



Pharmacogenetics in Oncology

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Disclosures

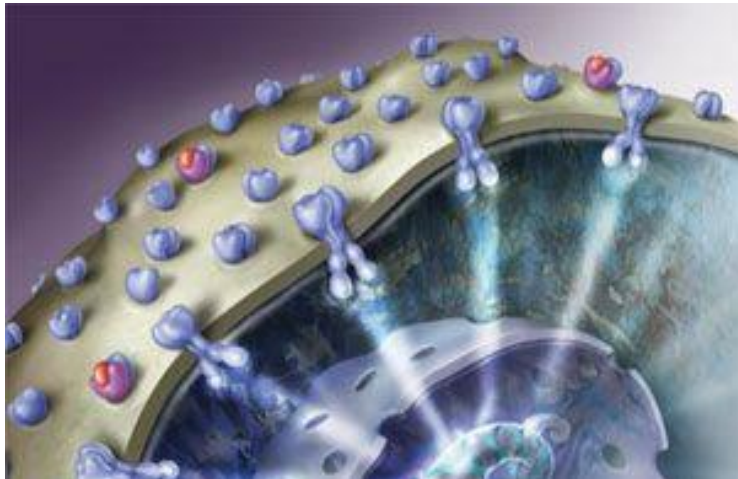
Unrestricted grants for investigator-initiated research
from:

Astellas, Bayer,
Boehringer-Ingelheim, Cristal Therapeutics,
Pamgene, Pfizer,
Novartis, Roche,
Sanofi, Servier



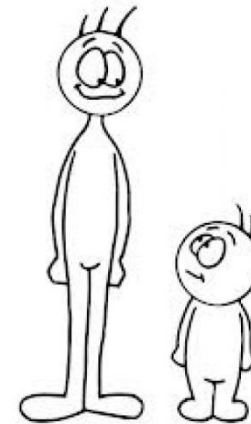
(my definition of) personalized medicine

