Should Pharmacogenomics in Colon Cancer be for everyone or not?

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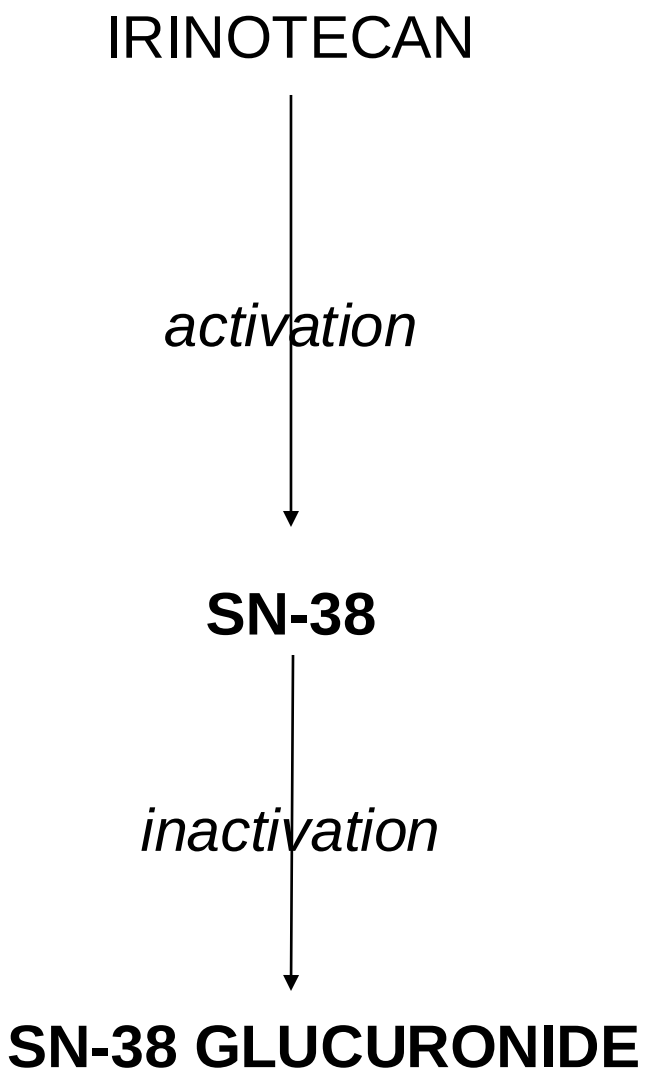
USC Norris Comprehensive Cancer Center

Agenda

- UGT1A
- DPD

Irinotecan and UGT1A1

- Irinotecan
  - IV backbone chemotherapy of several regimens for solid tumors
- Unpredictable severe toxicity in 25-30% of patients
- Prodrug – activated to SN-38, inactivated by glucuronidation
- High PK variability



From basic genetics to a clinical trial and label change

Gilbert's syndrome and UGT1A1*28

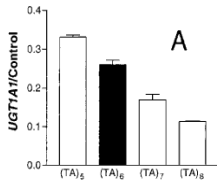
1995

Bosma

UGT1A1*28 molecular effect

1998

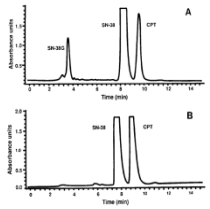
Beutler



UGT1A1: metabolic gene of irinotecan

1998

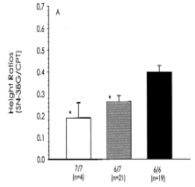
Iyer



UGT1A1*28 and irinotecan metabolism

1999

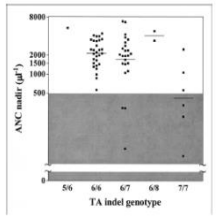
Iyer



UGT1A1*28 and clinical validation

1998-2004

Innocenti



FDA revised drug label

2005

FDA Label Information of Camptosar

For complete labelling information, please visit https://www.fda.gov/drugsatfda

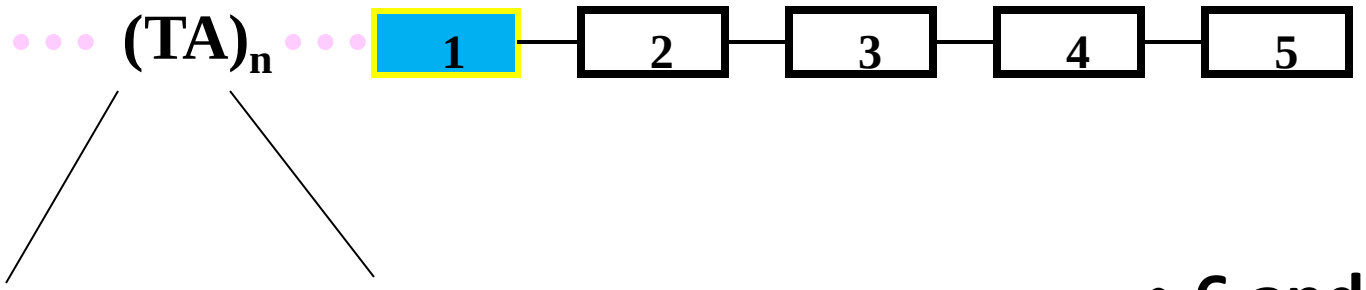
population is homozygous for the UGT1A1*28 allele. In a prospective study in which irinotecan was administered as a single-agent on a once-every-3-week schedule, patients

Patients with Reduced UGT1A1 Activity

Individuals who are homozygous for the UGT1A1*28 allele are at increased risk for neutropenia following initiation of CAMPTOSAR treatment. A reduced initial dose should be considered for patients known to be homozygous for the UGT1A1*28 allele (see DOSAGE AND ADMINISTRATION). Heterozygous patients (carriers of one variant allele and one wild-type allele which results in intermediate UGT1A1 activity) may be at increased risk for neutropenia; however, clinical results have been variable and such patients have been shown to tolerate normal starting doses.

A reduction in the starting dose by at least one level of CAMPTOSAR should be considered for patients known to be homozygous for the UGT1A1*28 allele (See CLINICAL PHARMACOLOGY and WARNINGS). The appropriate dose reduction in this patient population is not known.

