
# Relevancia clínica de las mutaciones germinales en la terapia antineoplásica

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Unidad Farmacia oncológica
Hospital Virgen de la Victoria

pkgen
Grupo de Farmacocinética de la sefh

gedefo
Grupo de Farmacia Oncológica de la sefh

- **Incertidumbre sobre traslación de resultados** de pruebas genéticas a la prescripción/dosificación de fármacos[1]
- Dificultad en el **acceso a plataformas** de pruebas **farmacogenéticas** de la línea germinal[1]
- Falta de directrices de cómo y cuando prescribirlas[1]
- **Escasez de sistemas de apoyo a las decisiones clínicas**[1]
- Mutaciones germinales implicadas fundamentalmente en prevenir **toxicidad**
- Investigaciones fundamentalmente **académicas**

**Later-Line Choices for Patients With Metastatic Breast Cancer** : Episode 21

## UGT1A1 Status Underutilized in Predicting Sacituzumab Toxicity in MBC

April 8, 2024
By Targeted Oncology Staff

*Commentary* *Article*

*During a Case-Based Roundtable® event, Mark Pegram, MD, discussed the value of testing for UGT1A1 status in patients receiving sacituzumab govitecan for hormone receptor–positive breast cancer in the second article of a 2-part series.*

MEDIA ▾ PUBLICATIONS ▾ CASE-BASED ROUNDTABLE PARTNERS RESOURCES ▾ SUBSCRIBE

**g the UGT1A1 status's for anticipating the safety outcomes of patients in**

38, which is the active metabolite of irinotecan, is predicated by this enzyme
ans; there are multiple, but there are some that impact the metabolism of SN-
e *28/*28 patients who have the polymorphism in both alleles of this gene.

*Mark Pegram, MD*

*ızy Yuan-Huey Hung Endowed Professor of Medical Oncology*

*Stanford University School of Medicine*

*Associate Director of Clinical Research*

*Stanford Comprehensive Cancer Institute*

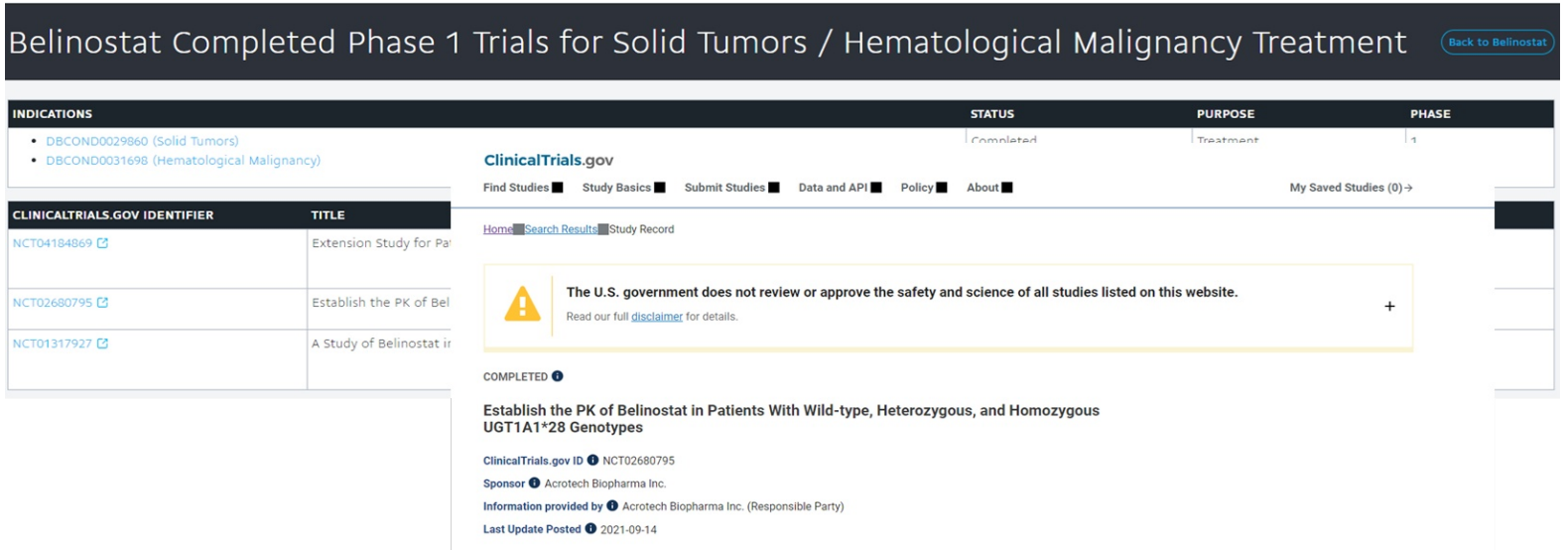
*Stanford, CA*

[Some institutions use] germline DNA sequence analysis to understand the UGT1A1 gene sequence before prescribing sacituzumab govitecan or irinotecan. We don't…[and] I don't know why that is—we probably should. We can do it. It's expensive, and I assume that's the main reason why we're not doing it on everybody routinely. You could start at a lower dose; if you knew for a fact that you have a *28/*28 genotype, you wouldn't want to give that patient a full dose on cycle 1. The same is true for irinotecan in colon cancer and other neoplasms. I've never tried to get reimbursed before; I don't know the answer. But I would think if somebody got sick on the first cycle and then you get it, you can probably get reimbursed for [testing]. But at that point, you're going to hold and then dose reduce anyway. [The test] would be just for the chart, but it's not going to change anything. Even if you have to explain the cycle and toxicity. It's satisfying because you have an explanation, but it's not going to change your action. So some patients might be able to live without it. If a test result isn't going to change what you're going do, then do you need to do the test in any discipline?

But the pharmacologists in the world are [disappointed] when we don't do these genotypes, because they spent their whole career developing this association and now clinicians are [less enthusiastic] about it. That will probably change in the next generation.

