ISOPP International Society of Oncology Pharmacy Practitioners

gedefo Grupo de Farmacia Oncológica de la sefh

sefh Sociedad Española de Farmacia Hospitalaria

Advancing Oncology Pharmacy Care Globally

Implementation of Pharmacogenomics: Perspectives from Spain and the UK

Individualization of irinotecan, busulfan, tacrolimus and asparaginase in clinical practice

Pau Riera Armengol, PharmD, BCOP, PhD
Pharmacy Department
Hospital de la Santa Creu i Sant Pau
Thursday, 2nd March 2023

HOSPITAL DE LA SANTA CREU I SANT PAU
UNIVERSITAT AUTÒNOMA DE BARCELONA

Learning objectives

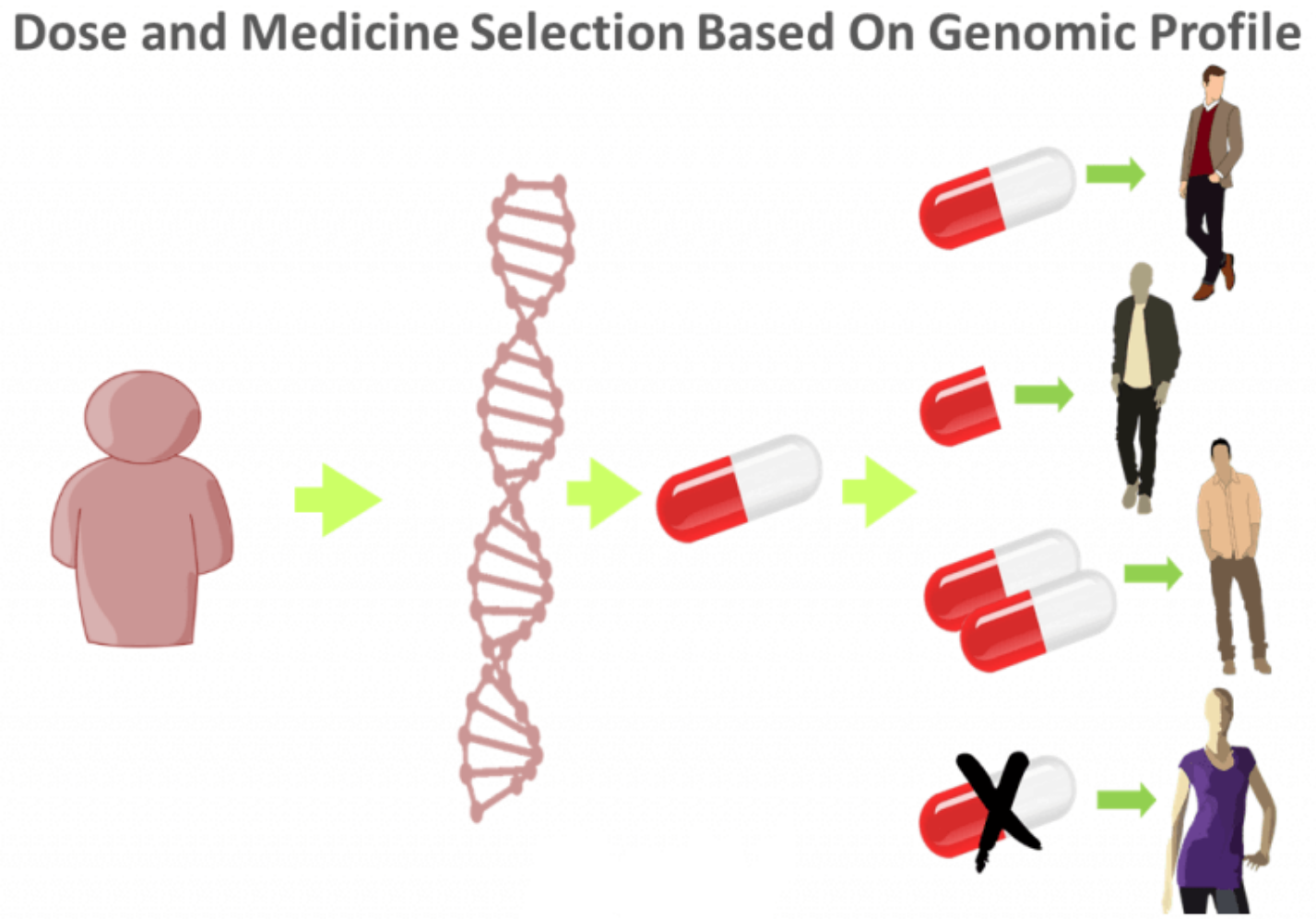
1. Role of *UGT1A1* gene variants on irinotecan and sacituzumab govitecan toxicity

