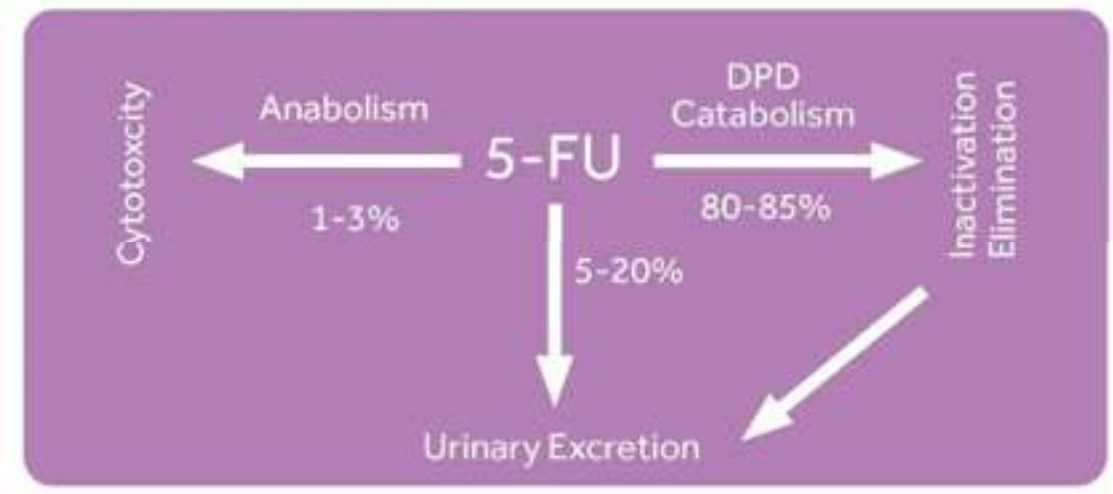
B. Prior to fluoropyrimidine therapy for patients at highest risk of toxicity

C. Prior to fluoropyrimidine therapy based on clinical judgment of the oncologist

D. After receiving fluoropyrimidine therapy if excessive toxicity is observed

E. Not sure / not implemented at my practice site

DPYD Genetics on Fluoropyrimidine Metabolism



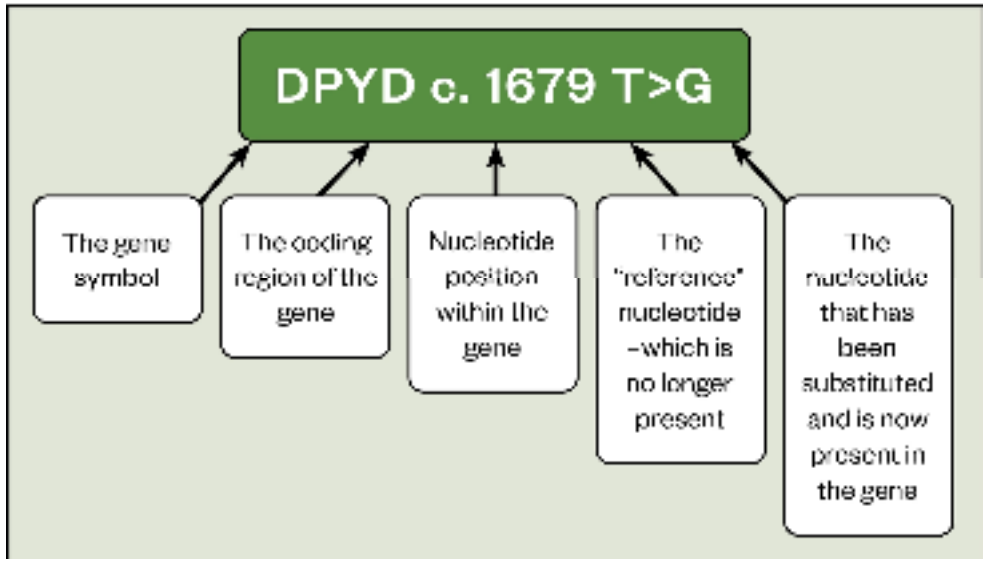
80-85% of 5-FU is catabolized by Dihydropyrimidine Dehydrogenase (DPD) to inactive metabolites

DPD enzyme is encoded by the gene, ***DPYD***

Adrucil (fluorouracil injection) [prescribing information]. North Wales, PA: Teva Pharmaceuticals Inc; October 2017.