[1]Wellmann R, et al. Cancer 2018;124(14):3052-65


- ✓ Incremento en la evidencia disponible sobre alteraciones genéticas germinales con impacto terapéutico




- ✓ Implicación Agencias reguladoras

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agencia española de medicamentos y productos sanitarios

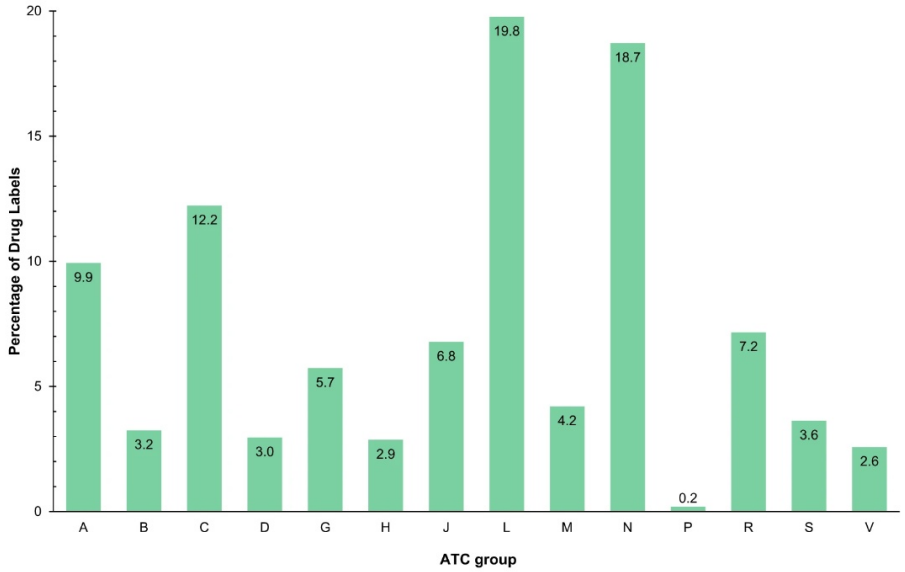
ARTICLE

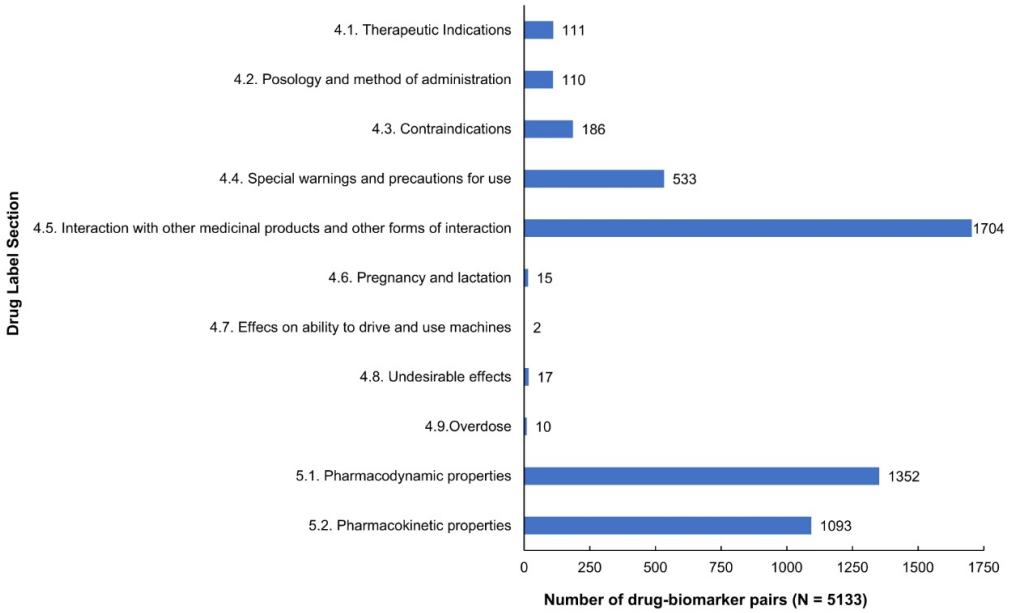
Check for updates

# Pharmacogenomic biomarker information on drug labels of the Spanish Agency of Medicines and Sanitary products: evaluation and comparison with other regulatory agencies

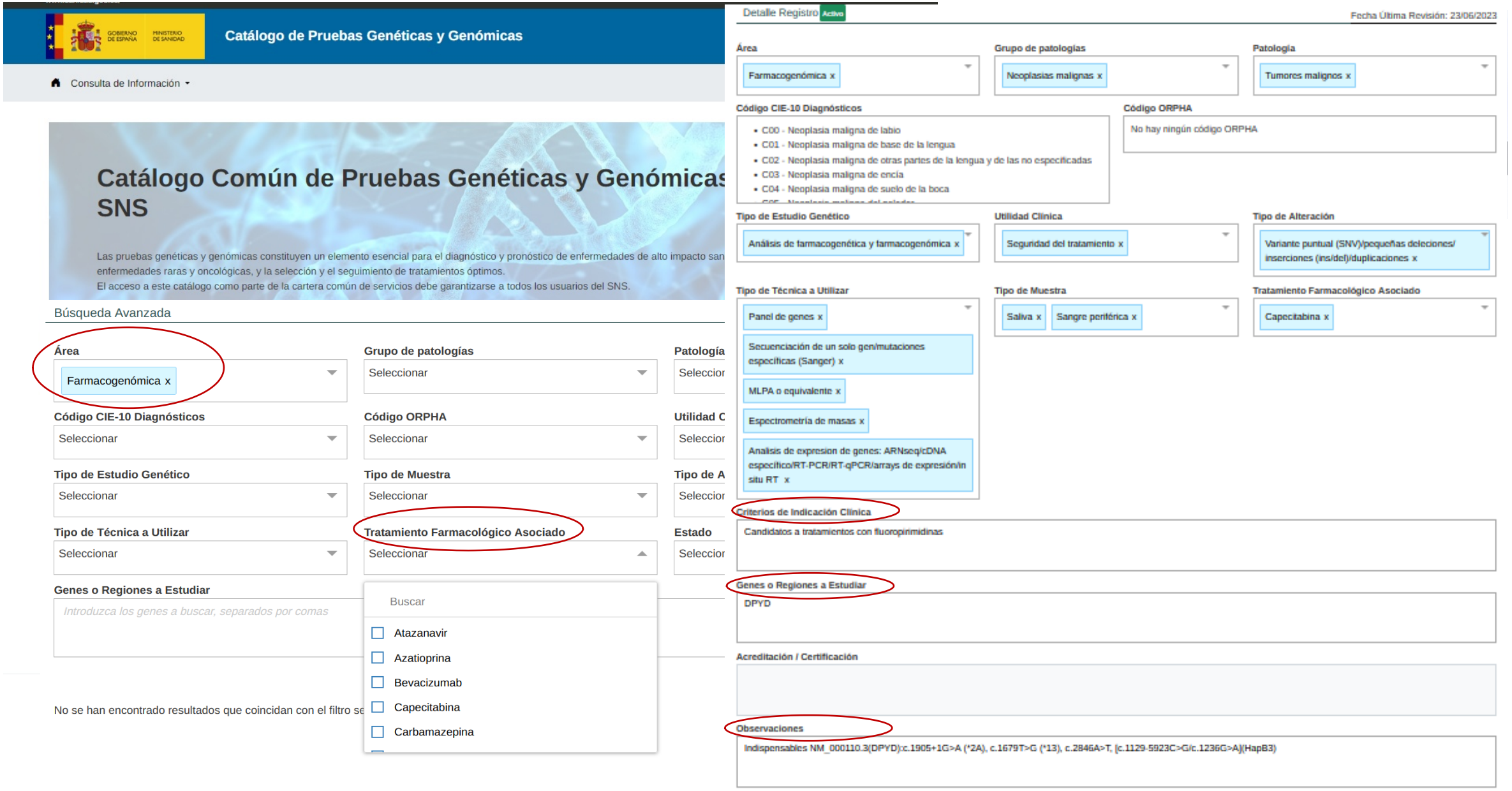
María Estévez-Paredes[1,2], M. Carmen Mata-Martín[1,2], Fernando de Andrés[1,2,3] and Adrián LLerena[1,2,4]✉