Common *UGT1A1* polymorphism



TATATATATA=$(TA)_5$

TATATATATATA=$(TA)_6$ = *1

TATATATATATATATA=$(TA)_7$=*28

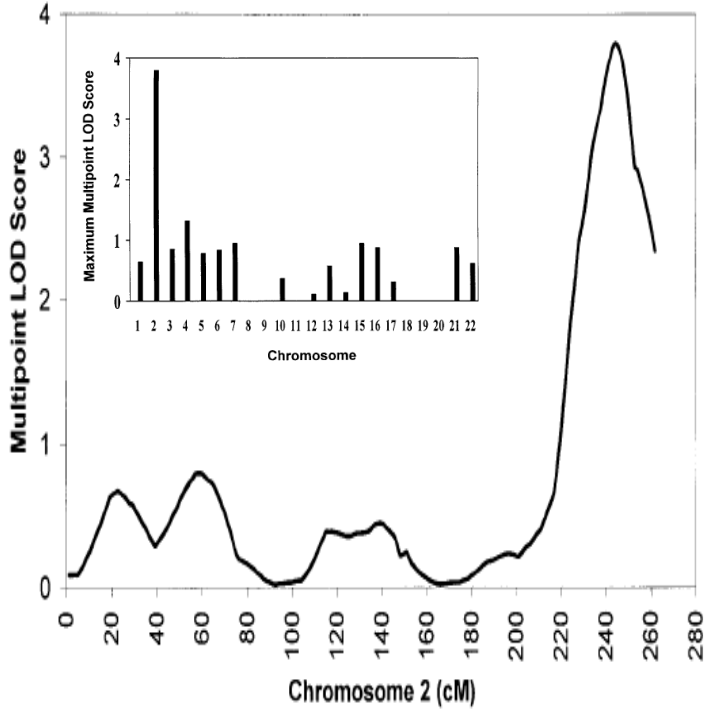
TATATATATATATATATA=$(TA)_8$

- **<u>6 and 7 are the common alleles</u>**
- **5 and 8 are rare**

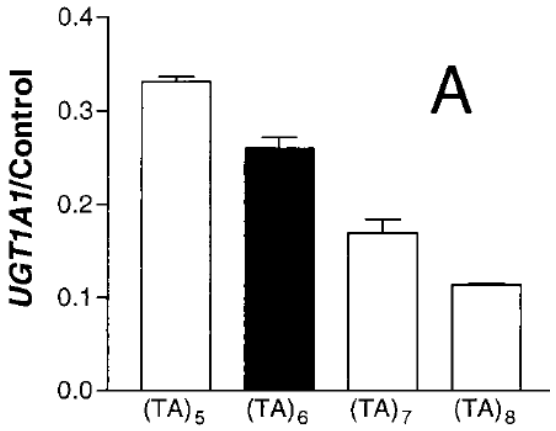
UGT1A1 defects and hyperibilirubinemia syndromes

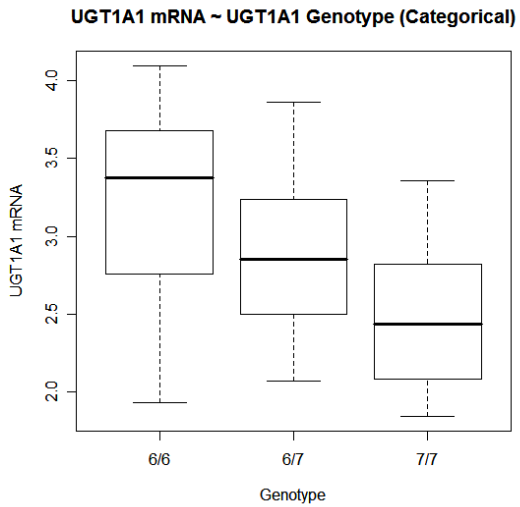
Bilirubin is mainly eliminated by conversion to its glucuronides by UGT1A1

- **Gilbert's syndrome**
  - **2-19%**
  - **Mild hyperbilirubinemia**
  - **Asympthomatic**
  - **In Caucasians**
    - **7/7 genotype (10%)**



UGT1A1: in vitro phenotypes





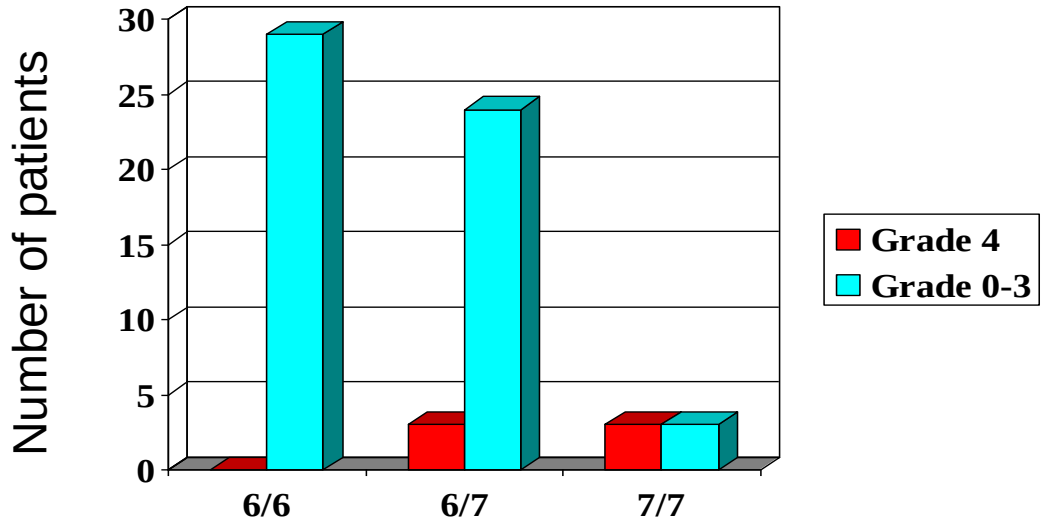
*UGT1A1*28* and severe neutropenia of irinotecan

Genetic Variants in the *UDP-glucuronosyltransferase 1A1* Gene Predict the Risk of Severe Neutropenia of Irinotecan

Federico Innocenti, Samir D. Undevia, Lalitha Iyer, Pei Xian Chen, Soma Das, Masha Kocherginsky, Theodore Karrison, Linda Janisch, Jacqueline Ramírez, Charles M. Rudin, Everett E. Vokes, and Mark J. Ratain

VOLUME 22 · NUMBER 8 · APRIL 15 2004

JOURNAL OF CLINICAL ONCOLOGY



p=0.001

Risk level: Low Medium High

Severe Neutropenia: Translating Associations into a Predictive Test

Assumption: Genotyping assay is 100% accurate for detection of UGT1A1*28 allele

	Clinical Sensitivity	Clinical Specificity	PPV*	NPV*
Innocenti	0.5	0.94	0.5	0.94
Rouits	0.29	0.95	0.57	0.85
Marcuello	0.18	0.92	0.4	0.79
Ando	0.15	0.97	0.57	0.8
Overall	0.22	0.95	0.5	0.83

* PPV, positive predictive value; NPV, negative predictive value.