Understanding DPYD Genetic Changes

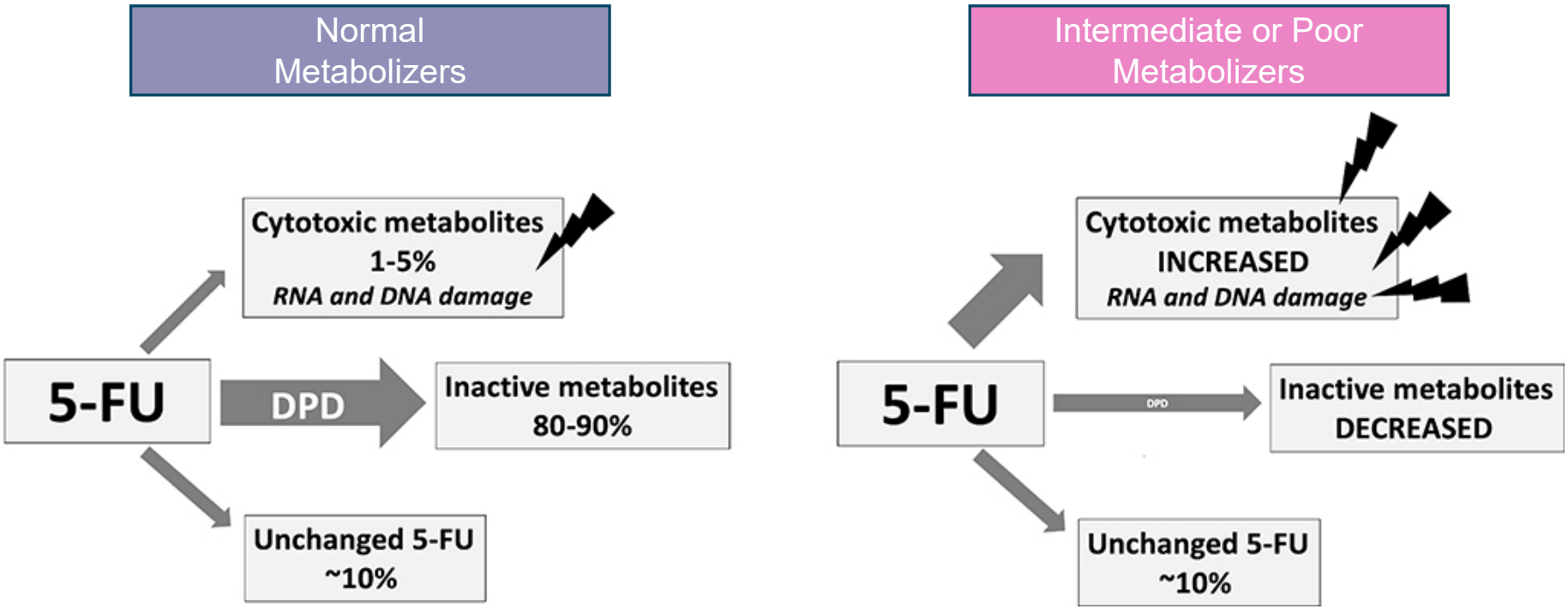
Nucleotide Change	Genotype	Phenotype



Star Allele: *13
Standard name for genetic variants compared to wild-type (*1)

Genotype	Phenotype
*1/*1 Homozygous	• Normal Metabolizer
*1/*13 Heterozygous	• Intermediate Metabolizer
*13/*13 Homozygous	• Poor Metabolizer
*2A/*13 Compound Heterozygous	• Poor Metabolizer

DPYD impact on Fluoropyrimidines

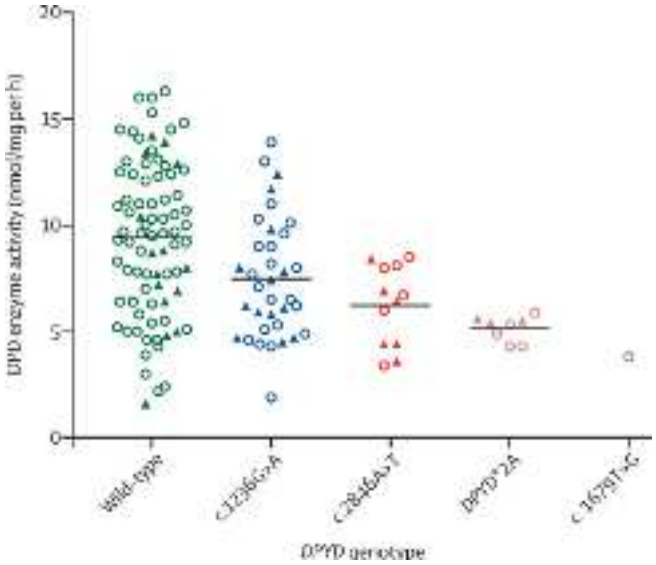


Risks of 5-FU Toxicity

- The mortality rate from 5-FU has been estimated at 0.5%-1%
- It can be estimated that for every 1,000 patients treated with either FU or capecitabine in the United States, 10 patients will die of treatment-related toxicity

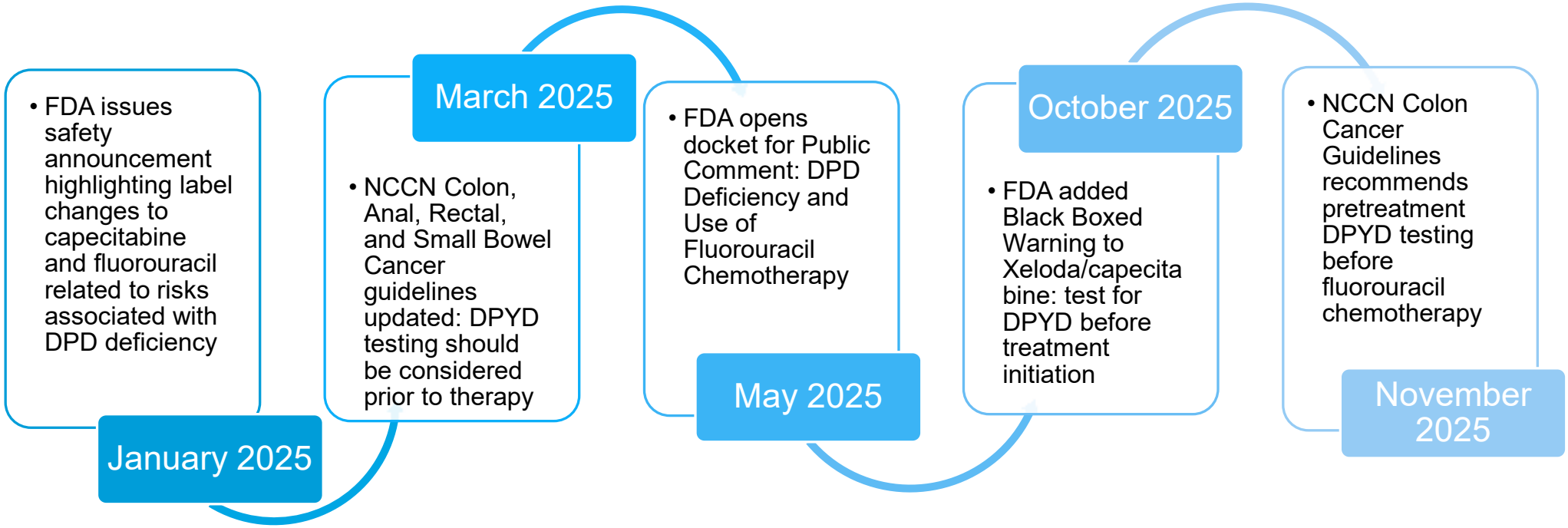
Common *DPYD* Variants and their impact on DPYD Function