- 55,4% FT incluyen información sobre biomarcadores farmacogenéticos
- 509 biomarcadores farmacogenéticos distintos

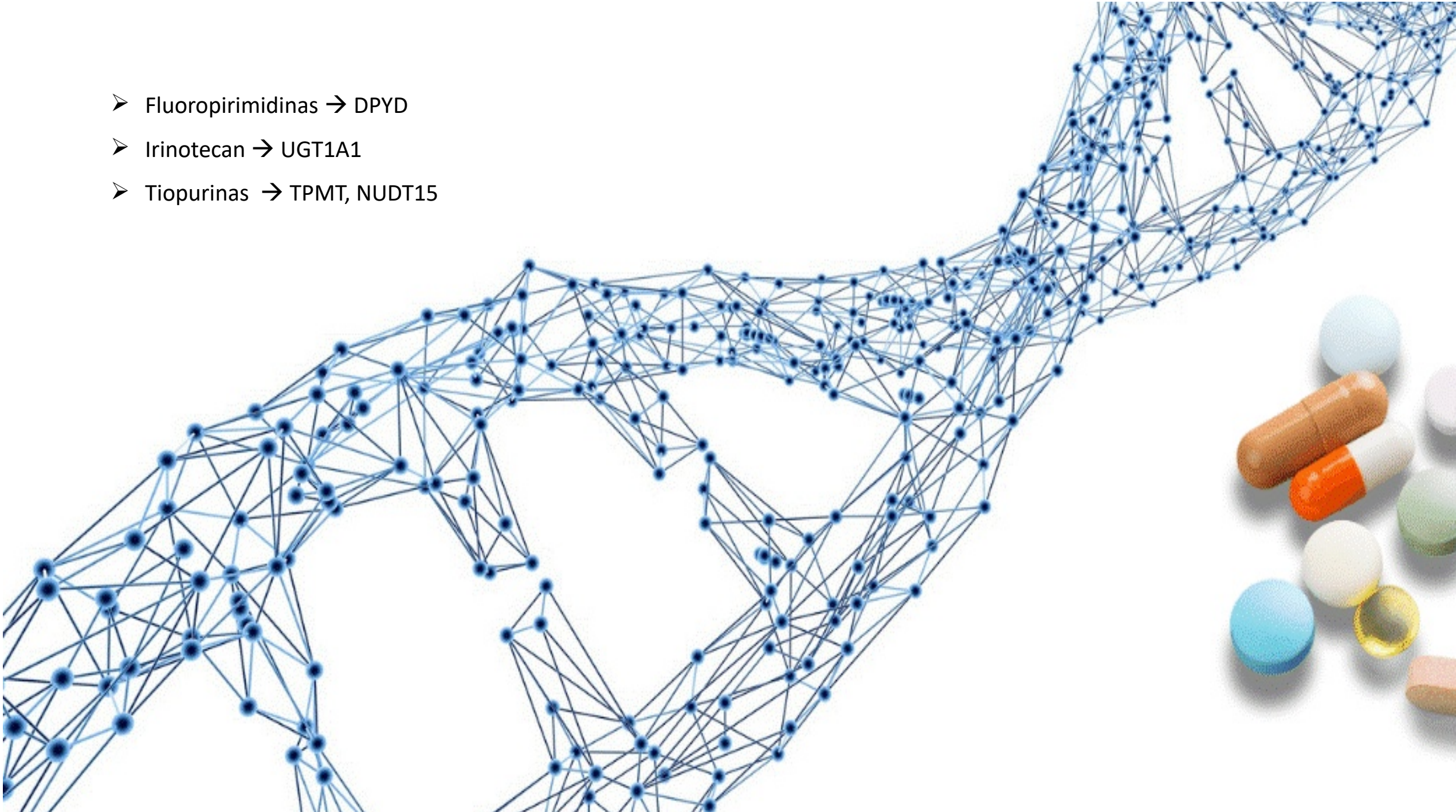



Estevez-Paredes M, et al. Pharmacogenomics Journal 2024;24(2):1-11


Catálogo de Pruebas Genéticas y Genómicas
Consulta de Información
Catálogo Común de Pruebas Genéticas y Genómicas SNS
Las pruebas genéticas y genómicas constituyen un elemento esencial para el diagnóstico y pronóstico de enfermedades de alto impacto san
enfermedades raras y oncológicas, y la selección y el seguimiento de tratamientos óptimos.
El acceso a este catálogo como parte de la cartera común de servicios debe garantizarse a todos los usuarios del SNS.
Búsqueda Avanzada
Área
Farmacogenómica x
Grupo de patologías
Seleccionar
Patología
Código CIE-10 Diagnósticos
Código ORPHA
Utilidad C
Tipo de Estudio Genético
Tipo de Muestra
Tipo de A
Tipo de Técnica a Utilizar
Tratamiento Farmacológico Asociado
Estado
Genes o Regiones a Estudiar
Introduzca los genes a buscar, separados por comas
Buscar
Atazanavir
Azatioprina
Bevacizumab
Capecitabina
Carbamazepina
No se han encontrado resultados que coincidan con el filtro se
Detalle Registro
Activo
Fecha Última Revisión: 23/06/2023
Área
Farmacogenómica x
Grupo de patologías
Neoplasias malignas x
Patología
Tumores malignos x
Código CIE-10 Diagnósticos
C00 - Neoplasia maligna de labio
C01 - Neoplasia maligna de base de la lengua
C02 - Neoplasia maligna de otras partes de la lengua y de las no especificadas
C03 - Neoplasia maligna de encía
C04 - Neoplasia maligna de suelo de la boca
Código ORPHA
No hay ningún código ORPHA
Tipo de Estudio Genético
Análisis de farmacogenética y farmacogenómica x
Utilidad Clínica
Seguridad del tratamiento x
Tipo de Alteración
Variante puntual (SNV)/pequeñas deleciones/inserciones (ins/del)/duplicaciones x
Tipo de Técnica a Utilizar
Panel de genes x
Secuenciación de un solo gen/mutaciones específicas (Sanger) x
MLPA o equivalente x
Espectrometría de masas x
Análisis de expresión de genes: ARNseq/cDNA específico/RT-PCR/RT-qPCR/arrays de expresión/in situ RT x
Tipo de Muestra
Saliva x
Sangre periférica x
Tratamiento Farmacológico Asociado
Capecitabina x
Criterios de Indicación Clínica
Candidatos a tratamientos con fluoropirimidinas
Genes o Regiones a Estudiar
DPYD
Acreditación / Certificación
Observaciones
Indispensables NM_000110.3(DPYD):c.1905+1G>A (*2A), c.1679T>G (*13), c.2846A>T, |c.1129-5923C>G/c.1236G>A)(HapB3)

- Fluoropirimidinas → DPYD
- Irinotecan → UGT1A1
- Tiopurinas → TPMT, NUDT15



# DPYD – Fluoropirimidinas

**Upfront Genotyping of *DPYD*2A* to Individualize Fluoropyrimidine Therapy: A Safety and Cost Analysis**

Authors: Maarten J. Deenen, Didier Meulendijks, Annemieke Cats, Marjolein K. Sechterberger, Johan L. Severens, Henk Boot, Paul H. Smits, Hilde Rosing,

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

Linda M Henricks, PharmD [a,b,†] · Carin A T C Lunenburg, MSc [c,†] · Femke M de Man, MD [d,†] · Didier Meulendijks, PharmD [a,b,e] · Geert W J Frederix, PhD [f] · Emma Kienhuis, BSc [d] · et al. Show more

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

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Fluorouracilo, capecitabina, tegafur y flucitosina en pacientes con déficit de dihidropirimidina deshidrogenasa

- Estudios prospectivos demostraron que el genotipado DPYD previo a la administración de fluoropirimidinas reducía la toxicidad y además era coste-efectivo
- En 2017 CPIC publica guía para genotipado y recomendaciones de dosificación