How to improve the predictive value of the *UGT1A1*28* diagnostic test?

Bilirubin X genotype

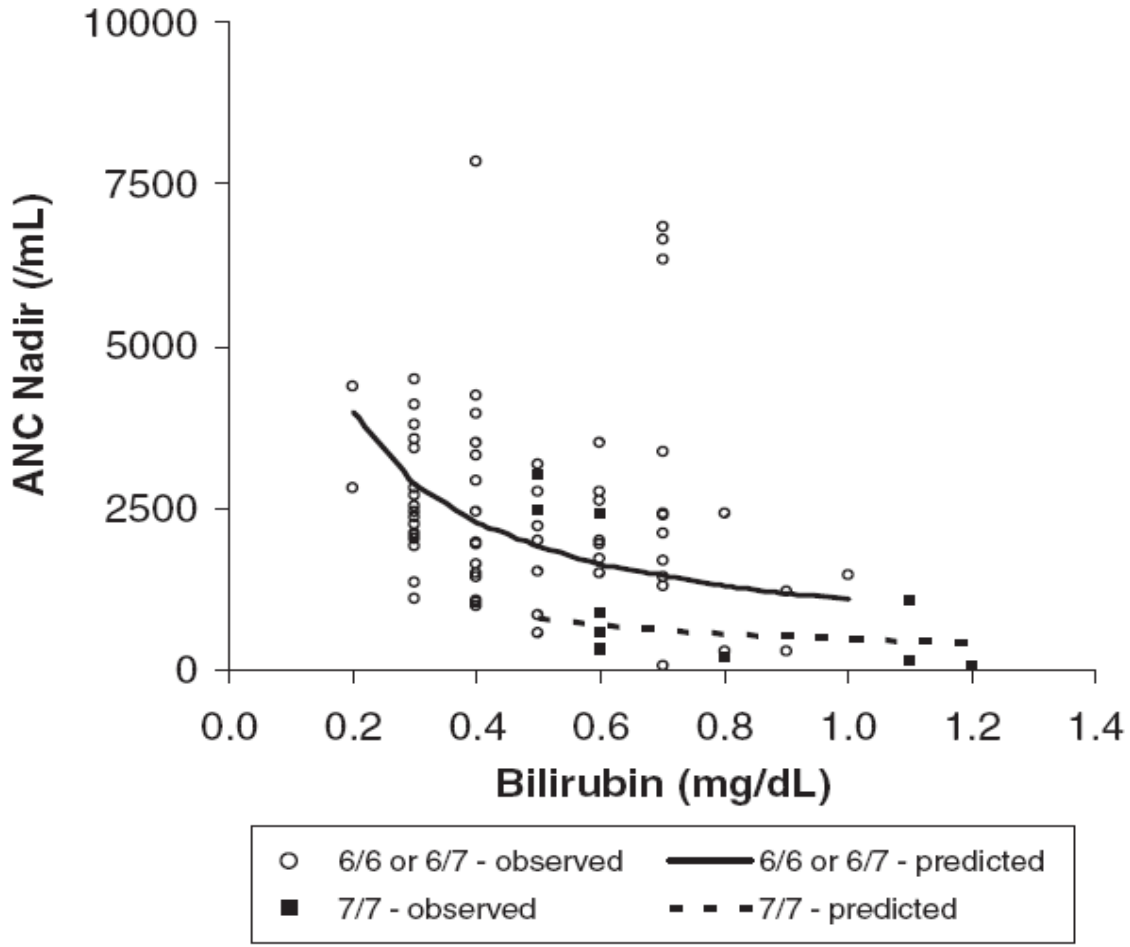
Gene X genotype

Ethnicity X genotype

Drug regimen X genotype

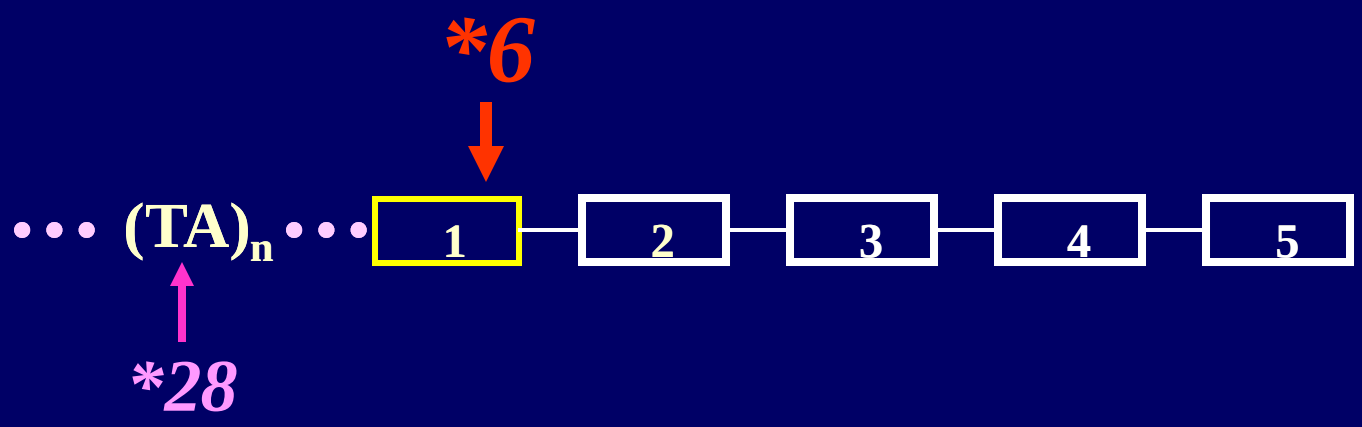
Dose X genotype

Bilirubin, *UGT1A1*28*, or both?



Gilbert's syndrome

- In Asians
  - 7/7 genotype
  - *6 (G71R, reduced enzyme activity)



*UGT1A1*6* in Asians and toxicity (Han et al., 2006)

		G4 neutropenia
*28		
	-/-	26%
	-/+	33%
*6		
	-/-, -/+	24%
	+/+	67%

p=0.03 for *6

Can genotype be used to optimize dosing?