Genotype	Nucleotide Change	Prevalence in heterozygous state	Average reduction in DPD enzyme	Incidence of Grade ≥3 Adverse Events
N/A	c.1236G>A	2.6%	~25%	59%
p.D949V	c.2846A>T	1.1%	~25%	81.5%
**2A*	c.1905+1G>A	0.94%	~50%	88%
**13*	c.1679T>G	0.14%	~50%	50%



DPYD: dihydropyrimidine dehydrogenase

Key Milestones for DPYD Testing



Pharmacogenomic Dose Adjustment for DPYD

Guideline Recommendations for Dose Adjustment

Clinical Pharmacogenetics Implementation Consortium (CPIC), 2022

Genotype	Phenotype	Activity Score	Implications
*DPYD*1/*1*	Normal Metabolizer	2.0	No adverse influence
*1/D949V 1/c.1236G>A	Intermediate Metabolizer	1.5	Elevated fluoropyrimidine concentrations & High risk of toxicity
*1/*2A *1/*13 D949V/ D949V	Intermediate Metabolizer	1.0	
D949V/*2A D949V/*13	Poor Metabolizer	0.5	Very High risk of toxicity
*2A/*2A *13/*13	Poor Metabolizer	0	Extremely High risk of toxicity

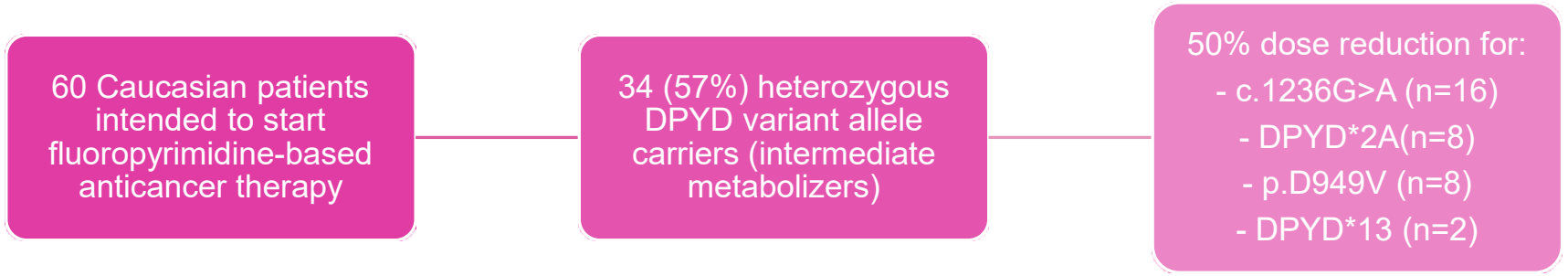
Pharmacogenomic Dose Adjustment for DPYD

Guideline Recommendations for Dose Adjustment

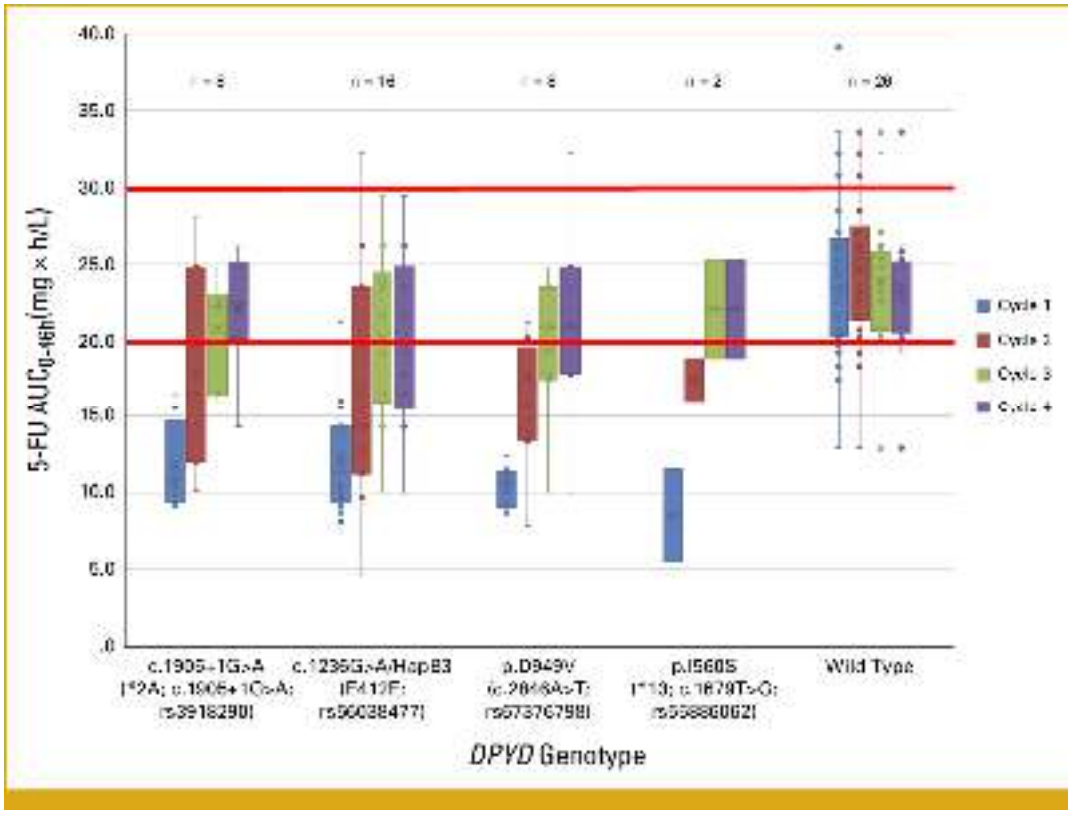
Clinical Guidance	*DPYD* Normal Metabolizer	*DPYD* Intermediate Metabolizer	*DPYD* Poor Metabolizer
Dutch Pharmacogenetics Working Group **(DPWG), 2020**	Standard dosing	Reduce dose by 50%	Avoid fluoropyrimidines
French National Network of Pharmacogenetics **(RNPGx), 2017**	Standard dosing	Reduce dose by 50%	Avoid fluoropyrimidines
Spanish Pharmacogenetics and Pharmacogenomics Society and the Spanish Society of Medical Oncology **(SEFF and SEOM), 2022**	Standard dosing	Reduce dose by 50%	Avoid fluoropyrimidines

