COLLEGE OF PHARMACY UNIVERSITY OF MICHIGAN

FDA Denial of Petition to Recommend FP Dose Adjustment in *DPYD* Carriers

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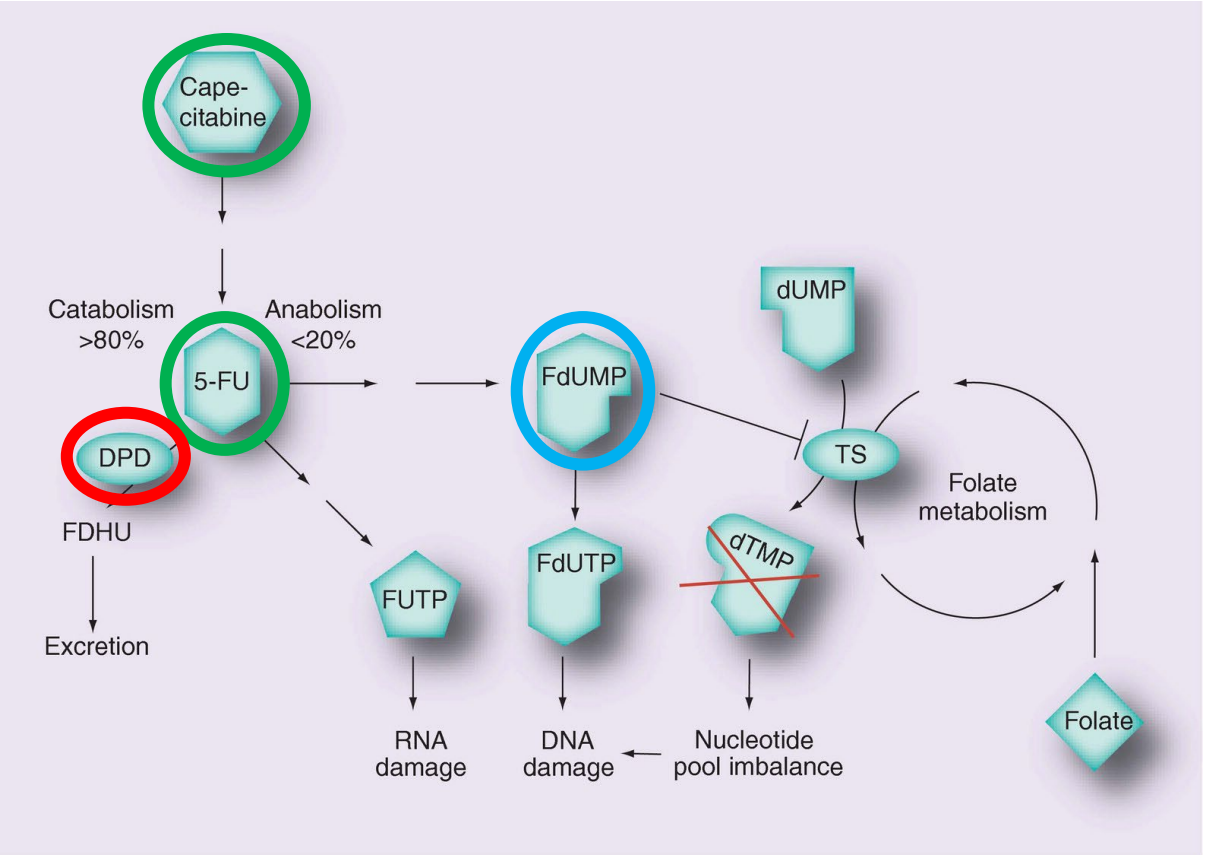
CPIC Monthly Meeting

ROGEL CANCER CENTER
MICHIGAN MEDICINE

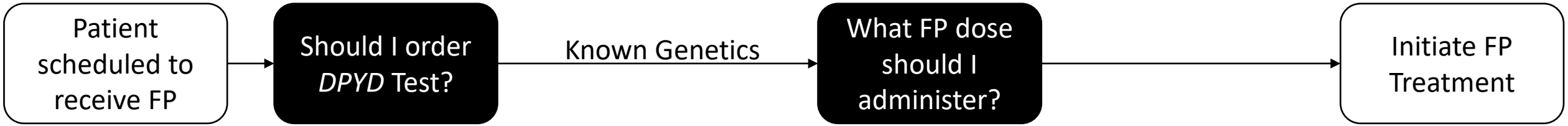
Fluoropyrimidines (FP) & DPD/*DPYD*

- IV 5-fluorouracil (5-FU) and oral prodrug capecitabine (Xeloda)
  - Breast, colorectal, pancreatic, esophageal, head and neck cancers
  - Toxicities: neutropenia, GI, mucositis, and hand-foot syndrome