Standard dosage is well tolerated in 6/6 and 6/7 patients and they might tolerate higher doses

Higher doses (up to 500 mg/m^2) were safe in selected patients in European trials

UGT1A1 genotype not taken into account during early phase I trials

Testing for DPD

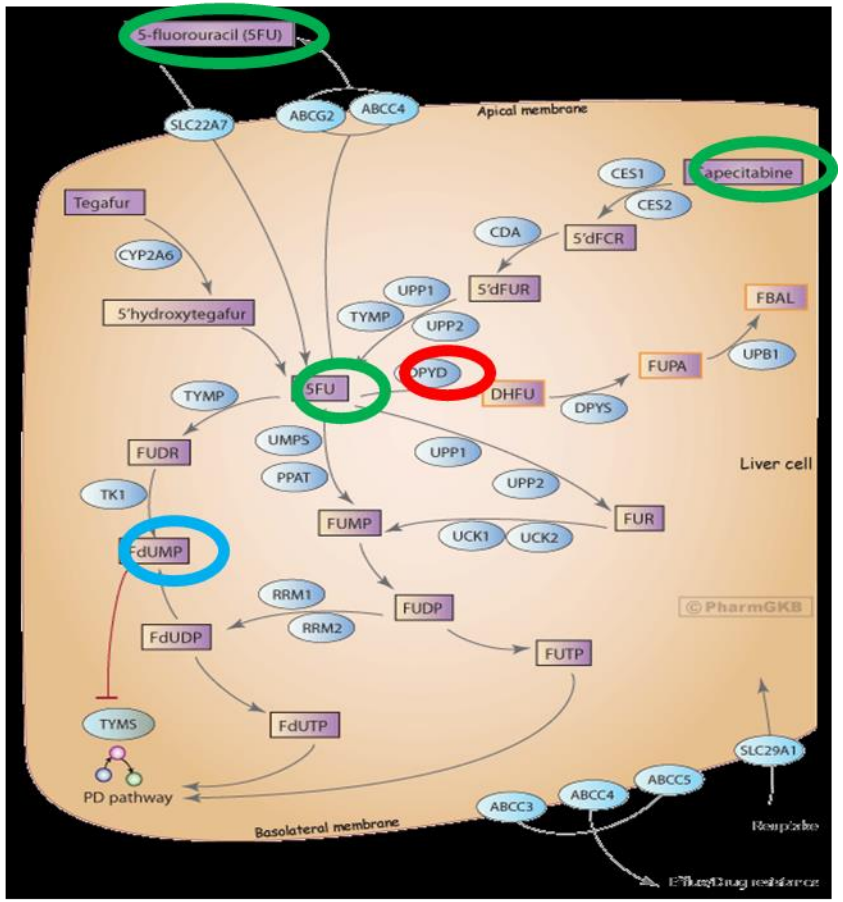
Mandated in EU and UK
Recommended by NCCN

Metabolisms of Fluoropyrimidines

Fluoropyrimidines (FP) & *DPYD*

- IV 5-fluorouracil (5-FU) and oral prodrug capecitabine
  - 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 DPYD



Fluoropyrimidines (FP) & *DPYD*

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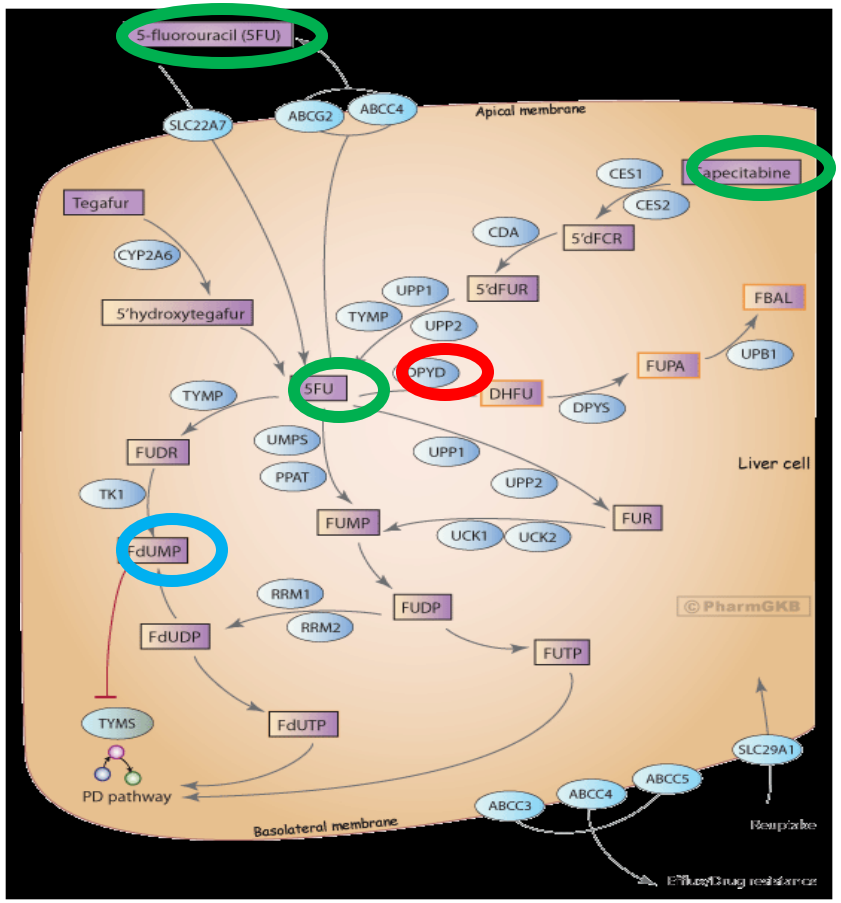
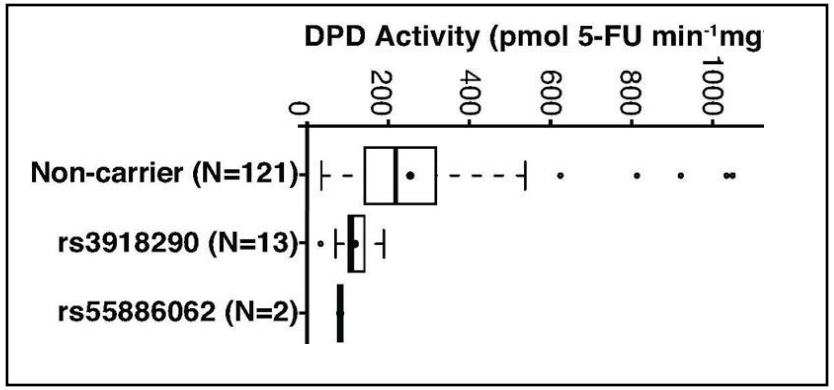