Evidence for *DPYD* Guided Dose-Adjustments

Intermediate Metabolizer Dose Adjustments



Evidence for *DPYD* Guided Dose-Adjustments



All *DPYD* variant patients (n = 34) started on a 50% reduced 5-FU dose, leading to 5-FU underexposure in 97% (n = 33; median AUC 10.1 mg × h/L)

During subsequent cycles, the 5-FU dose was increased stepwise. Most variant patients tolerated dose ≥70%.

Ten variant patients discontinued treatment due to disease progression:

n = 6 after cycle 1 n = 2 after cycle 2 n = 2 after cycle 3

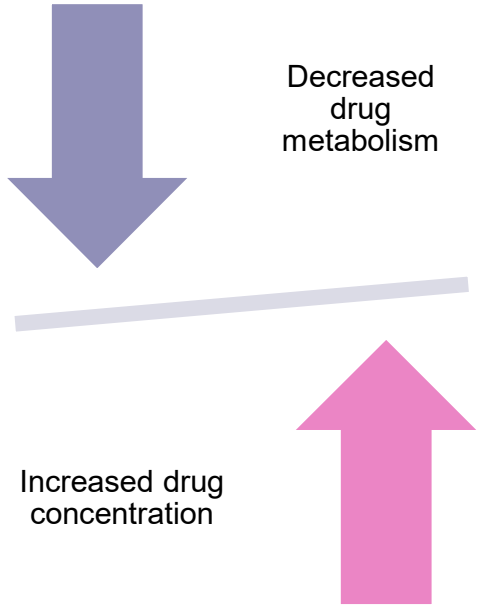
68% (n = 19) reached an $AUC_{0\text{-}46h}$ >20 mg × h/L.

32% (n=9) variant patients failed to reach the target AUC due to toxicity experienced during dose escalation

Preservation of antitumor efficacy of reduced dose FU

Can dose reducing 5-FU negatively affect efficacy oncology treatment?

- A concern of oncologists is the possibility that a dose reduction of 5-FU in *DPYD* carriers can negatively affect the efficacy of treatment.
  - Dose reduction in *DPYD* carriers is compensated by a normalization in systemic exposure to active drug, the dose reductions might not affect the efficacy of the treatment
- In patients with colorectal cancer treated in the adjuvant setting, no statistically significant associations were found with any DPYD variants and disease-free survival



Preservation of antitumor efficacy of reduced dose FU

Comparisons of disease-free survival (DFS) in DPYD intermediate metabolizers

Study Design

- *DPYD* variant carriers received a 25% (c.1236G>A and c.2846A>T) or 50% (*DPYD**2A and c.1679T>G)
- Each *DPYD* variant carrier was matched to three *DPYD* wild-type controls treated with a standard dose.

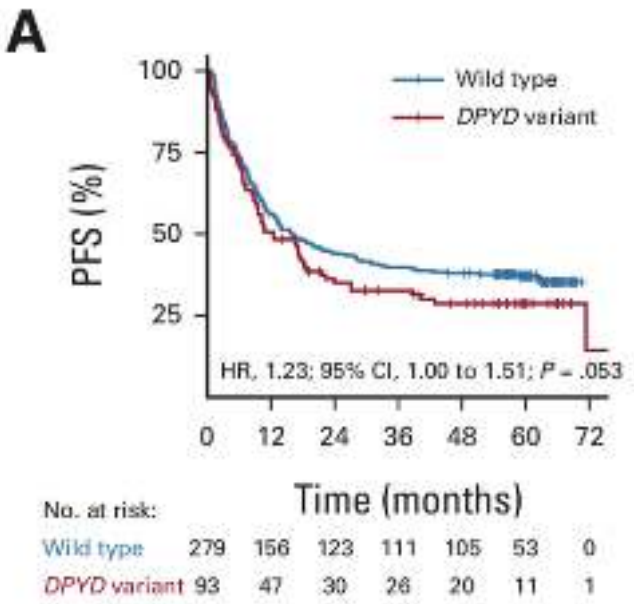
Population

- 156 *DPYD* variant carriers and 775 *DPYD* wild-type controls were available for analysis
- When pooled—93 *DPYD* variant carriers could each be matched to three unique *DPYD* wild-type controls.