- Tumor characteristics



+

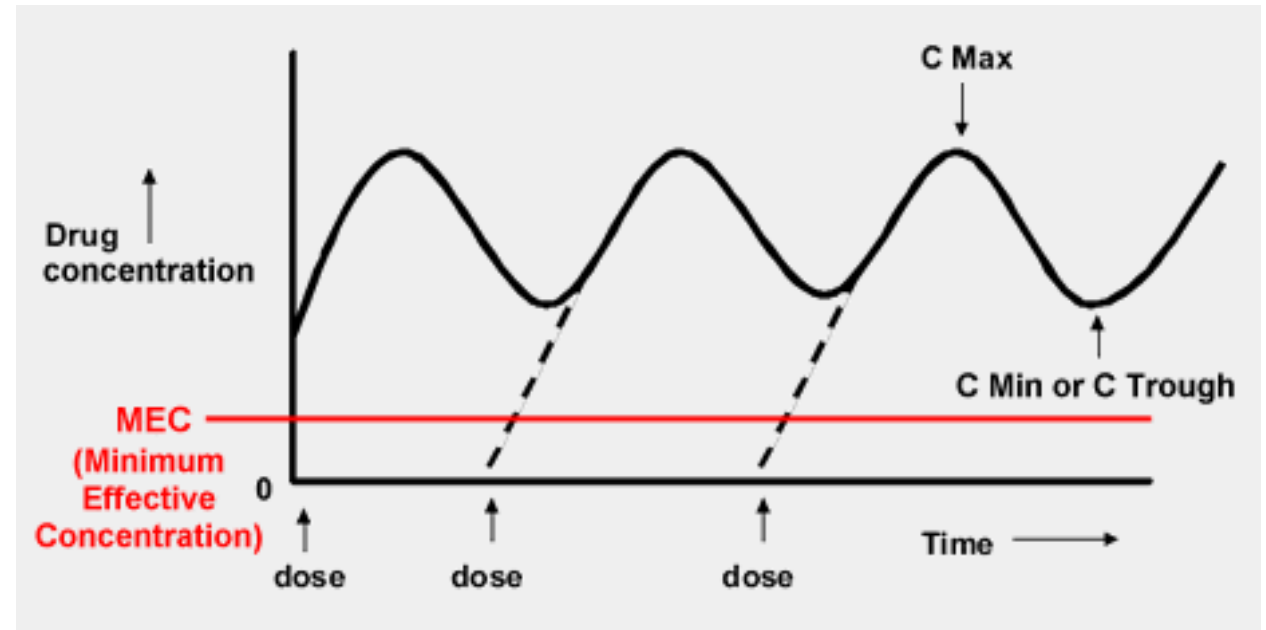
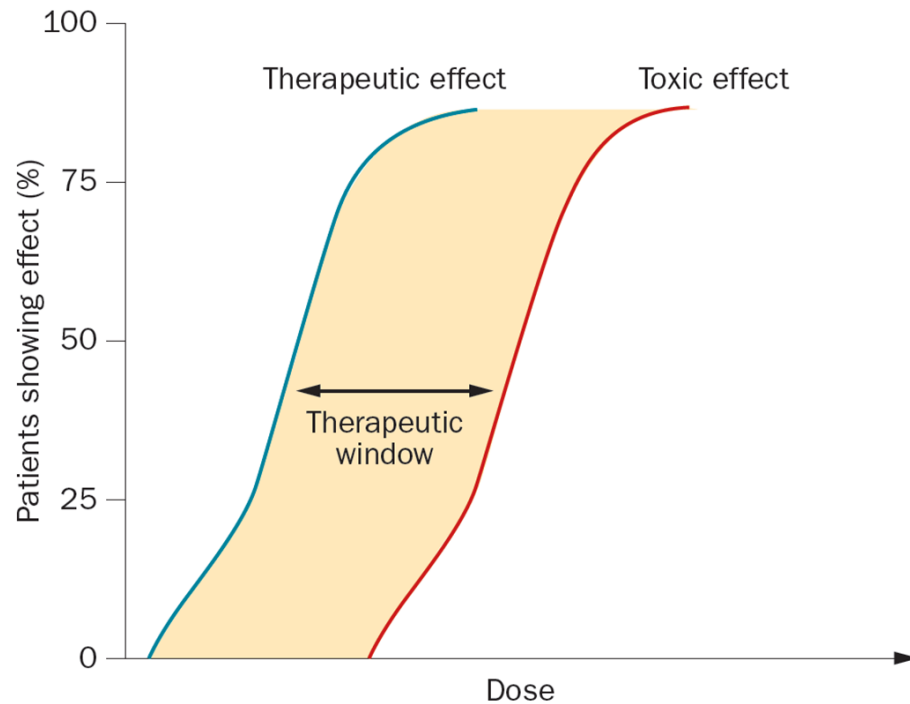
- Patient characteristics