2. Influence of *GSTA1* genetic variants on busulfan exposure

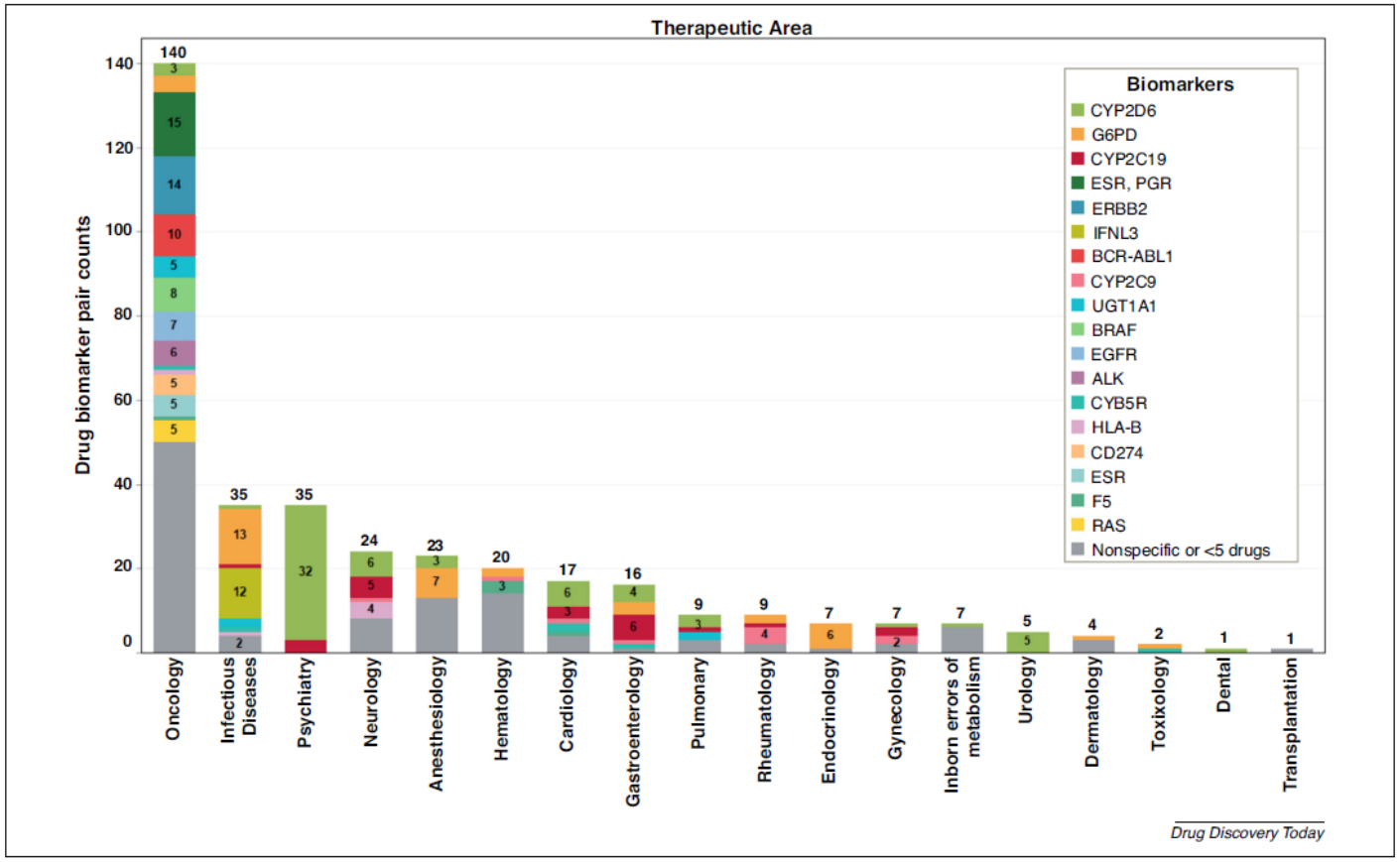
3. Relevance of CYP3A5 metabolizer status to tacrolimus clearance

4. Clinical utility of monitoring asparaginase activity

Pharmacogenomics: personalised medicine



Area of most relevance: oncology



Mehta D, Uber R, Ingle T, et al. Study of pharmacogenomic information in FDA-approved drug labeling to facilitate application of precision medicine. Drug Discov Today 2020; 25(5):813-820.

Implementation of pharmacogenomics: the situation in Spain

Heterogeneity between regions

- Different degree of concretion in health plans
- Several initiatives
- Organization: reference center?
- Integration of genomic data in clinical records

Medicina personalizada de precisión en España: mapa de comunidades. Fundación Instituto Roche. 2019.

Genetic biomarkers determined in Hospital de Sant Pau

Tumour markers:
KRAS, *BRAF*, *EGFR*, *ALK*…

DPYD (fluoropyrimidines)

UGT1A1 **(irinotecan and sacituzumab govitecan)**

TPMT & *NUDT15*
(azathioprine)

CYP2D6, *CYP1A2*, *CYP2C19*
(antipsychotics and antidepressants)

CYP3A5
(tacrolimus)

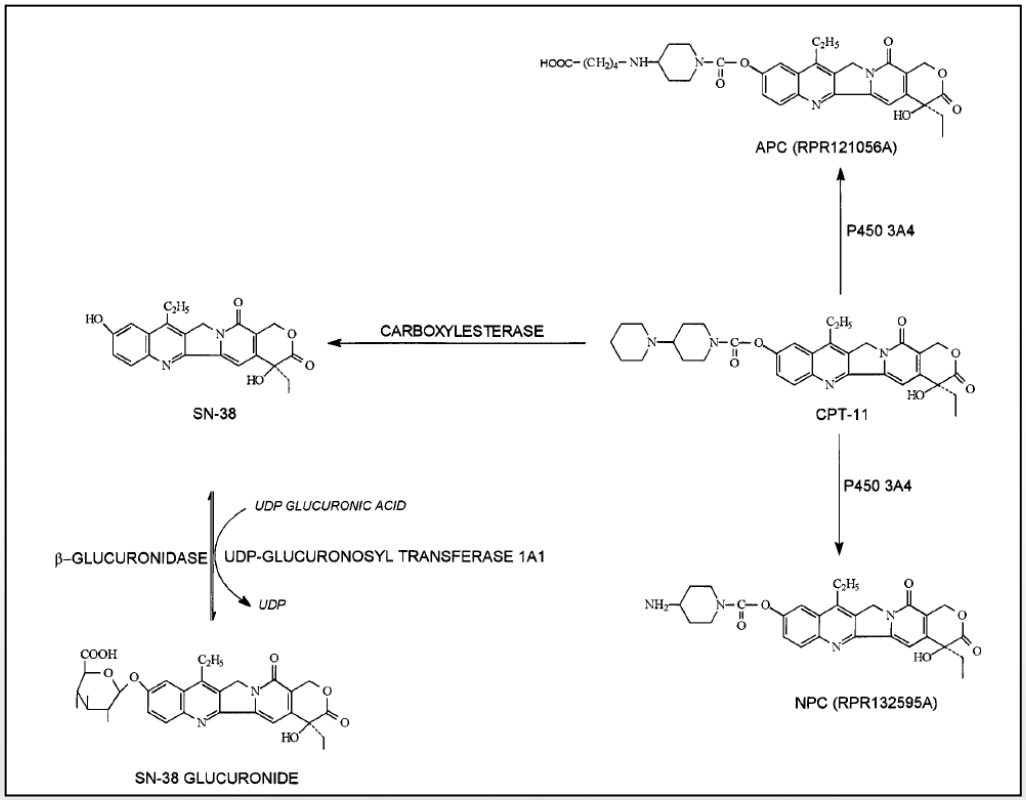
New action 2023

GSTA1 **(busulfan)**

HOSPITAL DE LA SANTA CREU I SANT PAU
UNIVERSITAT AUTÒNOMA DE BARCELONA

Irinotecan (CPT-11)

- SN-38 prodrug
- Used in **colorectal cancer**, lung cancer, sarcomas
- Common toxicities: **diarrhoea** and **neutropenia**



Santos A, Zanetta S, Cresteil T, Deroussent A, Pein F, Raymond E, et al. Clin Cancer Res 2000;6(5):2012–20.