- Fluoropyrimidine pharmacology
  - 5-FU bioactivated to FdUMP for efficacy
  - 5-FU exposure determines toxicity
  - 5-FU metabolized by dihydropyrimidine dehydrogenase (DPD/*DPYD*)
    - ~80% of dose metabolized by DPD



Amstutz U. Pharmacogenomics. 2011



Decision	Ordering Test
Guidelines	ESMO: Test DPWG: Test NCCN: Don't test ASCO: No comment

FP Dosing in *DPYD* Carriers

CPIC Guidelines for *DPYD* Genotype and FP Dosing

***DPD* Phenotype**	***DPYD* Diplotype**	**DPD Activity**	**Dosing Recommendation**
Normal metabolizer (AS=2)	Two normal alleles	Normal	Use label recommended dosage and administration.
Intermediate metabolizer (AS 0.5-1.5)	One normal and one reduced function allele	Decreased	Reduce starting dose by **~50%** followed by titration based on tolerability
Poor Metabolizer (AS=0)	Two no function alleles	None	Avoid use or reduce starting dose by ~90% followed by titration based on tolerability

https://cpicpgx.org/guidelines/guideline-for-fluoropyrimidines-and-dpyd/

Adapted from Amstutz et al. Clin Pharm Ther 2017

Full Text from FDA Response Regarding Dosing

- Whereas the scientific rationale for the recommendation to avoid fluoropyrimidines in patients with complete DPD deficiency is clear, **the available data about the use of these drugs in patients with partial DPD deficiency are less definitive**.
- As you note in the Petition, there is information in the published literature about the use of modified initial dosages of fluoropyrimidines in patients with known partial DPD deficiency (Petition at 5), and **certain international organizations** and health authorities **have authored** or endorsed **guidelines** on the subject (Petition at 3-4). In general, the types of **evidence used to support recommendations** made in journal articles and treatment guidelines are different from, and **can be less rigorous than**, the evidence used to support regulatory decision-making, including the text of **FDA-approved labeling**.
- FDA has not received or reviewed **data from well-controlled randomized clinical trials**, should they exist, that prospectively **evaluate whether the clinical efficacy outcomes** of cancer treatment in patients receiving reduced initial fluoropyrimidine doses because of partial DPD activity are no worse than (**non-inferior to**) outcomes in patients receiving standard doses. **Currently available information** reviewed by FDA on specific initial dosage regimens claimed to be both safe and effective in patients with partial DPD deficiency **are insufficient** to support the inclusion of such recommendations in labeling.

Summary of FDA Statements

1. Data about the use of standard-dose FP in patients with partial DPD deficiency (i.e., *DPYD* variant carriers, AS 0.5-1.5) are unclear

2. Rigorous data is required for FDA to recommend specific doses or dose adjustments

3. "Rigorous data" means prospective RCTs demonstrating that the specific doses/adjustments lead to non-inferior (or superior) clinical outcomes

1. Standard Dosing Unsafe for *DPYD* Carriers

- Chemotherapy dosed at "maximum tolerated dose (MTD)"
  - Highest dose with <33% risk of severe toxicity

- Patients with partial DPD deficiency have unacceptable toxicity
  - N0147: n=2,886 stage III colon cancer, standard-dose 5-FU regimens[1]
    - Severe 5-FU toxicity (wild-type patients: 33%)
    - *DPYD*1/*2A*: **88%** (22/25), *DPYD *1/p.D949V*: **82%** (24/27)
  - Meta-analysis of fatal toxicity (n=13,929)[2]
    - **2.3%** fatal toxicity (13/566), individual *DPYD* allele risk estimates: 0.4%-5.9%

1: Lee AM. J Natl Cancer Inst 2014
2: Sharma BB. Oncologist. 2021

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2. FDA Doses do not Require Rigorous Data