= *'Personalized medicine'*

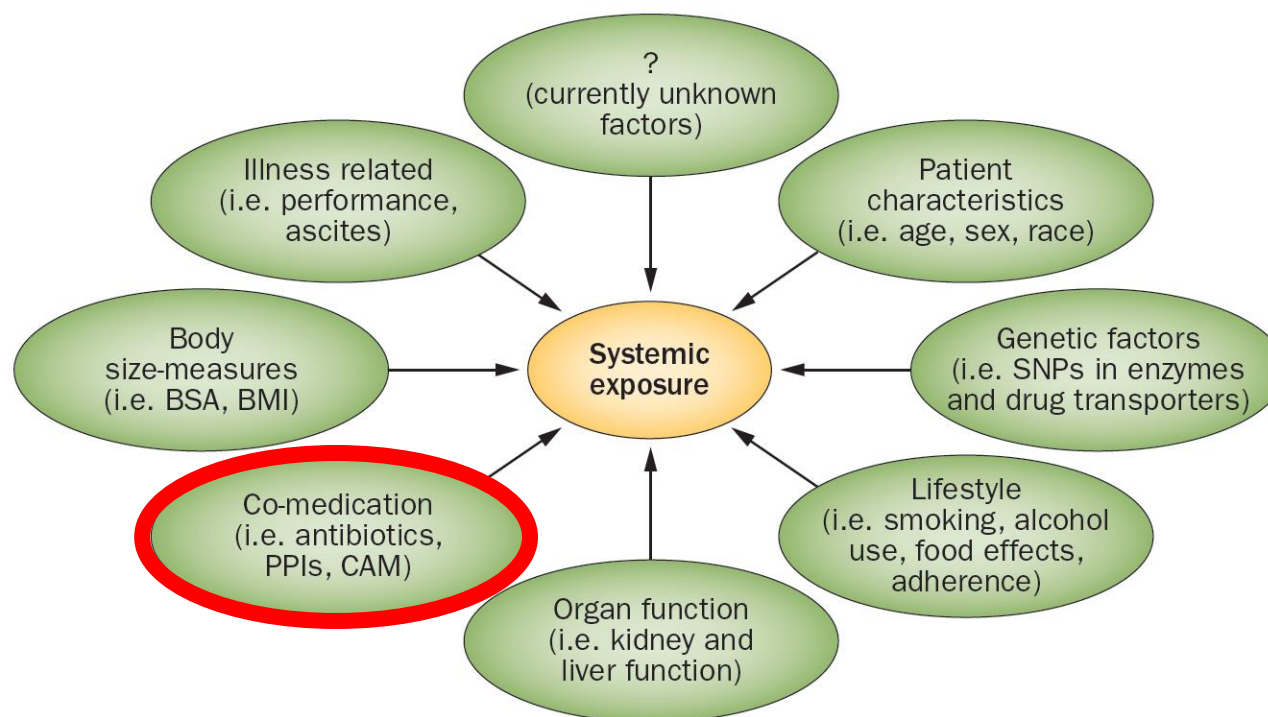


Basic principles of clinical pharmacology



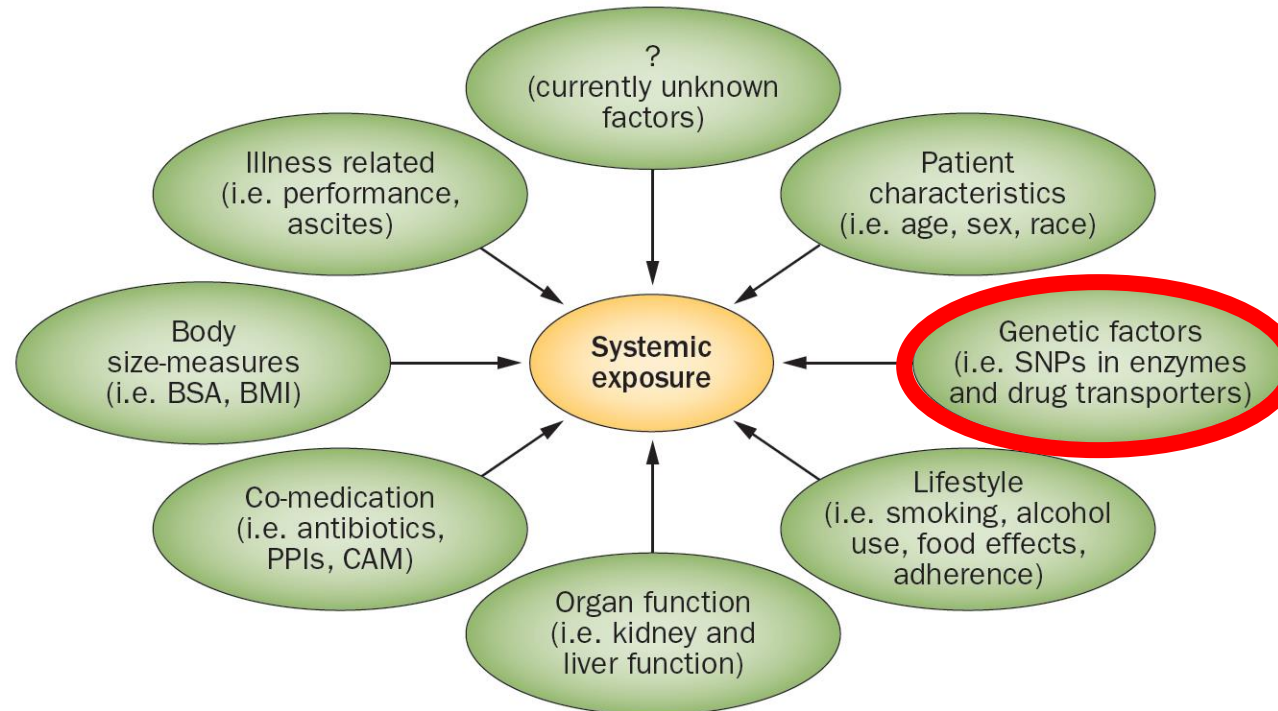


Factors influencing drug exposure





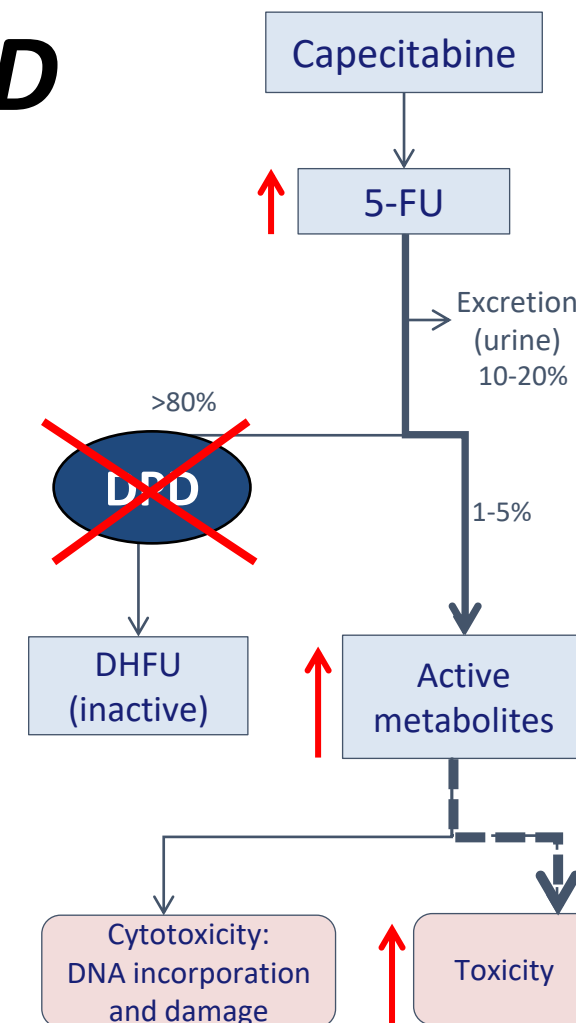
Factors influencing drug exposure





Fluoropyrimidines and DPD

- Fluoropyrimidines: 5-fluorouracil (5-FU) and capecitabine
 - ~10-30% of patients develop severe (grade ≥ 3) toxicity
 - This often results in hospitalization or suboptimal treatment
 - ~1% of patients develop **fatal** toxicity
- Dihydropyrimidine dehydrogenase (DPD)
 - DPD plays a key role in fluoropyrimidine metabolism
 - DPD deficiency occurs in 3-5% of the population
 - It is associated with highly increased risk of severe/fatal toxicity
- Upfront screening for DPD deficiency and dose individualization improves patient safety