*UGT1A1*28* and irinotecan

Uridin diphosphate glucuronosyltransferase 1A1 (*UGT1A1*) gene

↓

Uridin diphosphate glucuronosyltransferase 1A1 (UGT1A1) enzyme

↓

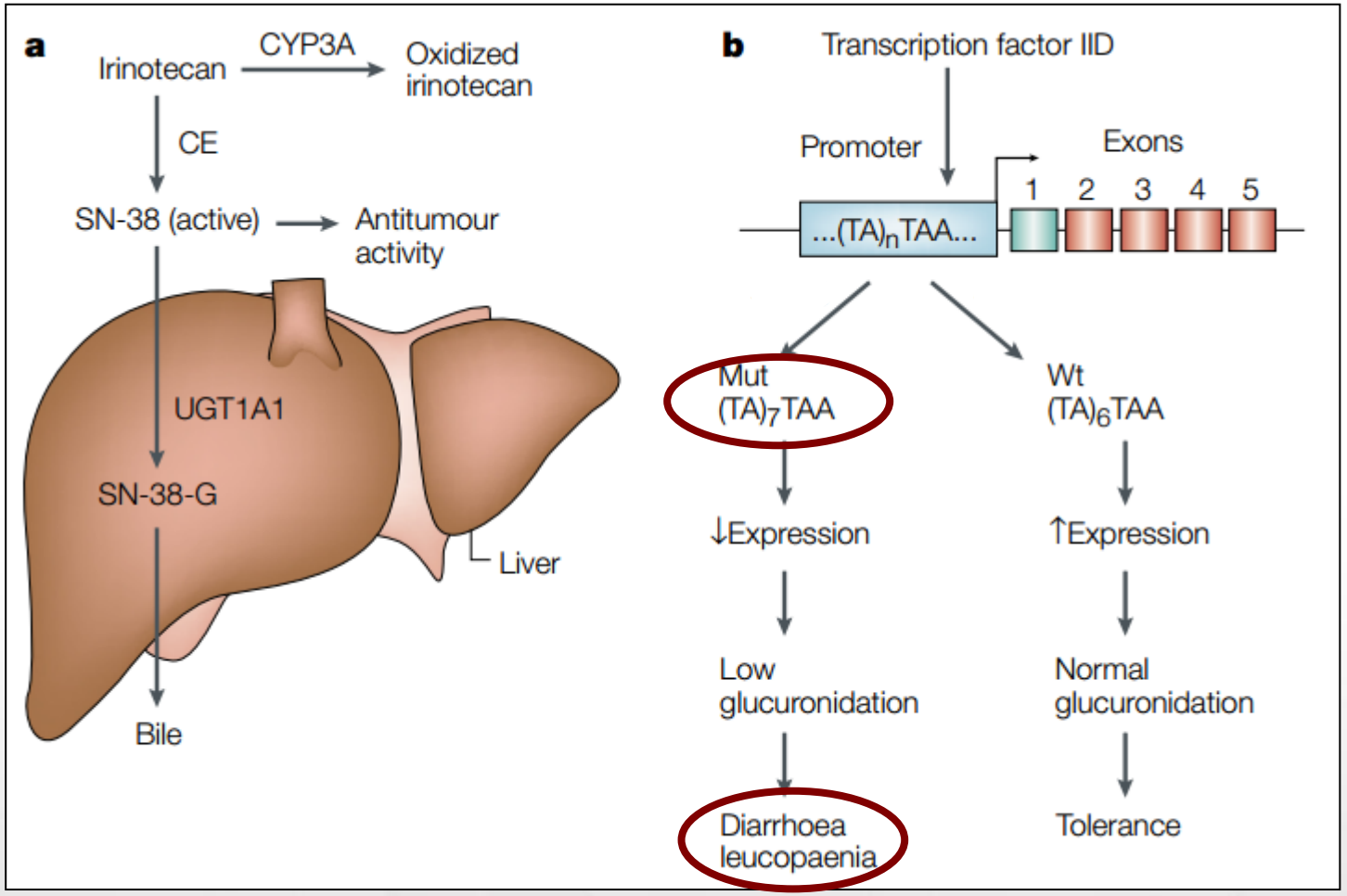
Catalyzes conjugation with glucuronic acid

Genetic study: determination of TA repeats in the TATA box (promoter):

- **6 repeats** (**1* allele): normal enzymatic activity
- **7 repeats** (**28* allele)
- **8 repeats** (**37* allele)

} reduced enzymatic activity

Irinotecan metabolism



Mary V. Relling & Thierry Dervieux. Pharmacogenetics and cancer therapy. *Nature Reviews Cancer* 2001; 1(2):99-108

*UGT1A1*28* and irinotecan

British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2018) **84** 1389–1392 1389

SHORT REPORT

Relevance of *CYP3A4*20*, *UGT1A1*37* and *UGT1A1*28* variants in irinotecan-induced severe toxicity

Pau Riera[1,2], Juliana Salazar[1,3], Anna C. Virgili[4], María Tobeña[4], Ana Sebio[4], Pía Gallano[1,3], Agustí Barnadas[4] and David Páez[4]

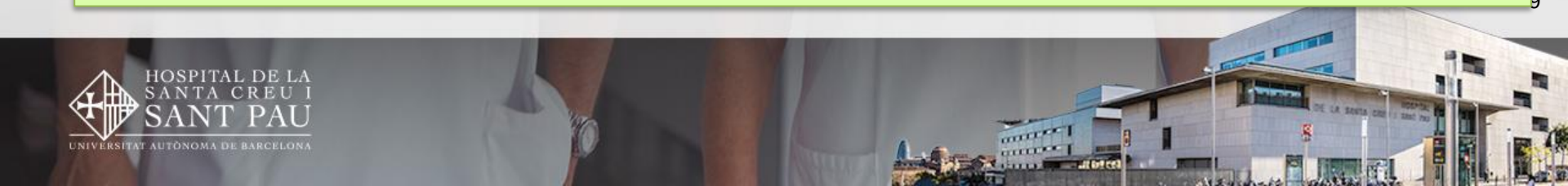
[1]*Genetics Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain,* [2]*Faculty of Pharmacy and Food Sciences, Universitat de Barcelona (UB), Barcelona, Spain,* [3]*U705, ISCIII Center for Biomedical Research on Rare Diseases (CIBERER), Barcelona, Spain, and* [4]*Medical Oncology Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain*