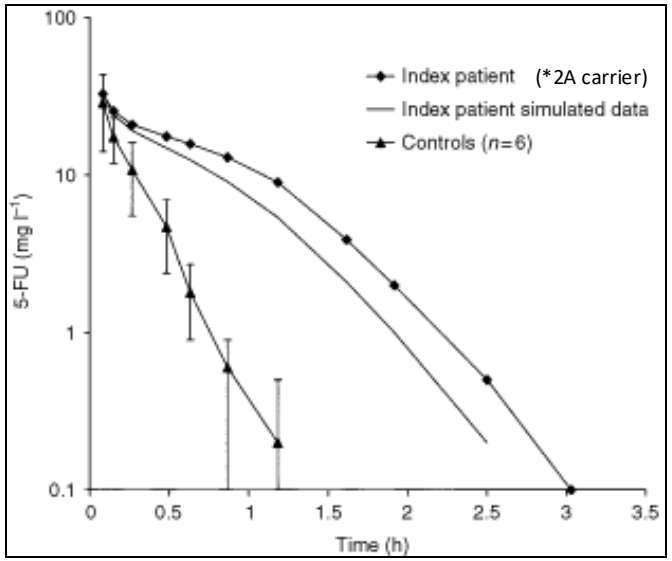
DPYD SNPs with reduced DPD activity

Activity	* Allele	rsID	Aliases	Genetic effect	Allele Freq.
Null	*2A	rs3918290	IVS14+1G>A, c.1905+1G>A	Splice site	0.008
	*13	rs55886062	c.1679T>G, p.I560S	Missense	0.001
Diminished	NA	rs67376798	c.2846A>T, p.D949V	Missense	0.004
	NA	rs56038477 (LD w/rs75017182)	1236G>A, p.E412E (LD w/1129-5923C>G, HapB3)	Nonfunctional transcript	0.020
	NA	rs115232898	c.557A>G, p.Y186C	Missense	0.008 (AA)

Consequences of *DPYD* SNPs



Clin Pharmacol Ther. 2017 Oct;102(4):662-670. Epub 2017 May 26.



Br J Cancer. 2002 Apr 8;86(7):1028-33.

DPYD SNPs with Reduced DPD activity

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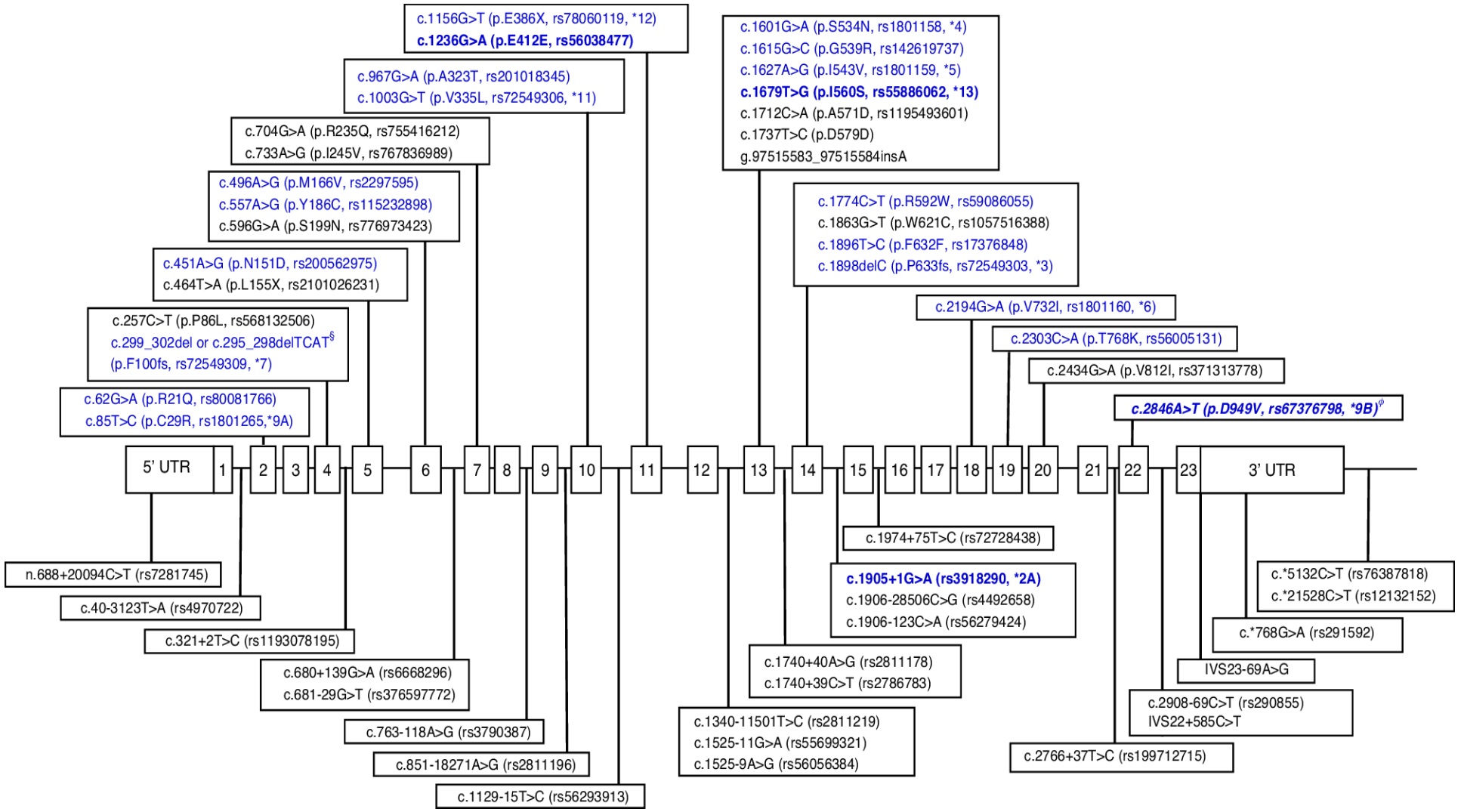
- Combined carrier frequency ~6% (~1/300 patients homozygous)
- Many other rare/singleton diminished activity variants reported