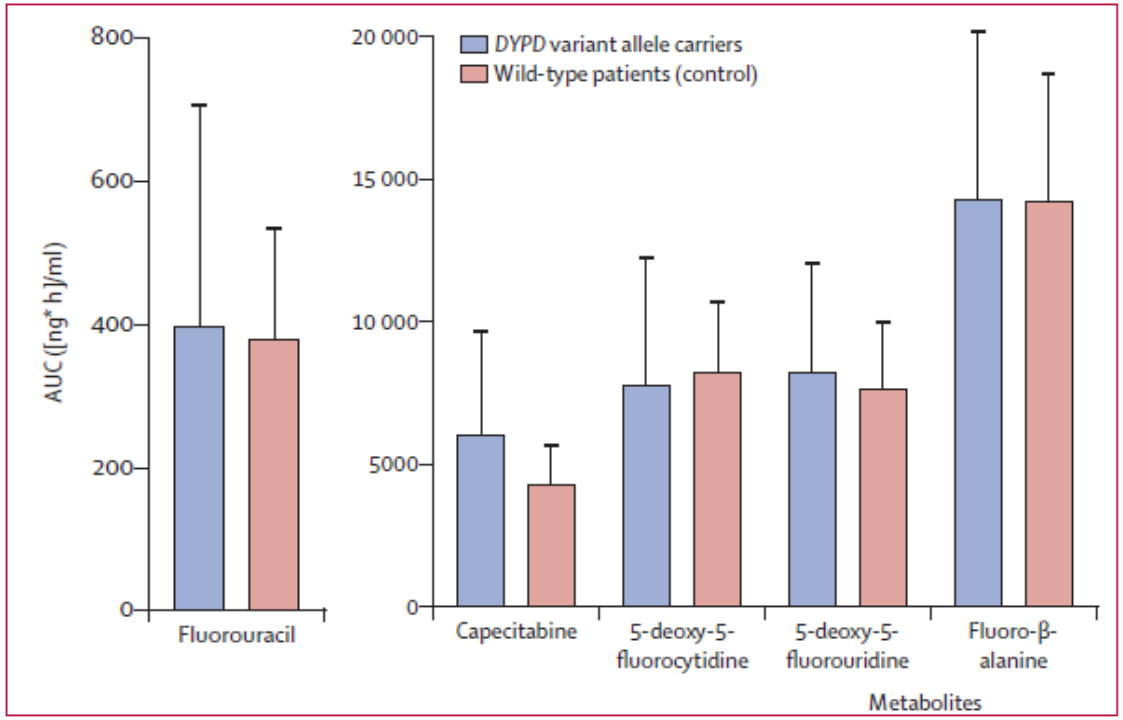
- FDA labels recommend dose adjustment for renal/hepatic impairment based on equivalent systemic exposure
  - 25% reduction in capecitabine dose in patients with moderate renal impairment
- FDA labels recommend genetics-guided doses for many drugs based on equivalent systemic exposure
  - e.g., aripiprazole, atomoxetine, belinostat, brexpiprazole, irinotecan, siponimod…
- FDA approves generic drugs based on bioequivalent systemic exposure
  - >30 FDA-approved generics of 5-FU or capecitabine
- FDA **“reduced”** approved ceritinib (cancer drug) dose from 750 QD fasted to 450 QD w/food based on equivalent exposure and reduced toxicity

FP Dose Adjustment Normalizes Exposure

- Prospective clinical trials demonstrate equivalent systemic exposure in *DPYD* carriers receiving reduced doses vs. wild-type patients receiving standard doses

DPYD Genotype	n	AS	Dose Reduction	Relative 5-FU AUC*
*1/*2A	14	1.5	40%-71%	**85%-115%**
*1/variant	26	1.0-1.5	25%-50%	**104%**

*Reduced dosing in *DPYD* variant carrier vs. standard dosing in *DPYD* wild-type patients
Deenen MJ. J Clin Oncol. 2016 Jan 20;34(3):227-34
Henricks LM. Lancet Oncol. 2018 Nov;19(11):1459-1467



Henricks LM. Lancet Oncol. 2018 Nov;19(11):1459-1467.

FP Dose Adjustment Normalizes Toxicity, Achieves MTD

- Prospective trials demonstrate equivalent toxicity in *DPYD* carriers receiving reduced doses vs. wild-type patients receiving standard doses
  - Dose reduction in *DPYD* carriers approximates MTD (~33% toxicity risk)

Study	DPYD Genotype	n	Activity Score	Dose Reduction	Toxicity Rate
Deenen	*1/*1	1,613	2.0	100%	**23%**
	*1/*2A	18	1.5	40%-71%	**28%**
Henricks	*1/*1	1,018	2.0	100%	**23%**
	*1/variant	85	1.0-1.5	25%-50%	**39%**

- Recommended dose re-escalation tolerated by ~50% of patients (12/23)

Henricks LM. Lancet Oncol. 2018 Nov;19(11):1459-1467, Deenen MJ. J Clin Oncol. 2016 Jan 20;34(3):227-34
Stavraka C. Breast Cancer Res Treat 2019 Jun;175(2):511-517, Lunenburg CA Pharmacogenomics 2016 May;17:721-9

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Data Required for FDA Dose Recommendations

- Pacanowski M, Schuck RN. Evidence, in Context: A Regulatory Perspective on Pharmacogenetics. CPT 2022
  - "When deviations from the population average are concerning, the FDA will offer treatment recommendations such as alternative dosages; **the principles of exposure matching are often applied** as would be done with any other intrinsic factor."

- FDA policy that genetics-guided dose recommendations require **prospective RCTs** with **similar clinical outcomes** would be a **MAJOR SETBACK** for CPIC and PGx.

What should we (CPIC) do?

- Would CPIC (leadership and/or members) be interested in contributing to a statement that FDA should:
  - Accept that genotype-guided dosing recommendations should be based on equivalent systemic exposure, not clinical outcomes
  - Ensure that reviews of PGx data include FDA's experts in PGx and clinical pharmacology and follow their published statements

Time for Questions and Discussion

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AUDT

https://test4dpd.org/