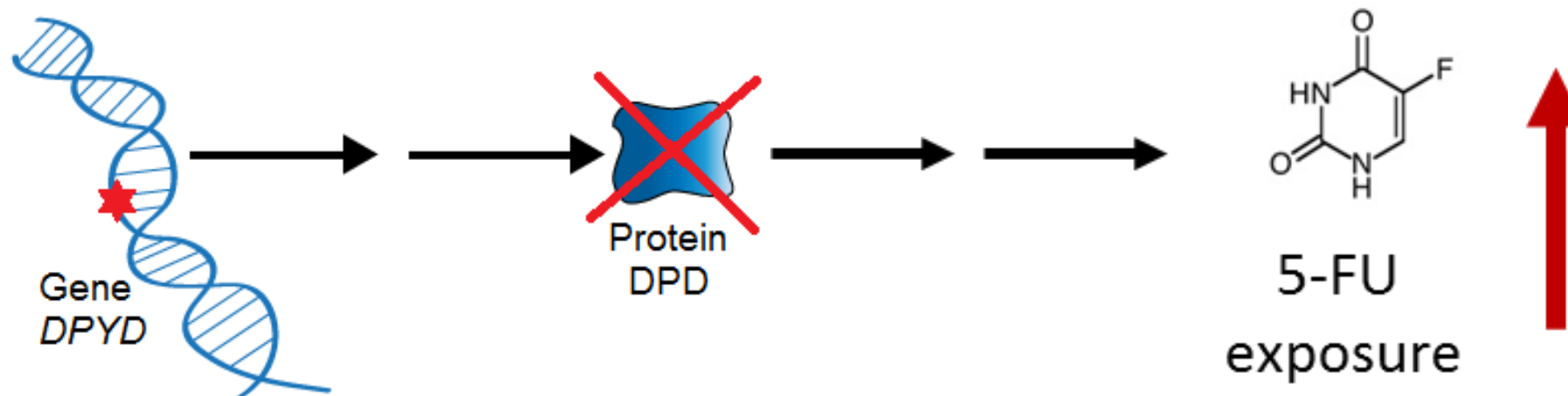




DPYD genotyping

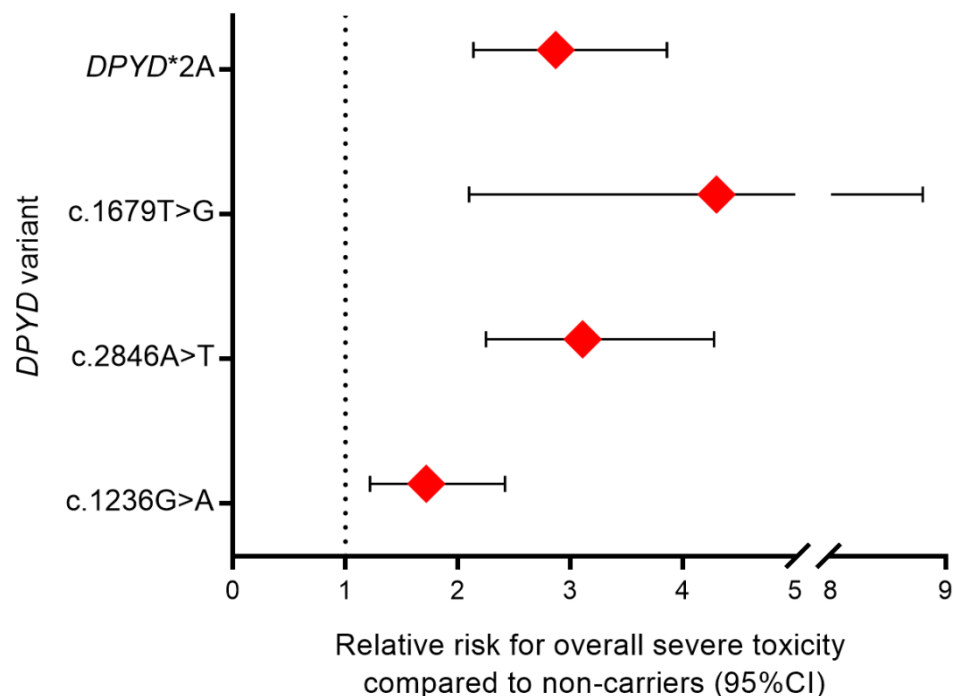
Screening for DPD deficiency: ***DPYD*** genotyping

DPD deficiency often the result of polymorphisms in the *DPYD* gene





Risk of severe toxicity!