- En 2020 EMA y AEMPS recomiendan genotipado previo al inicio de tratamiento y se incorpora a práctica asistencial
- DPYD es altamente polimórfico en población española → variantes no funcionales en aproximadamente 4% de la población

| | Reducción Actividad Enzimática |
|---|---|
| c.1905+1G>A (*2A) | 50% Heteroc - 75% Homoc |
| c.1679T>G (*13) | [illegible]% Heteroc - 75% Homoc |
| c.2846A>T | 30% Heteroc - 39-59% Homoc |
| c.1236G>A | 35% Heteroc - 41-55% Homoc |

Deenen MJ et al. J Clin Oncol 2016;34(3):227-34
Henricks LM et al. Lancet Oncol 2018;19(11):1459-67
Nunez-Torres R et al. Pharmaceutics 2023;15:1286-99
https://files.cpicpgx.org/data/guideline/publication/fluoropyrimidines/2017/29152729.pdf

CPIC
Clinical Pharmacogenetics Implementation Consortium

**Table 1 Assignment of likely DPD phenotypes based on *DPYD* genotypes**

| Likely phenotype | Activity score[a] | Genotypes[b] | Examples of genotypes[c] |
|---|---|---|---|
| *DPYD* normal metabolizer | 2 | An individual carrying two normal function alleles. | c.[ = ];[ = ], c.[85T>C];[ = ], c.[1627A>G];[ = ] |
| *DPYD* intermediate metabolizer | 1 or 1.5 | An individual carrying one normal function allele plus one no function allele or one decreased function allele, or an individual carrying two decreased function alleles. | c.[1905+1G>A];[ = ], c.[1679T>G];[ = ], c.[2846A>T];[ = ]; c.[1129–5923C>G];[ = ][d]; c.[1129–5923C>G];[1129–5923C>G][d]; c.[2846A>T];[2846A>T] |
| *DPYD* poor metabolizer | 0 or 0.5 | An individual carrying two no function alleles or an individual carrying one no function plus one decreased function allele. | c.[1905+1G>A];[1905+1G>A], c.[1679T>G];[1679T>G], c.[1905+1G>A];[2846A> c.[1905+1G>A]; [1129-5 |

[a]Calculated as the sum of the two lowest individual variant activity scores. See text for further information. [b]Allele definitions, assignment of allele can be found on the CPIC website (*DPYD* Allele Functionality Table available at [ref 4]) [c]HGVS nomenclature using the reference sequence NM_000 causal variant. See *DPYD* Allele Functionality Table available at [ref 4] for other HapB3 proxy SNPs.

Table 1: Recommended dosing of fluoropyrimidines by genotype

*Adapted from Tables 1 and 2 of the 2017 guideline manuscript (November 2018 Update on Pharm*

| LIKELY PHENOTYPE | ACTIVITY SCORE[a] | GENOTYPES[b] | EXAMPLES OF GENOTYPES[c] | | | |
|---|---|---|---|---|---|---|
| *DPYD* Normal Metabolizer | 2 | An individual carrying two normal alleles | c.[=];[=], c.[85T>C[e]];[=], c.[1627A>G[f]];[=] | | | |
| *DPYD* Intermediate Metabolizer | 1 or 1.5 | An individual carrying one normal function allele plus one no function allele or one decreased function allele, or an individual carrying two decreased function alleles | c.[1905+1G>A[g]];[=], c.[1679T>G[h]];[=], c.[2846A>T[i]];[=]; c.[1129–5923C>G[j]];[=]; c.[1129–5923C>G];[1129–5923C>G]; c.[2846A>T];[2846A>T] | | | |
| *DPYD* Poor Metabolizer | 0 or 0.5 | An individual carrying two no function alleles or an individual carrying one no function plus one decreased function allele | c.[1905+1G>A];[1905+1G>A], c.[1679T>G];[1679T>G], c.[1905+1G>A];[2846A>T] c.[1905+1G>A];[1129-5923C>G] | increased risk for severe or even fatal drug toxicity when treated with fluoropyrimidine drugs | alternative agents are not considered a suitable therapeutic option, 5-fluorouracil should be administered at a strongly reduced dose[k] with early therapeutic drug monitoring.[l] Activity score 0: Avoid use of 5-fluorouracil or 5-fluorouracil prodrug-based regimens. | Strong |