Genotype	*n* (%)	Diarrhoea (%)	Neutropenia (%)	Asthenia (%)
*1/*1	136 (44.2%)	18 (13.2%)	23 (16.9%)	23 (16.9%)
*1/*28	143 (46.4%)	25 (17.5%)	34 (23.8%)	31 (21.7%)
*28/*28	28 (9.1%)	12 (42.9%)	10 (35.7%)	10 (35.7%)
*28/*37	1 (0.32%)	0 (0%)	1 (100%)	1 (100%)
P		0.002[a]	0.037[a]	0.041[a]

UGT1A1, UDP-glucuronosyltransferase isoform 1A1

[a]To perform the chi-square test, patients *28/*28 and *28/*37 were considered together

In patients carrying the **28/*28* genotype, a 25% dose reduction is recommended (if irinotecan dose is ≥ 180 mg/m²)



Case report

72-year-old patient

Diagnosis: unresectable **mCRC** disseminated to the liver and the lung

Genetic variants

- ***UGT1A1*28/*37***
- ***KRAS* mutated (G12S)**
- ***DPYD* not tested** (year 2017)

1st line: FOLFOX-6 + bevacizumab

Complications:

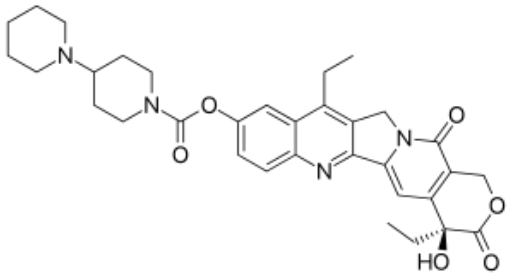
- Pulmonary embolism after the 7th cycle (bevacizumab is suspended)
- Allergic reaction to oxaliplatin + grade III neutropenia → oxaliplatin dose reduction + filgrastim

2nd line: irinotecan monotherapy, with reduced irinotecan dose (150 mg/m²)

Complications

- **Grade IV neutropenia and febrile neutropenia**, neutropenic colitis and **lethal septic shock**.

FDA irinotecan label



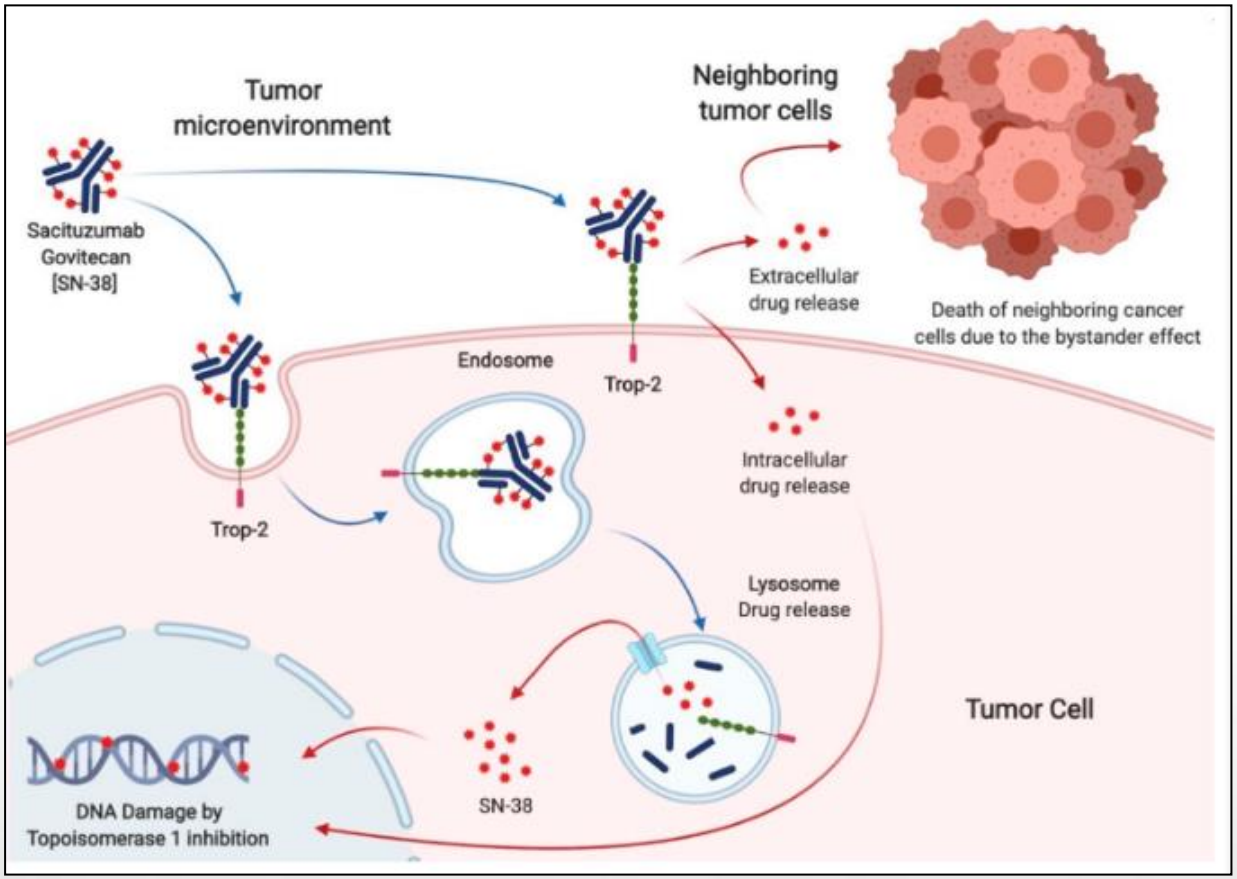
Individuals who are homozygous for the UGT1A1*28 allele (UGT1A1 7/7 genotype) are at increased risk for neutropenia following initiation of CAMPTOSAR treatment.

When administered in combination with other agents or as a single-agent, 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. However, the precise dose reduction in this patient population is not known and subsequent dose modifications should be considered based on individual patient tolerance to treatment *[see Dosage and Administration (2)]*.

UGT1A1 Testing

A laboratory test is available to determine the UGT1A1 status of patients. Testing can detect the UGT1A1 6/6, 6/7 and 7/7 genotypes.