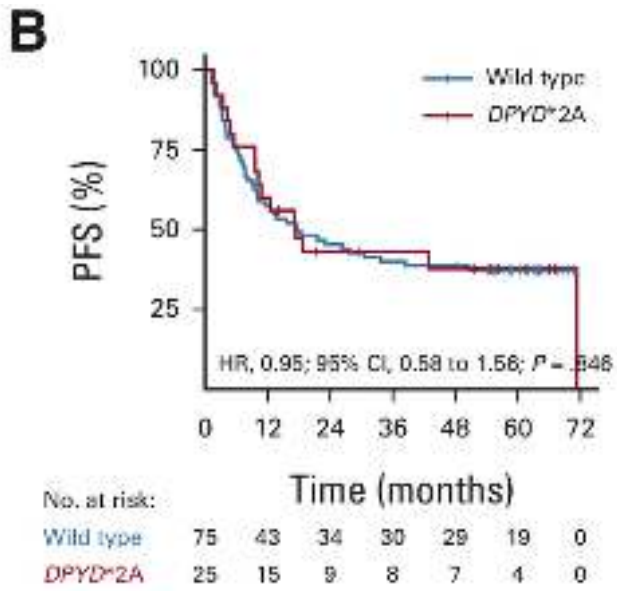
Preservation of antitumor efficacy of reduced dose FU

Comparisons of disease-free survival (DFS) in DPYD intermediate metabolizers

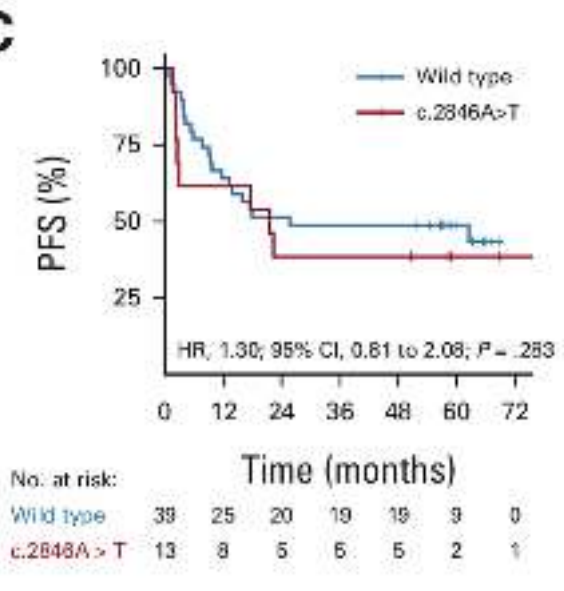
Pooled Analysis



c.2846A>T



*DPYD*2A*



ISMP Recommendations on Implementing DPYD Testing

Gather a multidisciplinary team. Create a team with representatives from pharmacy, oncology, clinical laboratory, and other relevant departments to oversee fluoropyrimidine safety and conduct a comprehensive review of current testing protocols, comparing them to established guidelines to identify gaps in current practice.

Establish DPYD testing guidelines. Develop guidelines that clearly define DPYD testing criteria, provide instructions for interpreting results, and outline appropriate clinical action that includes a system to track patients initiating fluoropyrimidine treatment. For additional information, please refer to the DPYD Genotyping Recommendations[3] which aim to promote consistency in DPYD genetic variant testing across clinical laboratories.

Utilize clinical decision support. Integrate the Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Fluoropyrimidines and DPYD into the electronic health record (EHR) to alert prescribers and recommend DPYD genetic variant testing before ordering fluorouracil or capecitabine. Integrate testing results with clinical decision support (e.g., alerts for contraindications, dose adjustments) directly into the EHR workflow.

Educate staff. Educate staff about your organization's guidelines and how to interpret test results and adjust or hold the fluoropyrimidine dose when needed.

Inform patients. Engage in shared decision-making with patients by reviewing their DPYD genetic variant test results before initiating therapy and explaining the implications on their treatment plan. Provide patients with detailed documentation of their test results and emphasize the importance of sharing this information with all healthcare professionals involved in their care.

Antidote availability. Ensure uridine triacetate, the antidote for fluoropyrimidine overdose or toxicity, is readily available and included in order sets that contain fluoropyrimidine drugs to ensure appropriate doses and timing for both adult and pediatric patients, should signs and symptoms of an overdose/toxicity present themselves.

Gathering a Multidisciplinary Team

Oncology Physician Leadership

Nursing Leadership

Pharmacogenomics Specialist

Oncology Clinical Pharmacy Manager

Establishing DPYD Testing Guidelines

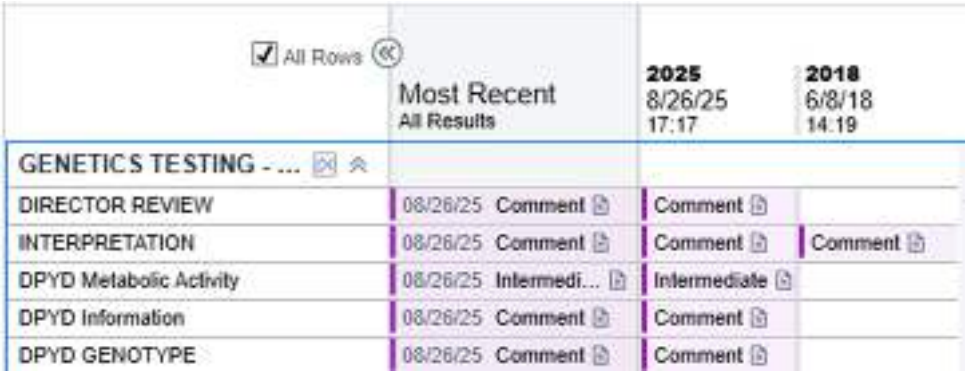
Who to test	• Patients who would be considered to start capecitabine or 5-FU therapy treatment at any point in treatment course
When to Test	• Order test at diagnosis or pre-treatment visit
What to test	• Epic order send out to Labcorp or through commercial laboratory (e.g. Guardant) using a paper requisition (*preferred)*
Authorized providers	• Oncologists, oncology advanced practice providers • (NPs, PAs)
Lab processing	• Targeted genotyping results in 7-10 days