## Consensus of experts from the Spanish Pharmacogenetics and Pharmacogenomics Society and the Spanish Society of Medical Oncology for the genotyping of *DPYD* in cancer patients who are candidates for treatment with fluoropyrimidines

P. García-Alfonso[1] · M. Saiz-Rodríguez[2] · R. Mondéjar[3] · J. Salazar[4] · D. Páez[5] · A. M. Borobia[6] · M. J. Safont[7] · I. García-García[6] · R. Colomer[8] · X. García-González[9] · M. J. Herrero[10] · L. A. López-Fernández[9] · F. Abad-Santos[11]

**Table 4** Dosing of fluoropyrimidines according to DPD phenotype based on genotype

| Phenotype | Genotype | Implications | Dosing recommendation |
|---|---|---|---|
| Normal metabolizer (Activity score 2) | Wild-type (absence of mutation) | Normal DPD activity and normal risk for fluoropyrimidine toxicity | According to the data sheet |
| Intermediate metabolizer (activity score 1–1.5) | Wild-type allele and mutated allele (*2A o *13 or c.2846A>T or HapB3)<br>Two mutated alleles (c.2846A>T or HapB3) | Decreased DPD activity (30–70%) and increased risk for severe or even fatal drug toxicity when treated with fluoropyrimidines | Reduce starting dose by 50% followed by titration of dose based on toxicity or pharmacokinetics |
| Poor metabolizer (Activity score 0–0.5) | Two mutated alleles (*2A or *13)<br>One mutated allele (*2A or *13) and one mutated allele (c.2846A>T or HapB3) | Complete or almost complete DPD deficiency and increased risk for severe or even fatal drug toxicity when treated with fluoropyrimidines | Contraindicated treatment with fluoropyrimidines; look for alternative agents* |

*5-FU* 5-fluorouracil, *CPIC* Clinical Pharmacogenetics Implementation Consortium, *DPD* dihydropyrimidine dehydrogenase

*In the event that alternative agents are not considered a suitable therapeutic option and patient has an activity score of 0,5, CPIC indicates that 5-FU could be administered at a strongly reduced dose (<25% of the normal dose) with early therapeutic drug monitoring of plasma concentration of 5-FU, to discontinue therapy if the drug level is too high [1]

https://doi.org/10.1007/s12094-021-02708-4

69 CONGRESO NACIONAL

# DPYD – Fluoropirimidinas

## Survival of Patients With Cancer With *DPYD* Variant Alleles and Dose-Individualized Fluoropyrimidine Therapy—A Matched-Pair Analysis

Jonathan E. Knikman, MSc[1,2]; Tycho A. Wilting, MSc[1]; Marta Lopez-Yurda, PhD[3]; Linda M. Henricks, PhD[4]; Carin A.T.C. Lunenburg, PhD[5]; Femke M. de Man, PhD[6]; Didier Meulendijks, PhD[1,7,8]; Peter Nieboer, PhD[9]; Helga J. Droogendijk, PhD[10]; Geert-Jan Creemers, PhD[11];

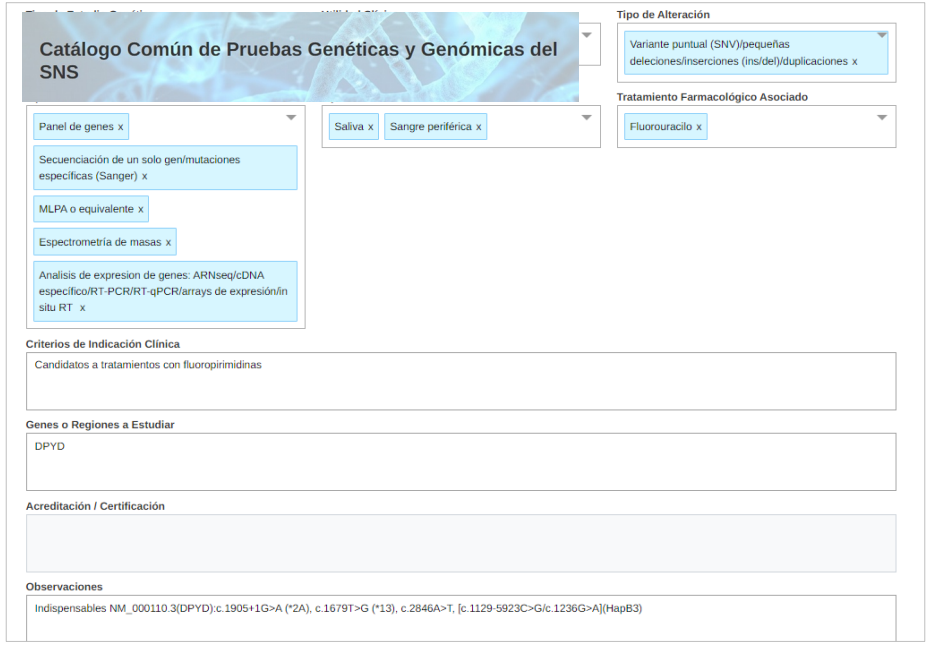
- Evaluó PFS y OS en portadores de variantes tratados con dosis reducidas de fluoropirimidinas
- Ni PFS ni OS se vieron afectadas por la dosis guiada por genotipado en pacientes portadores de variantes DPYD
- PFS más corta en portadores de la variante c.1236G>A

- Monitorizar estrechamente al paciente y...
  ...ajustar dosis en función de toxicidad