DPYD Variants in no European Patients

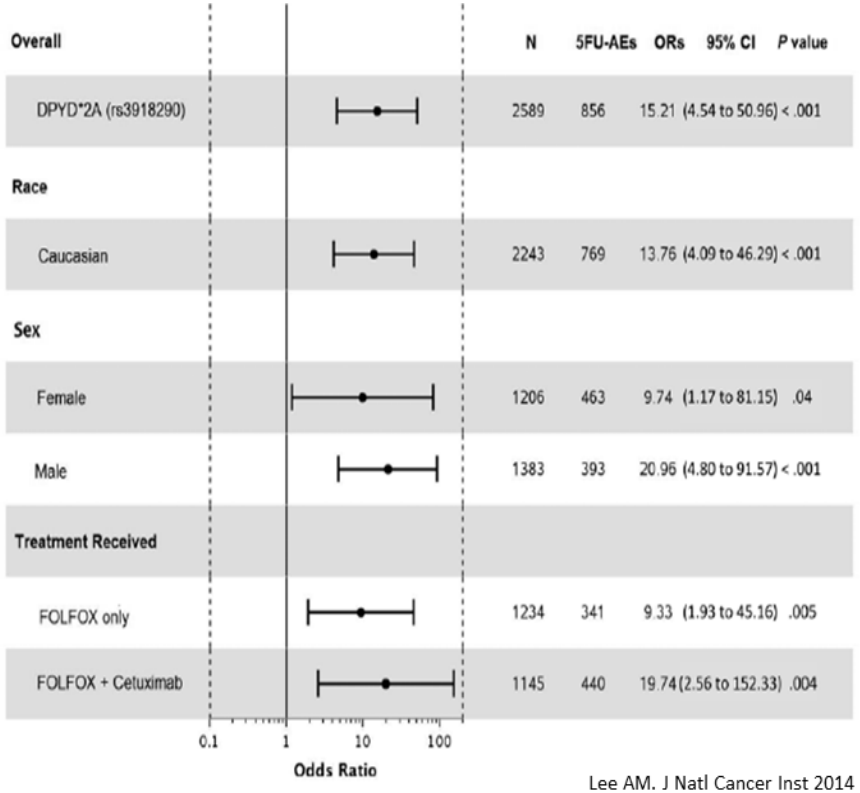


Chan et al Nature 2024

Retrospective Validation of Increased Toxicity

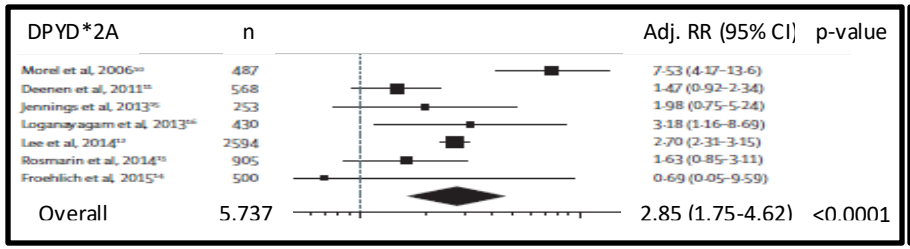
- NCCTG N0147
  - 2886 patients stage III colon cancer
  - Adjuvant FOLFOX or FOLFIRI (5-FU)
- Genotype: *DPYD*2A* and *p.D949V*
- 1° Outcome: grade 3+ 5-FU AE

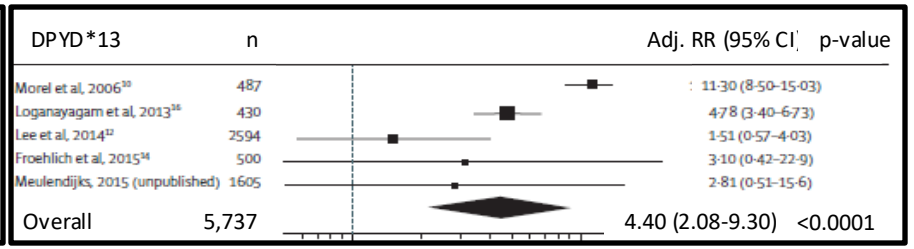
- *DPYD*2A*: 88% vs. 33%
  - OR=15.2, 95% CI: 4.5 to 51.0, p < .001
- *DPYD p.D949V*: 82% vs. 33%
  - OR= 9.1, 95% CI: 3.4 to 24.1, p < .001