Testing Results of *DPYD*

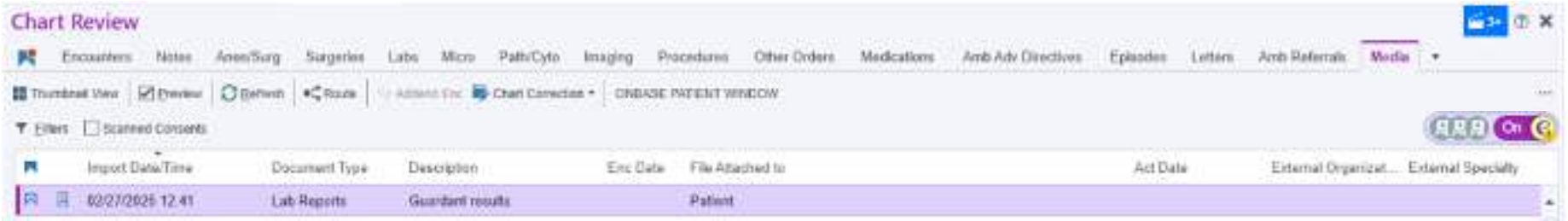
DPYD Test currently orderable via:

- Epic order sent-out to LabCorp

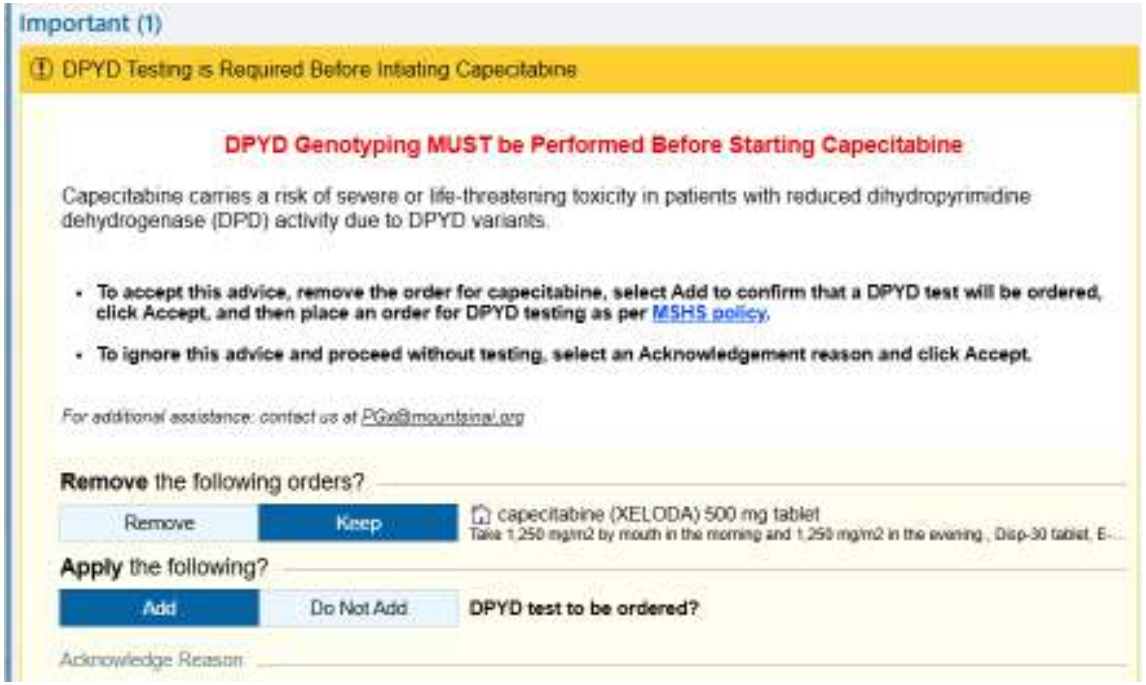
  (Epic Results)
- Guardant (Media)



All Rows	Most Recent All Results	2025 8/26/25 17:17	2018 6/8/18 14:19
GENETICS TESTING - ...			
DIRECTOR REVIEW	08/26/25 Comment	Comment	
INTERPRETATION	08/26/25 Comment	Comment	Comment
DPYD Metabolic Activity	08/26/25 Intermedi...	Intermediate	
DPYD Information	08/26/25 Comment	Comment	
DPYD GENOTYPE	08/26/25 Comment	Comment	



Utilizing Clinical Decision Support



Acknowledgement Reasons

- Patient is a normal metabolizer
- Patient is an intermediate metabolizer
- Patient is a poor metabolizer
- Test ordered and resulted as indeterminant.
- Test ordered, result pending
- Urgent treatment is clinically indicated
- Therapy was previously tolerated
- Patient declined testing
- Topical therapy indicated. Routine DPYD testing is not recommended. Consider testing only in patients with prior severe fluoropyrimidine toxicity or suspected DPD deficiency.