DOI https://doi.org/10.1200/JCO.22.02780

# DPYD – Fluoropirimidinas

- Otras variantes podrían tener repercusión importante en toxicidad




F24 | 5-fluorouracil (in vitro)

| | A | B | C | D | E |
|---|---|---|---|---|---|
| 1 | GENE: DPYD | | | | |
| 2 | Allele/cDNA/rsID | Activity Value (Optional) | Allele Biochemical Functional Status (Optional) | Allele Clinical Functional Status (Required) | Strength of Evidence (Required) |
| 3 | Reference | 1.0 | Normal function | Normal function | |
| 4 | c.46C>G | 1.0 | Normal function | Normal function | Limited |
| 5 | c.61C>T | 0.0 | No function | No function | Limited |
| 6 | c.62G>A | 1.0 | Normal function | Normal function | Moderate |
| 7 | c.85T>C (*9A) | 1.0 | Normal function | Normal function | Strong |
| 8 | c.295_298delTCAT (*7) | 0.0 | No function | No function | Moderate |
| 9 | c.313G>A | 1.0 | Normal function | Normal function | Limited |
| 10 | c.525G>A | 1.0 | Normal function | Normal function | Limited |
| 11 | c.557A>G | 0.5 | Decreased function | Decreased function | Moderate |
| 12 | c.601A>C | 0.0 | No function | No function | Limited |
| 13 | c.632A>G | 0.0 | No function | No function | Limited |
| 14 | c.703C>T (*8) | 0.0 | No function | No function | Moderate |
| 15 | c.775A>G | 1.0 | Normal function | Normal function | Limited |
| 16 | c.868A>G | 0.5 | Decreased function | Decreased function | Limited |
| 17 | c.929T>C | 1.0 | Normal function | Normal function | Limited |
| 18 | c.1003G>T (*11) | 1.0 | Normal function | Normal function | Moderate |
| 19 | c.1024G>A | 0.0 | No function | No function | Limited |
| 20 | c.1057C>T | 0.0 | No function | No function | Limited |
| 21 | c.1108A>G | 1.0 | Normal function | Normal function | Limited |
| 22 | c.1129-5923C>G | 0.5 | Decreased function | Decreased function | Strong |
| 23 | c.1129-5923C>G, c.1236G>A (HapB | 0.5 | Decreased function | Decreased function | Strong |
| 24 | c.1156G>T (*12) | 0.0 | No function | No function | Moderate |
| 25 | c.1181G>T | 1.0 | Normal function | Normal function | Limited |
| 26 | c.1218G>A | 1.0 | Normal function | Normal function | Moderate |
| 27 | c.1475C>T | 0.0 | No function | No function | Limited |
| 28 | c.1484A>G | 0.0 | No function | No function | Limited |
| 29 | c.1519G>A | 1.0 | Normal function | Normal function | Limited |
| 30 | c.1543G>A | 1.0 | Normal function | Normal function | Limited |
| 31 | c.1577C>G | 1.0 | Normal function | Normal function | Limited |
| 32 | c.1601G>A (*4) | 1.0 | Normal function | Normal function | Moderate |
| 33 | c.1627A>G (*5) | 1.0 | Normal function | Normal function | Strong |
| 34 | c.1679T>G (*13) | 0.0 | No function | No function | Moderate |
| 35 | c.1682G>T | 1.0 | Normal function | Normal function | Limited |
| 36 | c.1774C>T | 0.0 | No function | No function | Limited |
| 37 | c.1775G>A | 0.0 | No function | No function | Limited |
| 38 | c.1777G>A | 0.0 | No function | No function | Limited |
| 39 | c.1796T>C | 1.0 | Normal function | Normal function | Limited |
| 40 | c.1896T>C | 1.0 | Normal function | Normal function | Moderate |
| 41 | c.1898delC (*3) | 0.0 | No function | No function | Moderate |
| 42 | c.1905+1G>A (*2A) | 0.0 | No function | No function | Strong |
| 43 | c.1905C>G | 1.0 | Normal function | Normal function | Limited |
| 44 | c.2021G>A | 0.0 | No function | No function | Limited |
| 45 | c.2161G>A | 1.0 | Normal function | Normal function | Limited |

Allele Function | Column Definitions | Notes | Change log

# DPYD – Fluoropirimidinas



Published in final edited form as:
*Clin Pharmacol Ther*. 2013 July ; 94(1): 158–166. doi:10.1038/clpt.2013.69.

## A *DPYD* variant (Y186C) in individuals of African ancestry associated with reduced DPD enzyme activity

**Steven M. Offer**[1], **Adam M. Lee**[1], **Lori K. Mattison**[1,2], **Croix Fossum**[1], **Natalie J. Wegner**[1], and **Robert B. Diasio**[1,*]

[1]Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Clinic Cancer Center, Rochester, MN, U.S.A

and head & neck. The responses to 5-FU, both toxicity and efficacy, vary between racial groups, potentially due to variability in enzyme activity of dihydropyrimidine dehydrogenase (DPD, encoded by *DPYD*). In the present study, the genetic associations between *DPYD* variations and circulating mononuclear cell DPD enzyme activity were evaluated in 94 African American and 81 European American volunteers. The *DPYD-Y186C* variant was unique to individuals of African ancestry, and DPD activity was 46% reduced in carriers compared to non-carriers (279±35 compared to 514±168 pmol 5-FU $min^{-1}$ $mg^{-1}$; $P$=0.00029). 26% of the African Americans with reduced DPD activity in this study carried Y186C. In the African American cohort, following exclusion of Y186C carriers, homozygous carriers of C29R showed 27% higher DPD activity compared to non-carriers (609±152 and 480±152 pmol 5-FU $min^{-1}$ $mg^{-1}$, respectively; $P$=0.013).

Offer ST et al. Clin Pharmacol Ther. 2013 July ; 94(1): 158–166.

## Novel Genetic Variants Explaining Severe Adverse Drug Events after Clinical Implementation of *DPYD* Genotype-Guided Therapy with Fluoropyrimidines: An Observational Study

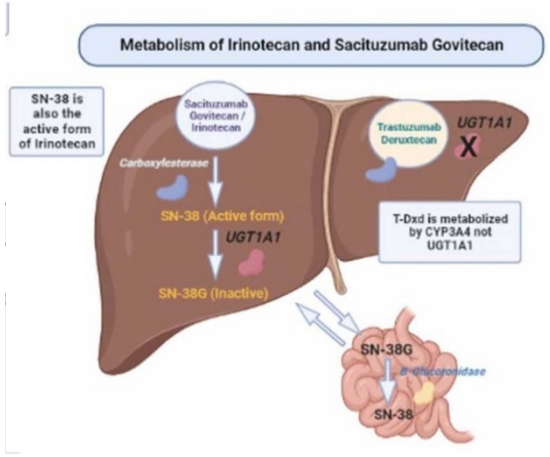
**Xando Díaz-Villamarín [1,*,†], María Martínez-Pérez [2,†], María Teresa Nieto-Sánchez [2], Gabriela Ruiz-Tueros [1], Emilio Fernández-Varón [1,3], Alicia Torres-García [1], Beatriz González Astorga [1,4], Isabel Blancas [1,4], Antonio J. Iáñez [5], José Cabeza-Barrera [1,2] and Rocío Morón [1,2]**