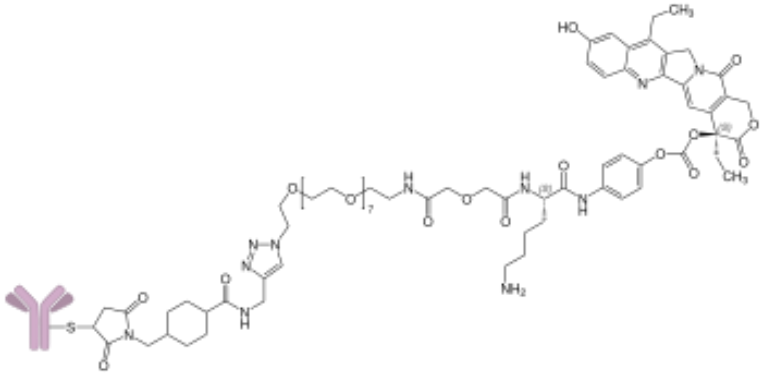
Sacituzumab govitecan



- SN-38 prodrug
- Used in **triple-negative breast cancer**
- Common toxicities: **diarrhoea** and **neutropenia**

Pavone, G.; Motta, L.; Martorana, F.; Motta, G.; Vigneri, P. A New Kid on the Block: Sacituzumab Govitecan for the Treatment of Breast Cancer and Other Solid Tumors. *Molecules* **2021**, *26*, 7294

FDA sacituzumab govitecan label



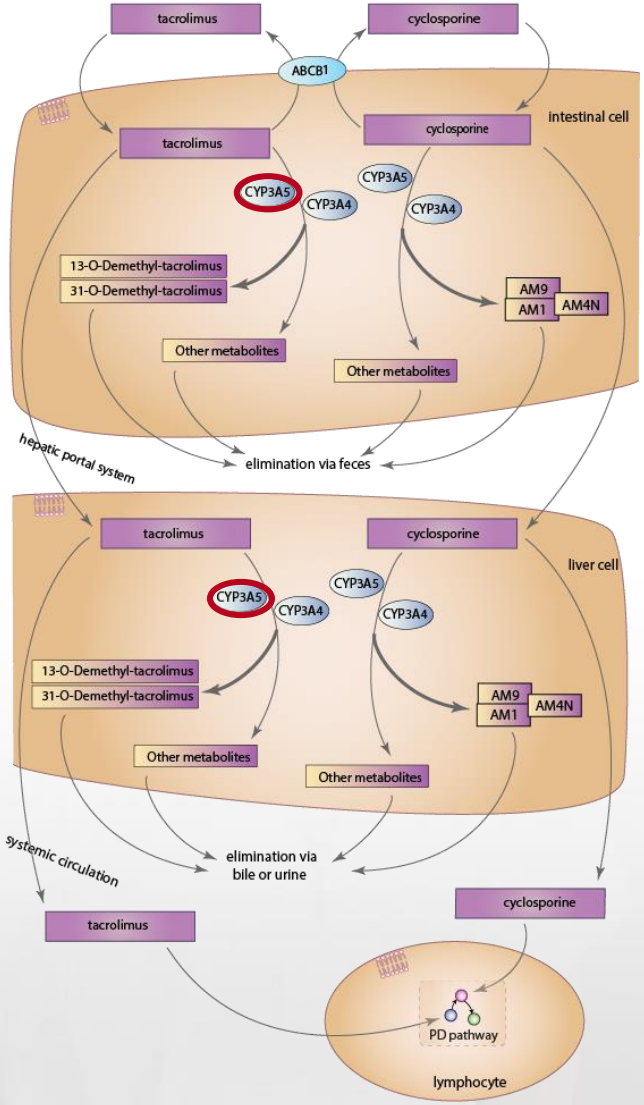
5.5 Increased Risk of Adverse Reactions in Patients with Reduced UGT1A1 Activity

Patients homozygous for the uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1)*28 allele are at increased risk for neutropenia, febrile neutropenia, and anemia; and may be at increased risk for other adverse reactions when treated with TRODELVY.

The incidence of neutropenia and anemia was analyzed in 701 patients who received TRODELVY and had UGT1A1 genotype results. In patients homozygous for the UGT1A1 *28 allele (n=87), the incidence of Grade 3-4 neutropenia was 67%. In patients heterozygous for the UGT1A1*28 allele (n=301), the incidence of Grade 3-4 neutropenia was 46%. In patients homozygous for the wild-type allele (n=313), the incidence of Grade 3-4 neutropenia was 46% *[see Clinical Pharmacology (12.5)]*. In patients homozygous for the UGT1A1 *28 allele, the incidence of Grade 3-4 anemia was 25%. In patients heterozygous for the UGT1A1*28 allele, the incidence of Grade 3-4 anemia was 10%. In patients homozygous for the wild-type allele, the incidence of Grade 3-4 anemia was 11%.

However, no initial dose reductions are recommended in patients carrying the **28/*28* genotype. More studies are needed to have more evidences in real practice.

Tacrolimus: role of CYP3A5



- Tacrolimus is used for the prevention of graft-versus-host disease in **hematopoietic stem cell transplantation**.

- Hepatic metabolism and important first-pass effect through **CYP3A5.**

Barbarino et al. PharmGKB summary: cyclosporine and tacrolimus pathways. *Pharmacogenetics and genomics.* 2013. https://www.pharmgkb.org/pathway/PA165986114

CYP3A5 gene

- Three **loss-of-function alleles: **3, *6, *7***
- **85%** of the patients harbours the ****3/*3* genotype**, and tacrolimus is dosified based on this fact.
- Tacrolimus **standard dose** is **optimal for patients**3/*3***

CYP3A5 allele	African Americans	South&Center Asians	East Asians	Europeans
**1*	0.4529	0.3267	0.2536	0.0741
**3*	0.3160	0.6733	0.7458	**0.9244**
**6*	0.1112	0.0000	0.0007	0.0015
**7*	0.1200		0.0000	0.0000

Allelic frequency of CYP3A5 genetic variants

CYP3A5 phenotypes

Likely phenotype	Genotypes	Examples of diplotypes[a]
Extensive metabolizer (CYP3A5 expresser)	An individual carrying two functional alleles	*1/*1
Intermediate metabolizer (CYP3A5 expresser)	An individual carrying one functional allele and one nonfunctional allele	*1/*3, *1/*6, *1/*7
Poor metabolizer (CYP3A5 nonexpresser)	An individual carrying two nonfunctional alleles	*3/*3, *6/*6, *7/*7, *3/*6, *3/*7, *6/*7

Birdwell KA, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for *CYP3A5* Genotype and Tacrolimus Dosing. Clin Pharmacol Ther 2015; 98(1):19-24.