Utilizing Clinical Decision Support

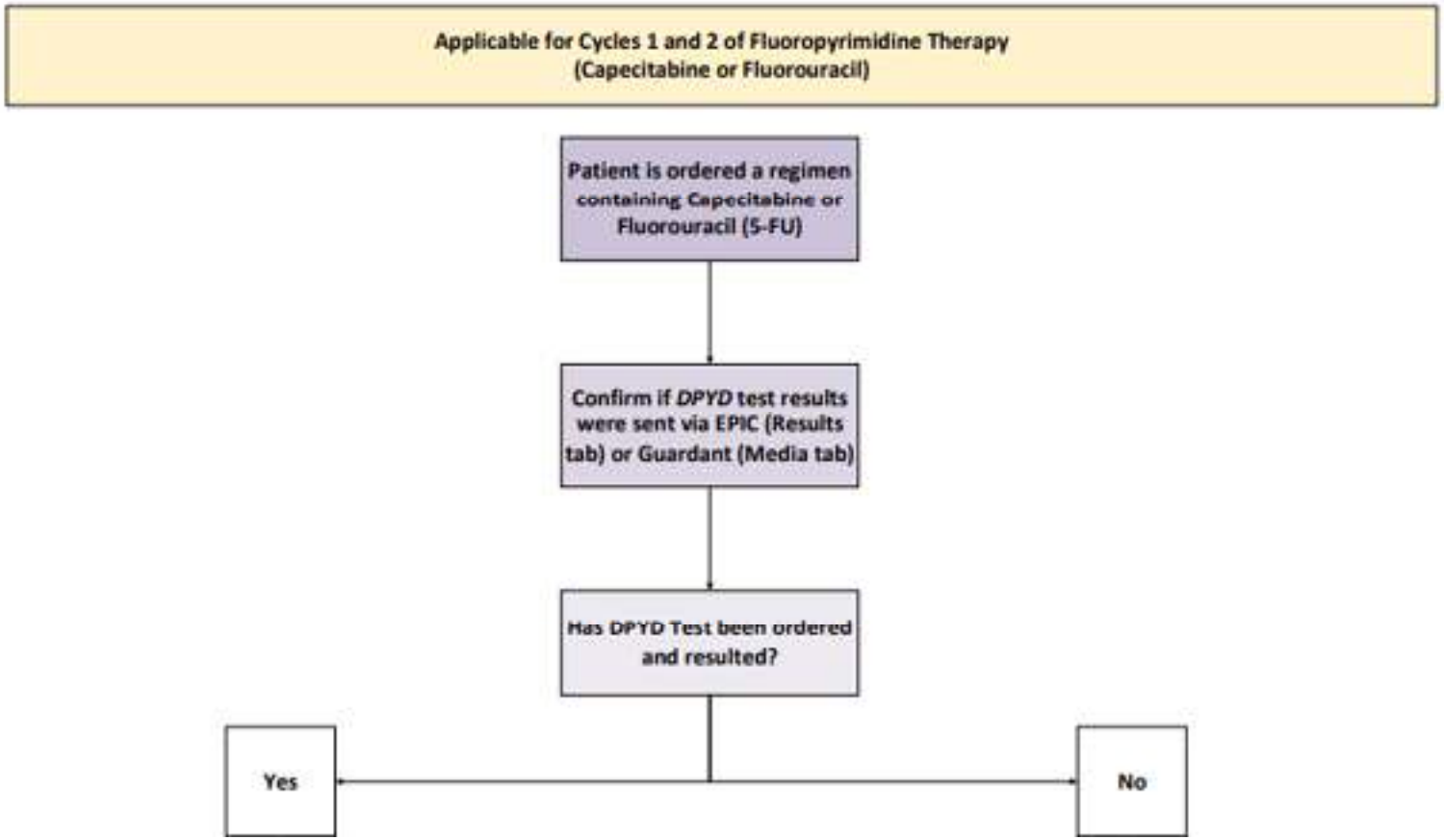
DPYD-Guided Dosing Recommendations

DPYD result	DPYD Phenotype	Activity Score	Dosing Recommendations
*1/*1	**Normal Metabolizer**	2.0	Standard dosing†
*1/c.2846A>T	**Intermediate metabolizer**	1.5	**Reduce starting dose by 50%**, followed by titration of dose based on toxicity (typically increase by 5% - 15%) in cycle 2 or 3. Some may be escalated to full dose if well-tolerated.
*1/*2A *1/*13 c.2846A>T/c.2846A>T	**Intermediate metabolizer**	1.0	**Reduce starting dose by 50%**, followed by titration of dose based on toxicity. Some may need further dose reductions due to adverse events.
c.2846A>T/*2A c.2846A>T/*13	**Poor Metabolizer**	0.5	**Avoid fluoropyrimidines.** If alternative agents are not an option, administer a strongly reduced dose (i.e., < 25% of normal starting dose), followed by titration of dose based on toxicity.
*2A/*2A *2A/*13 *13/*13	**Poor Metabolizer**	0	**Avoid fluoropyrimidines.** Use alternative agents.