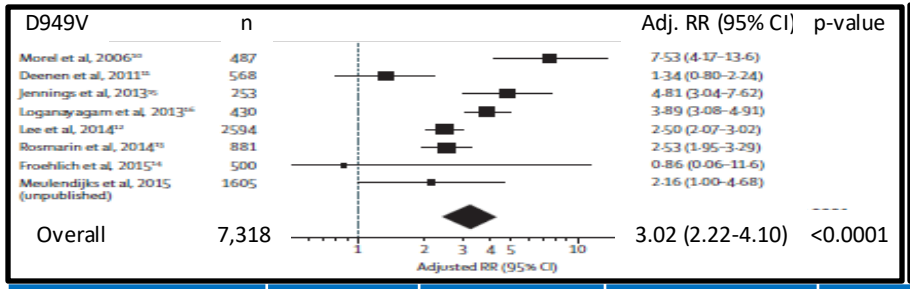


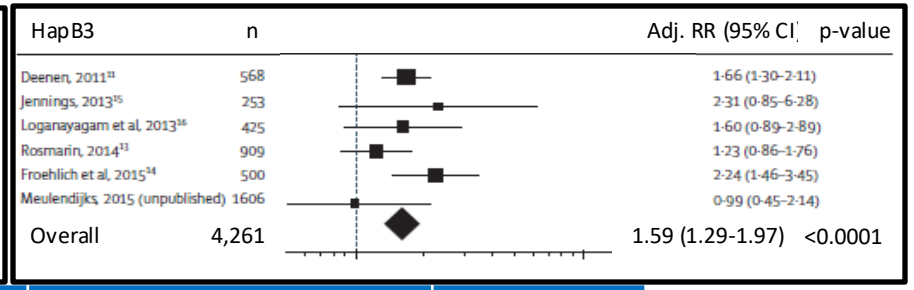
Lee AM. J Natl Cancer Inst 2014

Greater Toxicity in *DPYD* Variant Carriers





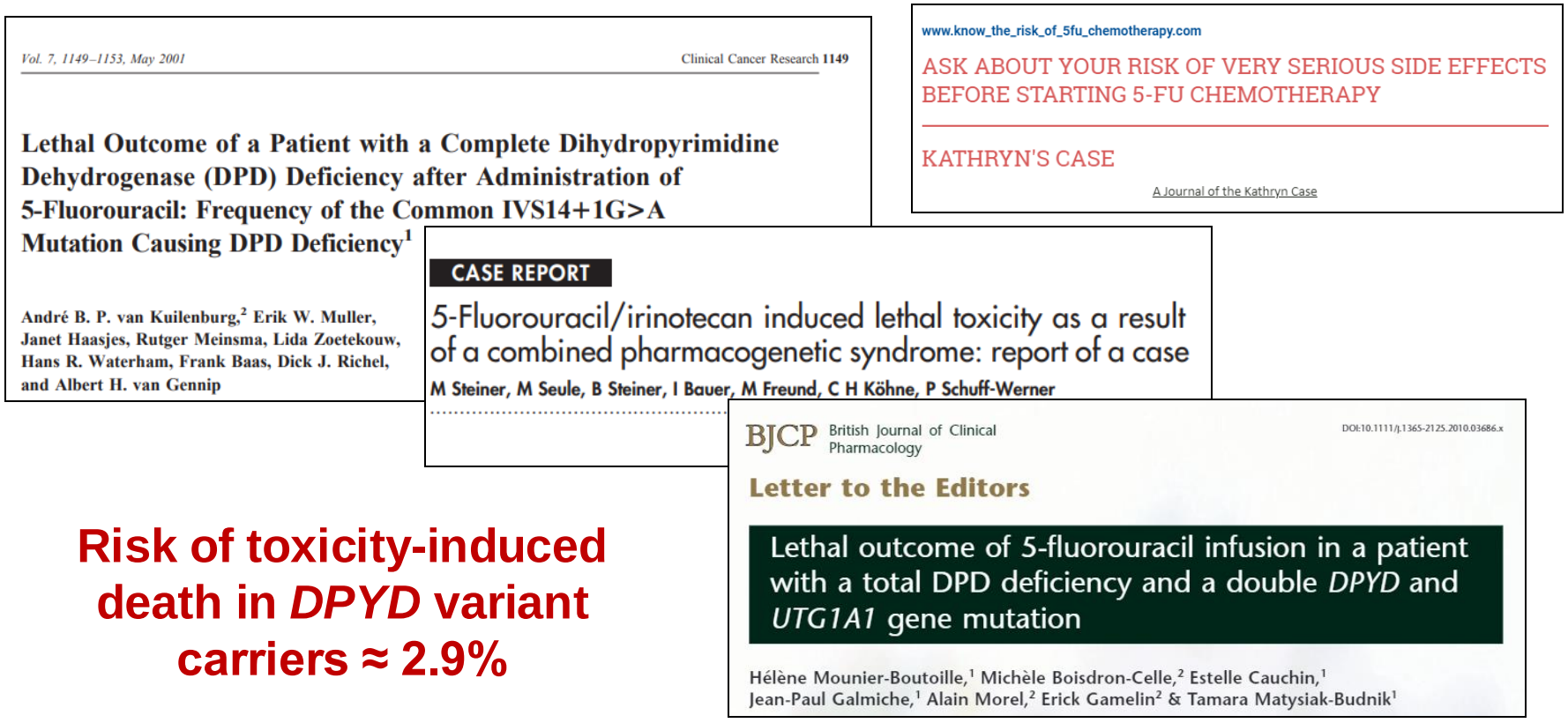




DPYD Activity	SNP	rsID	Allele Freq.	n	Adjusted RR (95% CI)	p-value
Inactive	*2A	rs3918290	0.008	5,737	2.85 (1.75-4.62)	p<0.0001
	*13	rs55886062	0.001	5,616	4.40 (2.08-9.30)	p<0.0001
Diminished	D949V	rs67376798	0.004	7,318	3.02 (2.22-4.10)	p<0.0001
	HapB3	rs56038477	0.020	4,261	1.59 (1.29-1.97)	p<0.0001

Muelendijks D. Lancet Oncol. **2015** Dec;16(16):1639-50.

Fluoropyrimidine Treatment Induced-Death



Vol. 7, 1149–1153, May 2001 Clinical Cancer Research 1149

Lethal Outcome of a Patient with a Complete Dihydropyrimidine Dehydrogenase (DPD) Deficiency after Administration of 5-Fluorouracil: Frequency of the Common IVS14+1G>A Mutation Causing DPD Deficiency[1]

André B. P. van Kuilenburg,[2] Erik W. Muller, Janet Haasjes, Rutger Meinsma, Lida Zoetekouw, Hans R. Waterham, Frank Baas, Dick J. Richel, and Albert H. van Gennip

www.know_the_risk_of_5fu_chemotherapy.com

ASK ABOUT YOUR RISK OF VERY SERIOUS SIDE EFFECTS BEFORE STARTING 5-FU CHEMOTHERAPY

KATHRYN'S CASE

A Journal of the Kathryn Case

CASE REPORT

5-Fluorouracil/irinotecan induced lethal toxicity as a result of a combined pharmacogenetic syndrome: report of a case

M Steiner, M Seule, B Steiner, I Bauer, M Freund, C H Köhne, P Schuff-Werner

BJCP British Journal of Clinical Pharmacology

DOI:10.1111/j.1365-2125.2010.03686.x

Letter to the Editors

Lethal outcome of 5-fluorouracil infusion in a patient with a total DPD deficiency and a double *DPYD* and *UTG1A1* gene mutation

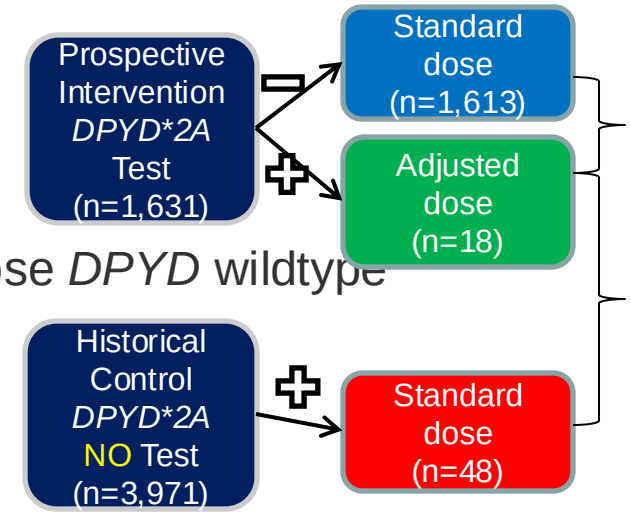
Hélène Mounier-Boutoille,[1] Michèle Boisdron-Celle,[2] Estelle Cauchin,[1] Jean-Paul Galmiche,[1] Alain Morel,[2] Erick Gamelin[2] & Tamara Matysiak-Budnik[1]

Risk of toxicity-induced death in *DPYD* variant carriers ≈ 2.9%

Rai K. J Clin Oncol (suppl; abstr e15132)

Prospective Single-Arm Trial (NCT02324452)