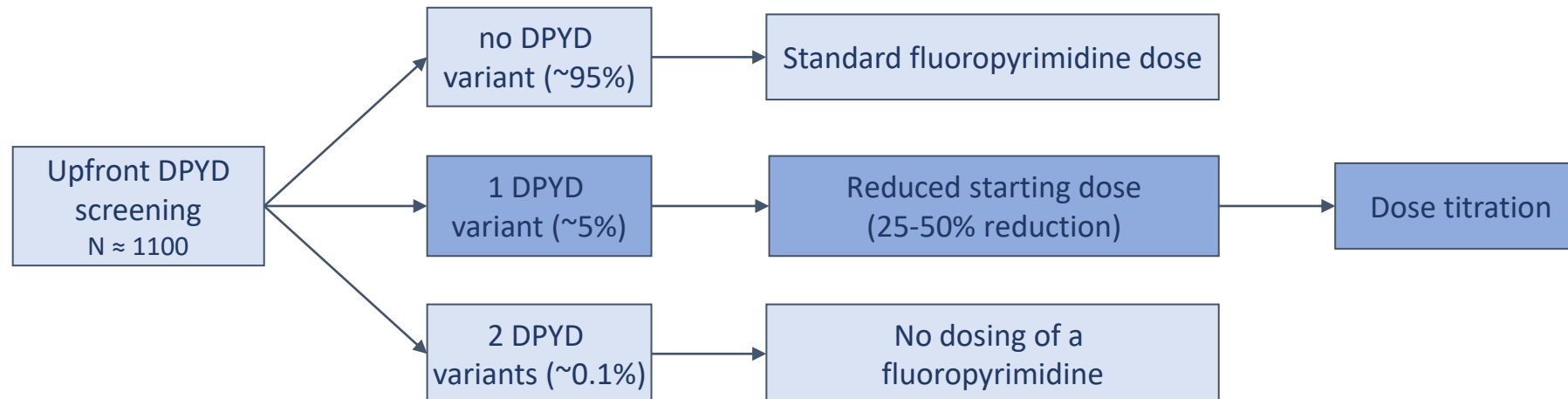


<i>DPYD</i> variant	Amount of dose reduction
<i>DPYD</i> *2A	50%
c.1679T>G	50%
c.2846A>T	25%
c.1236G>A	25%



Dutch DPYD Genotyping study 2015-2018

- Primary objective:
 - To determine if the risk of severe (grade ≥ 3) fluoropyrimidine-related toxicity is decreased by upfront *DPYD* genotyping and dose individualization of fluoropyrimidine treatment.