- **Poor metabolizers** achieve therapeutic concentrations of tacrolimus at the **standard dose**.
- **Extensive and intermediate metabolizers** require **higher tacrolimus doses** to achieve therapeutic concentrations

Tacrolimus pharmacogenetics: management based on CYP3A5 phenotype

CYP3A5 phenotype[a]	Implications for tacrolimus pharmacologic measures	Therapeutic recommendations[b]	Classification of recommendations[c]
Extensive metabolizer (CYP3A5 expresser)	Lower dose-adjusted trough concentrations of tacrolimus and decreased chance of achieving target tacrolimus concentrations.	Increase starting dose 1.5–2 times recommended starting dose.[d] Total starting dose should not exceed 0.3 mg/kg/day. Use therapeutic drug monitoring to guide dose adjustments.	Strong
Intermediate metabolizer (CYP3A5 expresser)	Lower dose-adjusted trough concentrations of tacrolimus and decreased chance of achieving target tacrolimus concentrations.	Increase starting dose 1.5–2 times recommended starting dose.[d] Total starting dose should not exceed 0.3 mg/kg/day. Use therapeutic drug monitoring to guide dose adjustments.	Strong
Poor metabolizer (CYP3A5 nonexpresser)	Higher ("normal") dose-adjusted trough concentrations of tacrolimus and increased chance of achieving target tacrolimus concentrations.	Initiate therapy with standard recommended dose. Use therapeutic drug monitoring to guide dose adjustments.	Strong

Birdwell KA, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for *CYP3A5* Genotype and Tacrolimus Dosing. Clin Pharmacol Ther 2015; 98(1):19-24.

Case report

A 5-year-old patient, diagnosed with B-cell ALL, in second complete response, candidate to **haploidentic bone marrow transplant**.

CYP3A5 genotype: **variants **3* and **7* found in heterozygosis** → considered a slow metabolizer (standard dose).

Tacrolimus initial dose (IV): 0.03 mg/kg/day (0.5 mg/day)

→ 1st level: 8.47 mcg/L (desired range: 5-10 mcg/L)

→ **Example of application of pharmacogenomics + pharmacokinetics**

Busulfan pharmacogenetics

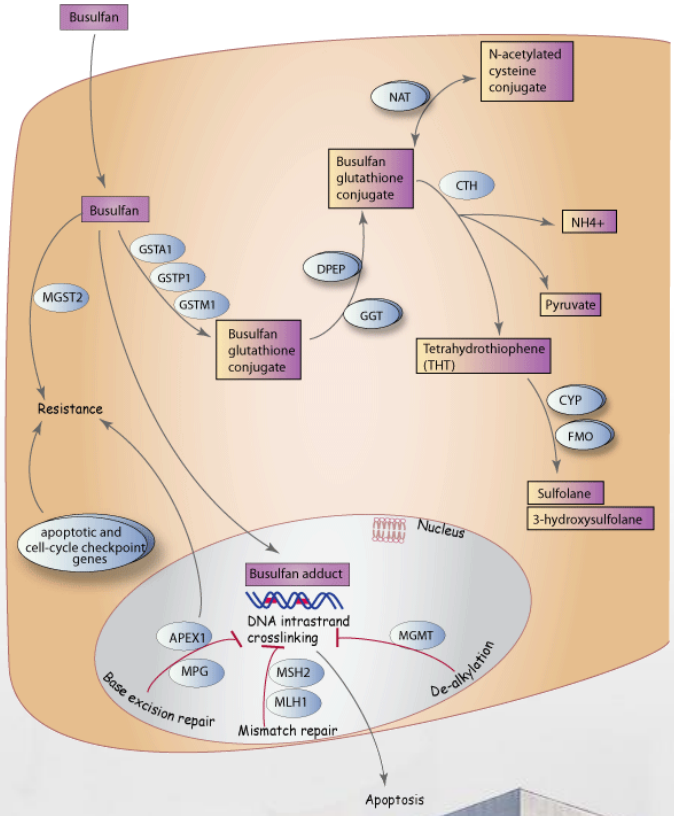
Busulfan is commonly used as a component of **conditioning regimens for hematopoietic stem cell transplantation.**

There are **individualized targets** according to transplantation and patients' characteristics.

Metabolism

- Busulfan is eliminated by **glutathione S-transferase-catalyzed conjugation** in the liver.

- Busulfan glutathione conjugate is further metabolized through oxidation in the liver. None of the metabolites significantly contribute to busulfan effectiveness or toxicity.



Whirl-Carrillo M, et al. An Evidence-Based Framework for Evaluating Pharmacogenomics Knowledge for Personalized Medicine. Clin Pharmacol Ther 2021; 110(3):563-572.

Busulfan pharmacogenetics

Enzymes involved

- **GSTA1** → main glutathione S-transferase involved in busulfan elimination
- GSTP1 y GSTM1 → less relevants despite being active *in vitro*

Table 1: *GSTA1* diplotype frequencies in the study population and proposed functional groups

GSTA1 Diplotype	Diplotype Frequencies N (%)	Proposed Functional group
*GSTA1*A2*A2*	12 (8.7)	I (9.4%)
*GSTA1*A2*A3*	1 (0.7)	
*GSTA1*A2*A1*	18 (13.0)	II (28.2%)
*GSTA1*A2*B1a*	11 (8.0)	
*GSTA1*A2*B2*	10 (7.2)	
*GSTA1*A1*A1*	17 (12.3)	III (47.8%)
*GSTA1*A1*B1a*	48 (34.8)	
*GSTA1*A1*B2*	1 (0.7)	
*GSTA1*B1b*A2*	3 (2.2)	IV (14.5%)
*GSTA1*B1a*B1a*	10 (7.2)	
*GSTA1*B2*B1a*	1 (0.7)	
*GSTA1*B1b*A1*	3 (2.2)	
*GSTA1*B1a*B1b*	3 (2.2)	

Rapid

Intermediate

Normal

Poor

Ansari M, et al. *GSTA1* diplotypes affect busulfan clearance and toxicity in children undergoing allogeneic hematopoietic stem cell transplantation: a multicenter study. Oncotarget 2017; 8(53):90852-90867.