1 Instituto de Investigación Biosanitaria de Granada (Ibs.Granada), 18012 Granada, Spain
2 Hospital Pharmacy, Hospital Universitario San Cecilio, 18016 Granada, Spain
3 Department of Pharmacology, Center for Biomedical Research (CIBM), University of Granada, 18016 Granada, Spain
4 Medical Oncology, Hospital Universitario San Cecilio, 18016 Granada, Spain

implemented the *DPYD* genotyping in our daily clinical routine, but we still found patients showing severe adverse drug events (ADEs) to FPs. We studied among these patients the *DPYD* rs1801265, rs17376848, rs1801159, rs1801160, rs1801158, and rs2297595 as explanatory candidates of the interindividual differences for FP-related toxicities, examining the association with the response to FPs . We also studied the impact of *DPYD* testing for FP dose tailoring in our clinical practice and characterized the *DPYD* gene in our population. We found a total acceptance among physicians of therapeutic recommendations translated from the *DPYD* test, and this dose tailoring does not affect the treatment efficacy. We also found that the *DPYD**4 (defined by rs1801158) allele is associated with a higher risk of ADEs (severity grade $\geq$ 3) in both the univariate (O.R. = 5.66; 95% C.I. = 1.35–23.67; $p$ = 0.014) and multivariate analyses (O.R. = 5.73; 95% C.I. = 1.41–28.77; $p$ = 0.019) among FP-treated patients based on the *DPYD* genotype. This makes it a candidate variant for implementation in clinical practice.

Doi.org/10.3390/pharmaceutics16070956

# UGT1A1 – Irinotecan




- Distintos polimorfismos genéticos en UGT1A1 conllevan función enzimática reducida (baja actividad en el proceso de glucuronidación)
- Varios alelos implicados, el más importante alelo *28 (también *6)
- Pacientes UGT1A1 *28/*28 presentan mayor toxicidad
- 30-40% individuos alelo *28, 10-15% homocigotos

**Catálogo Común de Pruebas Genéticas y Genómicas del SNS**

**Criterios de Indicación Clínica**

Candidatos a tratamiento con irinotecan

**Genes o Regiones a Estudiar**

UGT1A1

**Acreditación / Certificación**

**Observaciones**

Indispensable UGT1A1*28. Uso secundario de la información obtenida: este genotipado (UGT1A1) puede ser útil para el ajuste de tratamientos de sacituzumab-govitecan

agencia española de medicamentos y productos sanitarios

**Datos farmacocinéticos/farmacodinámicos**

La intensidad de las principales toxicidades obtenidas con irinotecán (p.ej, leuconeutropenia y diarrea), está relacionada con la exposición (AUC) al fármaco y al metabolito SN-38. En monoterapia, se observaron correlaciones significativas entre la toxicidad hematológica (disminución de glóbulos blancos y neutrófilos en el nadir) o la intensidad de la diarrea y los valores de AUC del irinotecán y del metabolito SN-38.

*Pacientes con actividad UGT1A1 reducida*

La uridina-difosfoglucuronosil transferasa 1A1 (UGT1A1) participa en la desactivación metabólica del SN-38, el metabolito activo de irinotecán, a glucurónido SN-38 inactivo (SN-38G). El gen UGT1A1 es altamente polimórfico, lo que da lugar a una gran variabilidad de capacidades metabólicas entre individuos. Una variación específica del gen UGT1A1 incluye un polimorfismo en la región del promotor y se conoce como variante UGT1A1*28. Esta variante y otras deficiencias congénitas en la expresión del gen UGT1A1 (como el síndrome de Crigler-Najjar y el síndrome de Gilbert) se asocian con una reducción de la actividad de la enzima. Datos de un metanálisis indican que los individuos con el síndrome de Crigler-Najjar (tipos 1 y 2) y los individuos homocigotos para el alelo UGT1A1*28 (síndrome de Gilbert) presentan un mayor riesgo de toxicidad hematológica (grados 3 y 4) tras la administración de irinotecán en dosis moderadas o altas (> 150 mg/m$^2$). No se estableció relación entre el genotipo UGT1A1 y la aparición de diarrea inducida por irinotecán.

A los pacientes homocigotos para el alelo UGT1A1*28 se les debe administrar la dosis inicial normal de irinotecán. Sin embargo, estos pacientes deben ser vigilados para detectar posibles reacciones adversas hematológicas. Se debe considerar una reducción de la dosis inicial de irinotecán en pacientes que hayan experimentado previamente reacciones adversas hematológicas con el tratamiento anterior. No se ha establecido la reducción exacta de la dosis para esta población de pacientes, y cualquier modificación posterior de la dosis debe basarse en la tolerancia del paciente al tratamiento (ver secciones 4.2 y 4.4.).

Por el momento no existen datos suficientes para extraer conclusiones acerca de la utilidad del genotipado del UGT1A1.

PHARMGKB

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# Annotation of FDA Label for irinotecan and UGT1A1

Testing Recommended | Dosing Info | Other Guidance | Prescribing Info | FDA Biomarker

**PharmGKB ID :** PA166104831

## Variants Discussed on Label

UGT1A1*28, UGT1A1*6

## Summary

The FDA-approved drug label for irinotecan (CAMPTOSAR) states that a reduc
should be considered for patients known to be homozygous for the UGT1A1*
label recommends to consider UGT1A1 genotype testing for the *28 and *6 al
approved drug label for irinotecan liposome injection (ONIVYDE) contains lan
homozygous for the UGT1A1*28 allele, but does not have a genotype testing

## Prescribing

Excerpt from the irinotecan (CAMPTOSAR) label:

> 2.3 Dosage in Patients With Reduced UGT1A1 Activity When administered ir
> consider a reduction in the starting dose by at least one level of CAMPTOSA
> or *6 alleles (*28/*28, *6/*6) or compound heterozygous for the UGT1A1*28
> may be required based on individual patient tolerance to treatment.

> Individuals who are heterozygous for either the UGT1A1*28 or *6 alleles (*1/*6, *1/*28) are UGT1A1 intermediate metabolizers and may also have an increased risk of severe or life-threatening neutropenia. Published studies have shown that individuals with UGT1A1*28 and *6 alleles may be at an increased risk of severe diarrhea.

> Closely monitor patients with UGT1A1*28 or *6 alleles for neutropenia during and after treatment with CAMPTOSAR.