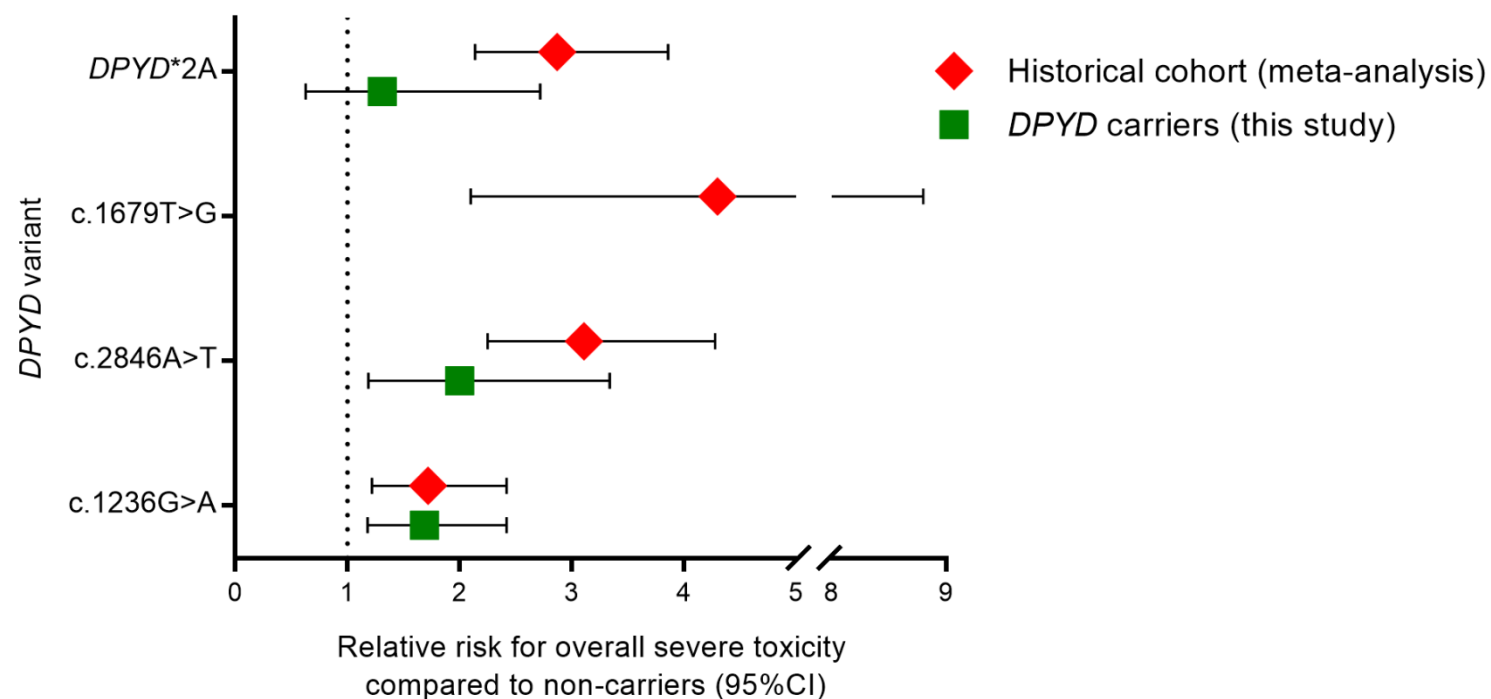


Dutch DPYD Genotyping study 2015-2018

- Patients who intended to start fluoropyrimidine-based chemotherapy (all regimens)
- Followed for toxicity during entire treatment
- Severe toxicity defined as CTC-AE grade ≥ 3
- Toxicity compared:
 - Between *DPYD* carriers and wild-type patients in the study
 - With a literature cohort (*DPYD* carriers treated with full dose) derived from published meta-analysis



Dutch DPYD Genotyping study 2015-2018





Publication

DPYD genotype-guided dose individualisation of fluoropyrimidine therapy in patients with cancer: a prospective safety analysis



Linda M Henricks, Carin A T C Lunenburg*, Femke M de Man*, Didier Meulendijks, Geert W J Frederix, Emma Kienhuis, Geert-Jan Creemers, Arnold Baars, Vincent O Dezentjé, Alexander L T Imholz, Frank J F Jeurissen, Johanna E A Portielje, Rob L H Jansen, Paul Hamberg, Albert J ten Tije, Helga J Droogendijk, Miriam Koopman, Peter Nieboer, Marlène H W van de Poel, Caroline M P W Mandigers, Hilde Rosing, Jos H Beijnen, Erik van Werkhoven, André B P van Kuilenburg, Ron H N van Schaik, Ron H J Mathijssen, Jesse J Swen, Hans Gelderblom, Annemieke Cats, Henk-Jan Guchelaar, Jan H M Schellens*



Consequence → recommendation EMA 2020



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

30 April 2020
EMA/229267/2020

EMA recommendations on DPD testing prior to treatment with fluorouracil, capecitabine, tegafur and flucytosine

EMA has recommended that patients should be tested for the lack of the enzyme dihydropyrimidine dehydrogenase (DPD) before starting cancer treatment with fluorouracil given by injection or infusion (drip) or with the related medicines, capecitabine and tegafur.



DPD NOW study (currently ongoing)

The previous *DPYD* study was mainly done in Caucasian cancer patients.

However, the incidence of these polymorphisms varies significantly among ethnicities →

Therefore, a study in patients of **Non-Western** descent started last year and is currently including patients.

<https://clinicaltrials.gov/ct2/show/NCT04300361>

Cell

Leading Edge

Commentary

The Missing Diversity in Human Genetic Studies

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<https://doi.org/10.1016/j.cell.2019.02.048>

The majority of studies of genetic association with disease have been performed in Europeans. This European bias has important implications for risk prediction of diseases across global populations. In this commentary, we justify the need to study more diverse populations using both empirical examples and theoretical reasoning.



More examples of pharmacogenetics in oncology

Other polymorphisms may also result in drug related toxicity;
e.g.:

- *TPMT**2/*3 in 6-MP
- *UGT1A1**28 in irinotecan
- *CYP3A4**22 in sunitinib/pazopanib