Busulfan pharmacogenetics

*B haplotypes are associated with lower busulfan metabolism → higher busulfan exposition → higher risk of toxicity

GSTA1 Haplotype	-52 rs3957356 G>A	-69 rs3957357 C>T	-513 rs11964968 G>A	-567 rs4715332 G>T	-631 rs4715333 G>T	-1142 rs58912740 C>G
*A1	G	C	A	T	T	C
*A2	G	C	A	T	G	C
*A3	G	C	A	T	T	G
*B1a	A	T	A	G	G	G
*B2	A	T	A	G	G	C
*B1b	A	T	G	G	G	G

Ansari M, et al. *GSTA1* diplotypes affect busulfan clearance and toxicity in children undergoing allogeneic hematopoietic stem cell transplantation: a multicenter study. Oncotarget 2017; 8(53):90852-90867.

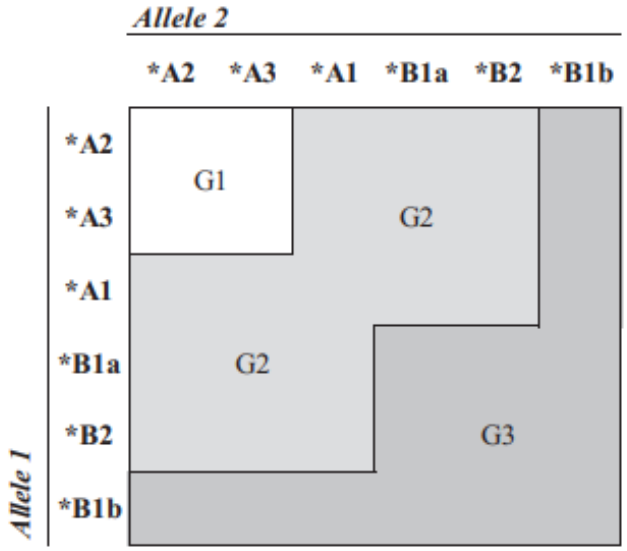


Figure 1. Grouping composition based on *GSTA1* diplotypes. G1 group contains homozygous patients for haplotypes associated with a rapid Bu metabolism, G3 contains homozygous for haplotypes associated with poor metabolism (*B) and heterozygous *B1b, and G2 contains diplotypes not classified as G1 or G3.

Nava T, et al. *GSTA1* Genetic Variants and Conditioning Regimen: Missing Key Factors in Dosing Guidelines of Busulfan in Pediatric Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transplant 2017; 23(11):1918-1924.

Relevance of busulfan pharmacogenetics

Case reports

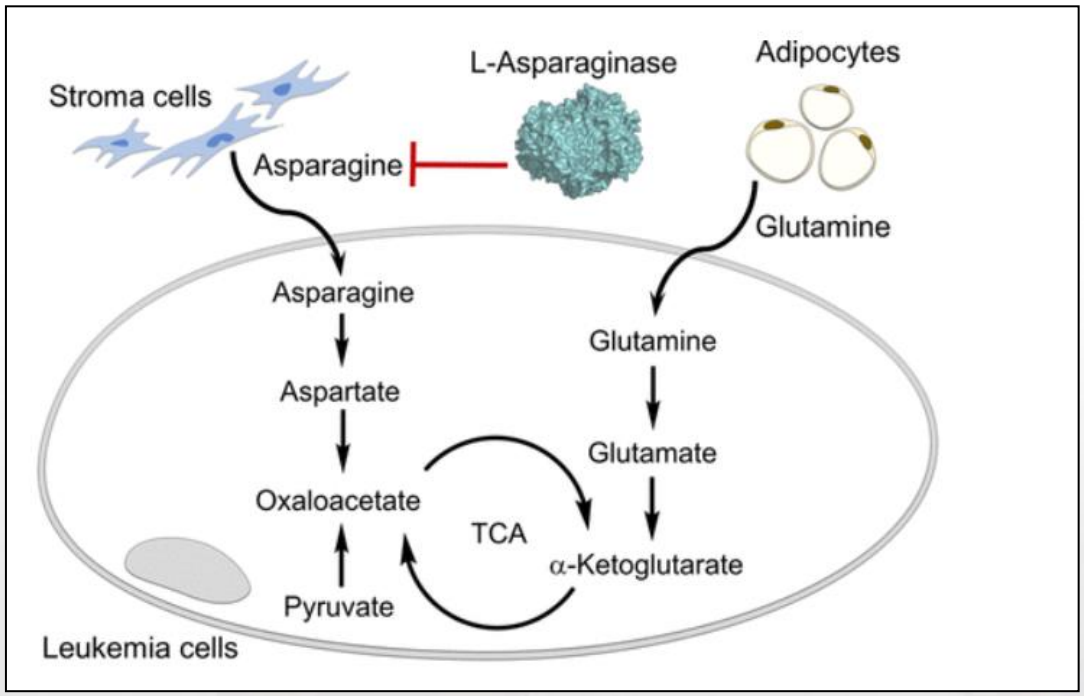
Patient	Indication	Busulfan dose	Exposure target: cumulative AUC (ng/ml x h)	AUC 1st dose (ng/ml x h)
1	B-cell ALL	3.2 mg/kg IV once daily for 4 days	95,000	**82,570**
2	B-cell ALL 2nd relapse	4 mg/kg IV once daily for 4 days	90,000	**82,000**
3	B-cell ALL 2nd relapse	3,8 mg/kg IV once daily for 4 days	90,000	**92,000**

The question is: do these patients carry *GSTA1*B* haplotypes?

L-Asparaginase

- Asparaginase is a component of multiagent chemotherapy regimens for the treatment of acute lymphoblastic leukemia (ALL).

- Adequate asparagine depletion is believed to be an important factor in achieving optimal therapeutic outcomes, as ALL cells lack the ability to synthesize their own asparagine de novo effectively (they lack asparagyne synthetase)



L-Asparaginase activity

- Asparaginase activity levels can be used to identify patients with silent inactivation and modify therapy in these patients.
- Patients with silent inactivation to asparaginase who are switched to therapy with an immunologically distinct asparaginase exhibit outcomes similar to patients who never developed silent inactivation.
- Patients presenting hypersensibility to PEG-asparaginase are also switched to Erwinase.