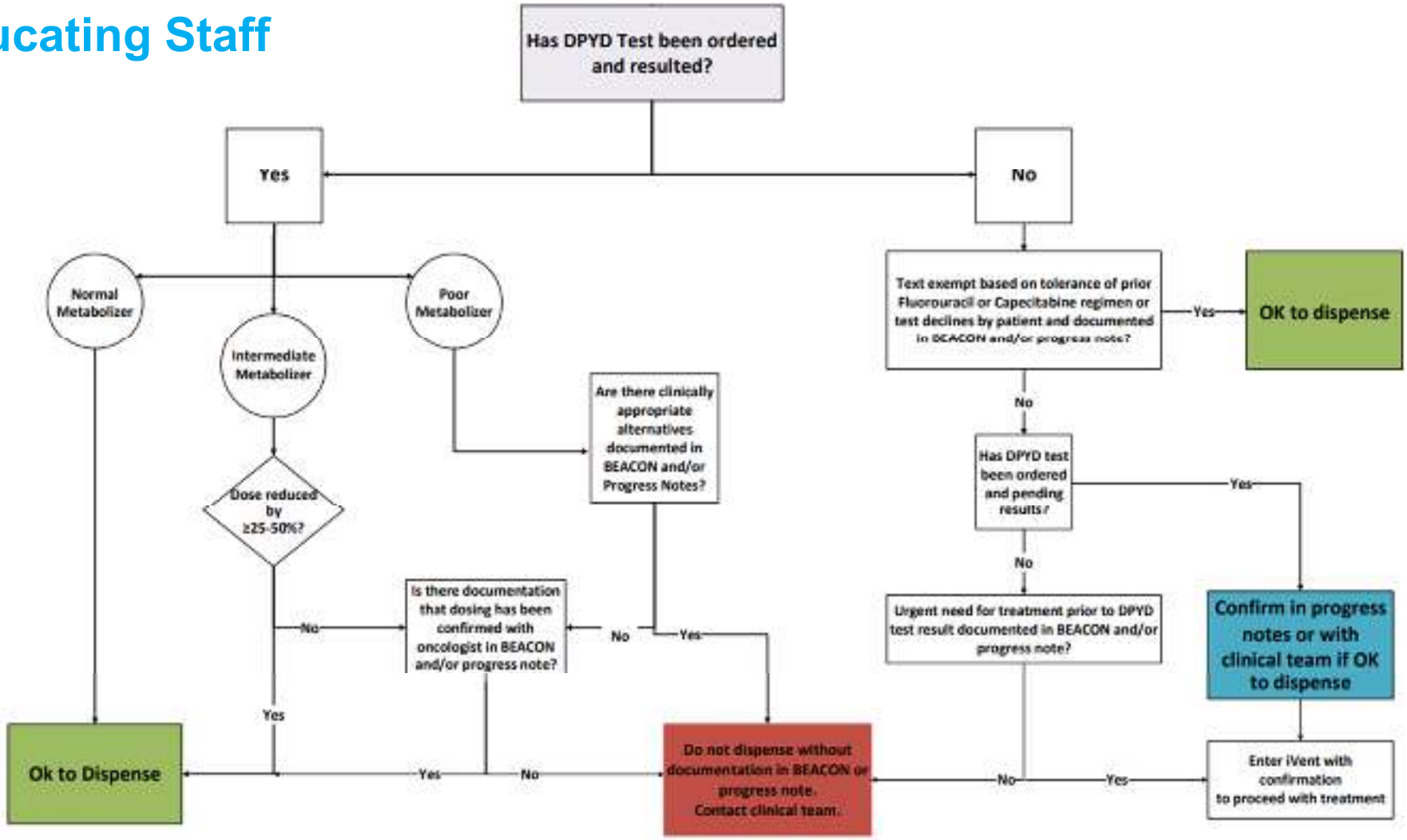
Decreased function alleles include c.1236G>A (tagging DPYD-HapB3), c.2846A>T (p.D949V). No function alleles include DPYD*2A (c.1905+1G>A), DPYD*13 (c.1679T>G). Refer to Clinical Pharmacogenetics Implementation Consortium (CPIC) for comprehensive list of alternative nomenclatures.

†For older, frail patients or those with multi-organ dysfunction, consider initiating fluoropyrimidines at a reduced dose.

Educating Staff



Educating Staff



Informing Patients

WHAT IS PHARMACOGENOMICS?

Pharmacogenomics (PGx) is the study of how your genes affect the way your body responds to medication.

Everyone's DNA is slightly different. These small differences can affect:

- How quickly your body breaks down a drug
- How well the drug works
- Whether you experience side effects

By testing certain genes before treatment, your doctor can choose the right medication and dose for you.

WHAT IS DPYD?

The DPYD gene helps your body break down chemotherapy drugs called fluoropyrimidines, such as:

- 5-fluorouracil (5-FU)
- Capecitabine (Xeloda)

If you have certain DPYD gene changes, your body may not clear these drugs well, leading to

- Severe diarrhea
- Mouth sores
- Infection risk
- Low white blood cell count

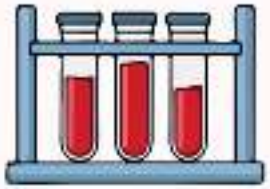
The DPYD testing can identify these variants before you start treatment so the doctor can adjust the dose or select another drug to keep you safe.

WHY GET TESTED?

Testing helps to:

- Prevent severe side effects
- Improve quality of life during cancer therapy

Testing only needs a blood sample.



Testing helps your care team find the right treatment balance, strong enough to work but gentle enough to be safe for you.

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DPYD Testing & Patient Counseling

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We perform a genetic test called DPYD testing before you start chemotherapy with 5-FU or capecitabine. This test checks how your body breaks down the drug. If your body processes it more slowly, the medication can build up and cause severe side effects.

Call your care team immediately if you experience any of the following symptoms:

If any of these occur after hours, go to the emergency department and call the on-call oncology provider.

Conclusions

- *DPYD* plays an important role in metabolism of fluoropyrimidines to inactive metabolites
- Pharmacogenomic guided *DPYD* dose adjustments result in reduced adverse events and no difference in outcomes
- ISMP methods to implement *DPYD* testing have been practical and successful at a large academic medical center


Questions?
Thank you!
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