- Dose-adjusted *DYPD*2A* vs. standard-dose *DPYD*2A* (historical control)
  - Reduced grade 3+ toxicity
    - 28% (5/18) vs. 73% (35/48), p<0.001
  - Nominally reduced toxicity-related death
    - 0% (0/18) vs. 10% (5/48), p=0.19
- Dose-adjusted *DYPD*2A* vs. standard-dose *DPYD* wildtype
  - Similar grade 3+ toxicity
    - 28% (5/18) vs. 23% (373/1,613), p=0.64
  - Similar drug concentrations
- *DPYD* screening saves $61 per patient



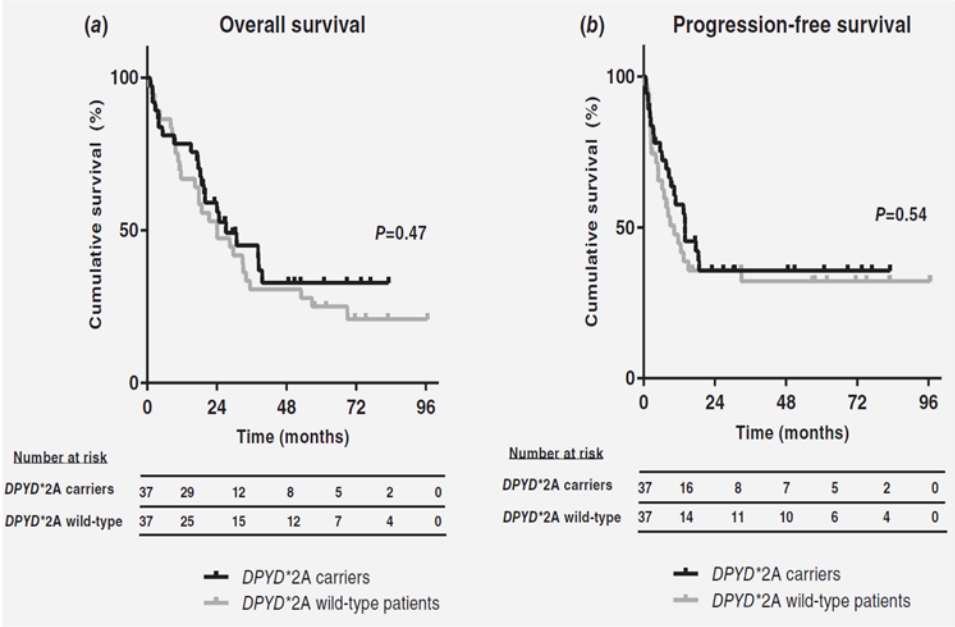
Deenen MJ. J Clin Oncol. 2016 Jan 20;34(3):227-34.

Dose-Adjustment Efficacy Study

- Paired analysis (n=37 pairs)
  - *DPYD*2A* dose-adjusted FP

  vs.
  - *DPYD* wild-type standard dose FP
  - Matched by tumor type, stage
    - Near match: institution, sex, age, treatment line, WHO status

- OS: 27 vs. 24 months
  - HR=0.82, 95% CI: 0.47-1.43, p=0.47
- PFS: 14 vs. 10 months
  - HR=0.83, 95% CI: 0.47-1.50, p=0.54



Henricks LM. Int. J. Cancer 2019: 144, 2347–2354

Dosing in *DPYD* Carriers

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing: 2017 Update

Ursula Amstutz[1], Linda M. Henricks[2], Steven M. Offer[3], Julia Barbarino[4], Jan H.M. Schellens[2,5], Jesse J. Swen[6], Teri E. Klein[4], Howard L. McLeod[7], Kelly E. Caudle[8], Robert B. Diasio[3,9] and Matthias Schwab[10,11,12]

DPYD Phenotype	*DPYD* Genotype	DPD Activity	Dosing Recommendation
Normal metabolizer	Two normal alleles	Normal DPD activity	Use label recommended dosage and administration.
Intermediate metabolizer	One normal and one no function allele	Decreased DPD activity	Reduce starting dose by ~50% followed by titration based on toxicity
Poor metabolizer	Two no function alleles	DPD deficiency	Avoid use or reduce starting dose by ~90% followed by titration based on toxicity

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

Amended from Amstutz et al. Clin Pharm Ther 2017

- Testing recommended throughout Europe
  - Required in France and Netherlands
  - Recently recommended in most of Europe
    - 3/2020: Europeans Medicine Agency
    - 10/2020: United Kingdom
    - 11/2020: Germany and Switzerland
- Testing not recommended in US
  - Not recommended by FDA, ASCO, or NCCN
  - Testing uncommon, though frequency unknown

https://smw.ch/article/doi/smw.2020.20375
https://www.gov.uk/drug-safety-update/5-fluorouracil-intravenous-capecitabine-tegafur-dpd-testing-recommended-before-initiation-to-identify-patients-at-increased-risk-of-severe-and-fatal-toxicity
https://www.ema.europa.eu/en/medicines/human/referrals/fluorouracil-fluorouracil-related-substances-capecitabine-tegafur-flucytosine-containing-medicinal

UM *DPYD* Survey Conclusions

- General agreement that:
  - DPD deficient patients have increased toxicity risk
  - *DPYD*/DPD testing decreases toxicity
  - *DPYD* information is actionable if it exists

- *DPYD*/DPD testing is rarely ordered due to:
  - Lack of clinical guidelines
  - Low prevalence of DPD deficiency
  - Some concern with decreased efficacy with FP dose reduction

- Survey approved for SWOG distribution

Uridine Triacetate
Antidot for FP Toxicity

Uridine triacetate (FDA approval 2015) antidote for FP toxicity
FDA approved dosing is 1 (10 gm) packet Q6H x 20
Cost to Rogel (provided by UM purchasing)
4,013/packet = $80,260 per course of treatment
Each use of UT ($80,260) would pay for 133 Mayo DPYD tests ($600)
Identify ~8 DPYD carriers → prevent ~4 severe toxicities and ~0.25 deaths

Predictive Test Performance

	DPYD	Notes	BRCA 1/2	Notes
Carrier frequency	~6%	Caucasians	>5%	NCCN threshold
Positive Predictive Value (PPV)	~70%	Severe toxicity in carrier	~50%	BC by age 70 in carrier
False Positive Risk	~30%	(unnecessary treatment change)	~50%	
NPV	~75%		~90%	
False Negative Risk	~25%	Toxicity in non-carrier (from standard of care tx)	~10%	BC by age 70 in non-carrier

Summary

- Consider *UGT1A1* and *DPYP* can reduce life threatening toxicity in carriers
- *UGT1A* is in the label
- *DYPD* mandatory in EU/UK
- Easy blood test (cheap,quick)
- Major Concerns:
  - Lack of clinical guidelines
  - Low prevalence