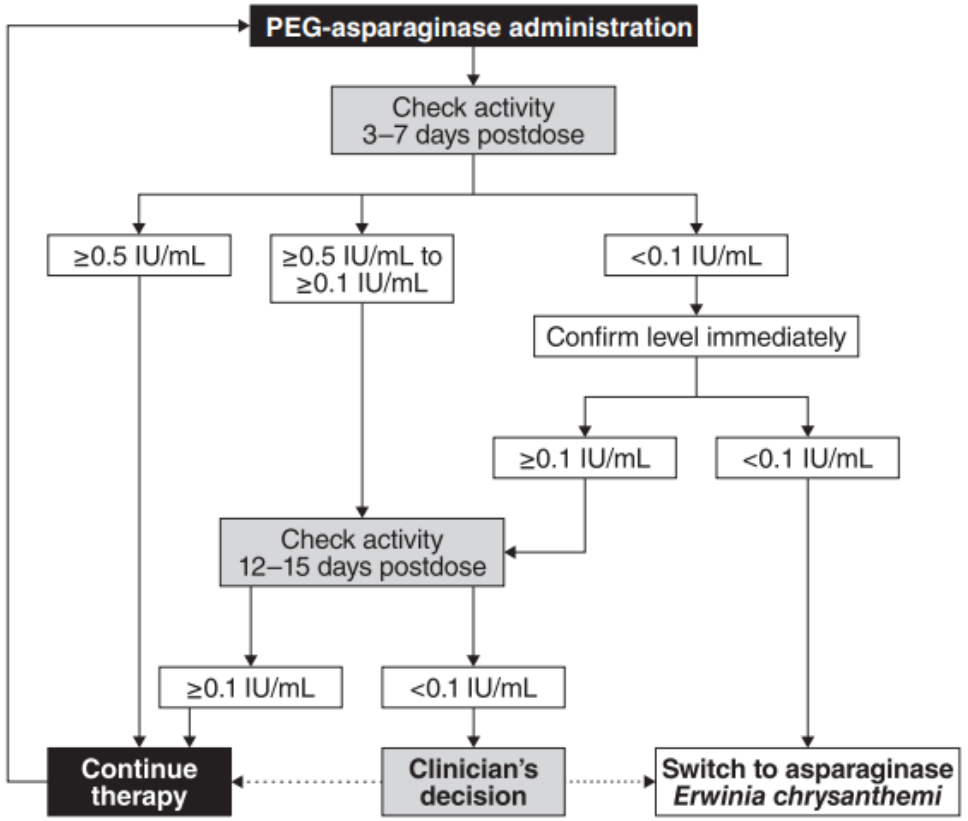


Figure 1. Algorithm for PEG-asparaginase activity monitoring administration. PEG: pegylated.

Salzer W, Bostrom B, Messinger Y, Perissinotti AJ, Marini B. Asparaginase activity levels and monitoring in patients with acute lymphoblastic leukemia. Leuk Lymphoma. 2018; 59(8):1797-1806.

Relevance of L-asparaginase activity

Case report

3-year-old patient diagnosed with B-cell ALL. The 2nd July 2021 begins reinduction with asparaginase, vincristine and doxorubicin (LAL/SEHOP PETHEMA 2013 protocol)

Pegaspargase
1000 UI/m²
(2-7-2021)

Erwinase
20000 UI/m²
(16-8-2021)

Erwinase
20000 UI/m²
(18-8-2021)

Erwinase
20000 UI/m²
(20-8-2021)

Activity (day +7)
<5 U/L (aim: >100 U/L)
SILENT INACTIVATION

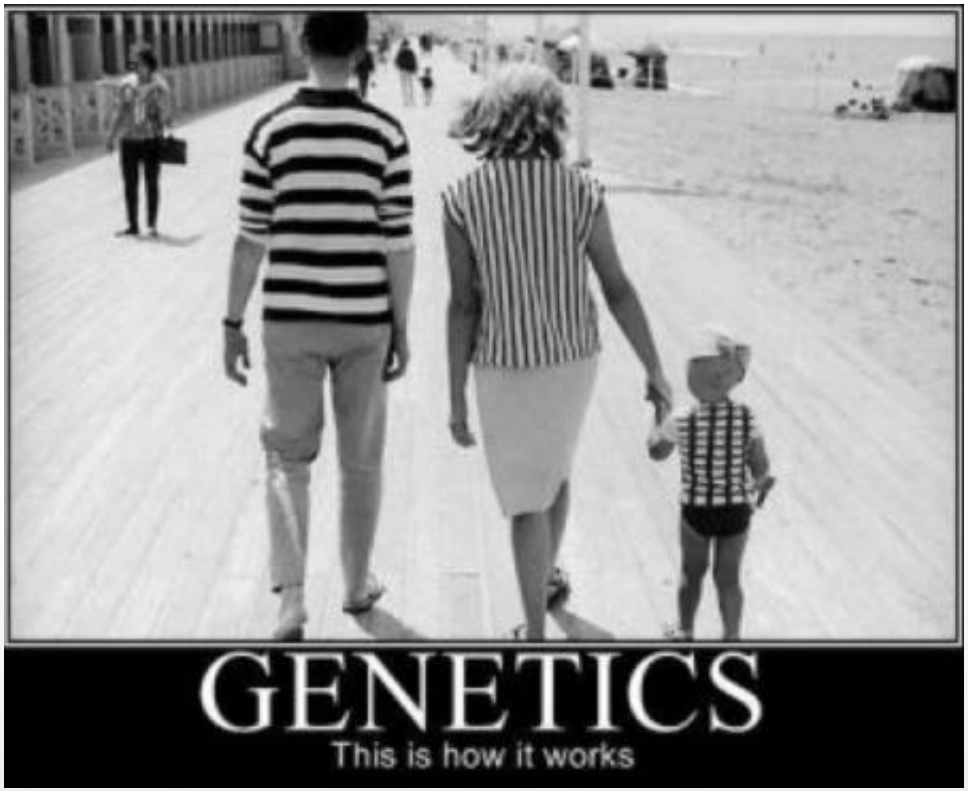
Activity (day +14)
<5 U/L (aim: >20 U/L)
SILENT INACTIVATION

Activity (day +2)
708 U/L
(aim: >100 U/L)

Activity (day +2)
617 U/L
(aim: >100 U/L)

Take-home messages...

- Therapeutic individualization is key to **optimize drug response/toxicity**
- In oncology, several germline pharmacogenetic markers, such as *UGT1A1*, *CYP3A5*, *GSTA1* or *DPYD*, are of interest.


GENETICS
This is how it works