and therefore dose reductions may be required/useful

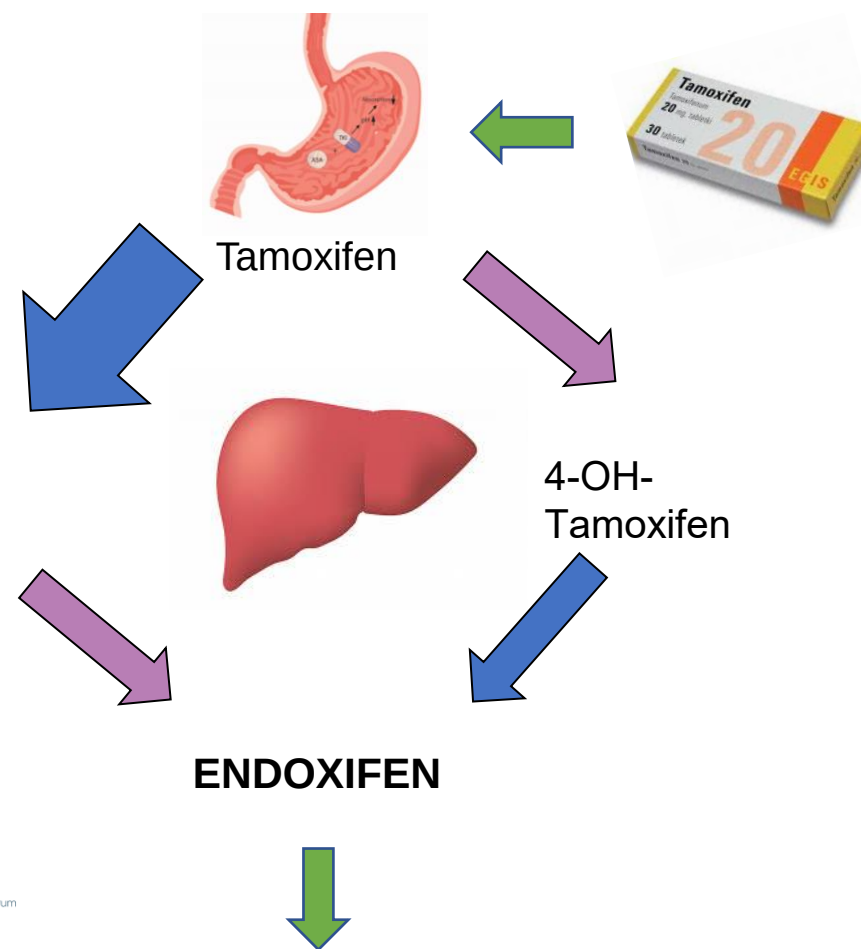


Pharmacogenetics is not only relevant for toxicity

Tamoxifen is a pro-drug of endoxifen

Endoxifen formation depends on CYP-mediated conversion in the liver

If SNPs lead to a lower CYP2D6 activity (purple arrows) less endoxifen will be formed





Tamoxifen/endoxifen

Screening for *CYP2D6* polymorphisms may help to explain why the threshold for efficacy is not reached...

Threshold set at ~16 nM for endoxifen

☐ CIDNA EGFR T790M	Bloed	-Volgt-		
☐ Trial/Studie	Bloed			GENO
☐ 25-OH Vit. D	Bloed	66	☰	
☐ Endoxifen	Bloed		13.20	☰
☐ Tamoxifen	Bloed		185.00	

De volgende rapporteert:

CYP2D6 *1/*4: 1 actief, 1 inactief allel.
CYP3A4 *1/*1: 2 actieve allelen.

Interpretatie (Hurkmans):

1. intermediair metabolizer CYP2D6
2. normaal metabolizer CYP3A4

--> subtherapeutische spiegel endoxifen (=13.20) mogelijk tgv 1.



CDDF SPRING CONFERENCE 2021

08 - 10 February 2021

Virtual Conference

Current and future challenges
of innovative oncology drug
development



DNA 'passport'

Naam: Test 1 Erasmus MC/RVS ID: 12345678				Geb. datum: 01/03/1980 Uitslagte saat: 16/09/2021	
Gene	Uitslag	Metabolisme	Prev. 1	Getest op	
CYP1A2	*1/*1	Normaal	45%	*1C, *1D	
CYP2B6	*1/*1	Normaal	25%	*4, 5, 6, 7	
CYP2C9	*1/*1	Normaal	17%	*2, 3	
CYP2C19	*1/*2	Normaal	80%	*2, 3, 17	
CYP2D6	*1/*1	Normaal	3%	25 varianten	
CYP3A4	*1/*2xN	Normaal	80%	*1B, 1G, 3-6, 1	
CYP3A5	*1/*1	Nonexpressor	80%	*3, *6	
BChE	*3/*3	Normaal	99%	A, K, F1, F2, H,	
DPYD	U/S	Normaal	2%	*2A	
HLA-B*57:01	*1/*2A	Normaal	96%		
TPMT	NEG	Gevoelig	89%		
VKORC1	*1/*1	Gevoelig	20%		
1 In blanke bevolking. Kan afwijken bij andere etniciteiten				-1639G>A	



Conclusions

Pharmacogenetics may help to:

- Predict toxicity
- Obtain an adequate systemic exposure

Therefore, pre-emptive genotyping, using a DNA profile may help to further optimize the dose of (oncological) drugs, potentially resulting in less side-effects and a higher efficacy



Thank you for your attention