Excerpt from the irinotecan (ONIVYDE) drug label:

> In combination with fluorouracil and leucovorin for the treatment of patients with metastatic pancreatic adenocarcinoma after disease progression following gemcitabine-based therapy [...]
>
> - The recommended dosage of ONIVYDE is 70 mg/m2 administered by intravenous infusion over 90 minutes every 2 weeks.
> - The recommended starting dose of ONIVYDE in patients known to be homozygous for the UGT1A1*28 allele is 50 mg/m2 administered by intravenous infusion over 90 minutes. Increase the dose of ONIVYDE to 70 mg/m2 as tolerated in subsequent cycles.

- Considerar reducción dosis irinotecan para pacientes homocigotos *28 o *6
- Pacientes heterocigotos (metabolizadores intermedios) podrían tener riesgo incrementado de neutropenia grave
- Irinotecan liposomal → 50 mg/m² en homocigotos *28 (incrementar a 70 mg/m² según tolerancia)

PHARMGKB

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# Annotation of EMA Label for irinotecan and UGT1A1

Actionable PGx | Dosing Info | Prescribing Info

**PharmGKB ID :** PA166182952

## Variants Discussed on Label

UGT1A1*28

## Summary

ent Report (EPAR) for irinotecan (ONIVYDE) states that a reduced starting dose of 50 mg/m2 should be
5T1A1*28/*28 genotype, with a dose increase to 70 mg/m2 if tolerated in subsequent cycles. Individuals
are at increased risk for neutropenia.

DE (liposomal irinotecan) of 50 mg/m2 should be considered for patients known to be homozygous for
ase of ONIVYDE to 70 mg/m2 should be considered if tolerated in subsequent cycles."

Excerpts from the irinotecan (ONIVYDE) EPAR:

> A reduced starting dose of ONIVYDE (liposomal irinotecan) of 50 mg/m2 should be considered for patients known to be homozygous for the UGT1A1*28 allele...A dose increase of ONIVYDE to 70 mg/m2 should be considered if tolerated in subsequent cycles.

> Individuals who are 7/7 homozygous for the UGT1A1*28 allele are at increased risk for neutropenia from non-liposomal irinotecan. In the clinical study evaluating ONIVYDE+5-FU/LV, the frequency of = Grade 3 neutropenia in these patients (2 of 7 (28.6%)) was similar to the frequency in patients not homozygous for the UGT1A1*28 allele who received a starting dose of ONIVYDE of 70 mg/m2 (30 of 110 (27.3%))...

> UGT1A1 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity such as the UGT1A1*28 polymorphism. In the population pharmacokinetic analysis in patients with ONIVYDE using the results of a subset with UGT1A1*28 genotypic testing, in which the analysis adjusted for the lower dose administered to patients homozygous for the UGT1A1*28 allele, patients homozygous (N=14) and non-homozygous (N=244) for this allele had total SN-38 average steady-state concentrations of 1.06 and 0.95 ng/ml, respectively.

For the complete EPAR text with sections containing pharmacogenetic information highlighted, see the irinotecan EPAR PDF

REVIEW ARTICLE

# Dutch pharmacogenetics working group (DPWG) guideline for the gene–drug interaction between *UGT1A1* and irinotecan

Emma C. Hulshof[1,2,20], Maarten J. Deenen[1,2,20], Marga Nijenhuis[3✉], Bianca Soree[3], Nienke J. de Boer-Veger[4], Anne-Marie Buunk[5], Elisa J. F. Houwink[6,7], Arne Risselada[8], Gerard A. P. J. M. Rongen[9,10], Ron H. N. van Schaik[11], Daan J. Touw[12,13], Jan van der Weide[14], Roos van Westrhenen[15,16,17], Vera H. M. Deneer[18,19], Henk-Jan Guchelaar[2,21] and Jesse J. Swen[2,21]

**Table 1.** Genotype-phenotype translation.

| Genotype | | Phenotype predicted based on genotype |
|---|---|---|
| **Description** | **Examples** | |
| two alleles with normal (or increased) enzyme activity | *1/*1, *1/*36 | NM |
| *28 and one allele with normal (or increased) enzyme activity | *1/*28, *28/*36 | IM (*1/*28) |
| one allele with decreased enzyme activity other than *28 and one allele with normal (or increased) enzyme activity | *1/*6, *1/*37, *36/*37 | IM other |
| two *28 alleles | *28/*28 | PM (*28/*28) |
| two alleles with decreased enzyme activity, of which at least one is not *28 | *6/*6, *6/*28, *28/*37 | PM other |

*NM* normal metaboliser, *IM* intermediate metaboliser, *PM* poor metaboliser.

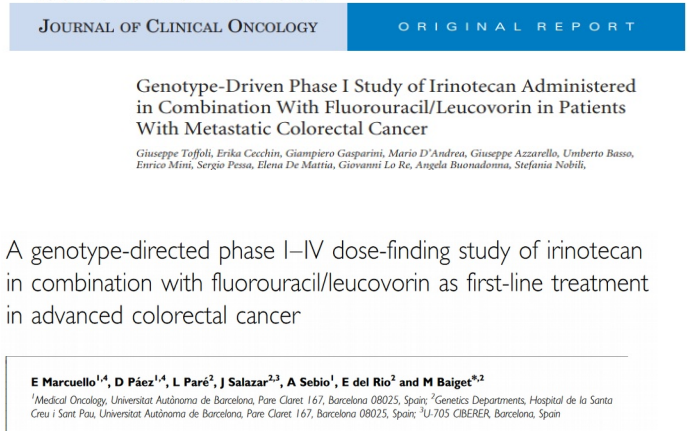
**Table 2.** Summary therapeutic recommendations based on *UGT1A1* predicted phenotype for irinotecan.

| ***UGT1A1* predicted phenotype** | **Therapeutic recommendation** |
|---|---|
| PM (*28/*28) | Start with 70% of the normal dose[a]. If the patient tolerates this initial dose, the dose can be increased, guided by the neutrophil count. |
| PM other | Start with 70% of the normal dose[a]. If the patient tolerates this initial dose, the dose can be increased, guided by the neutrophil count. |
| IM (*1/*28) | No action required. |
| IM other | No action required. |

*IM* intermediate metaboliser, *PM* poor metaboliser.
[a]The normal dose is defined as the dose the patient would receive if he/she would not have a gene variant.

Hulshof E et al. Eur J Hum Genet 2023;31:982-87

# UGT1A1 – Irinotecan


JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

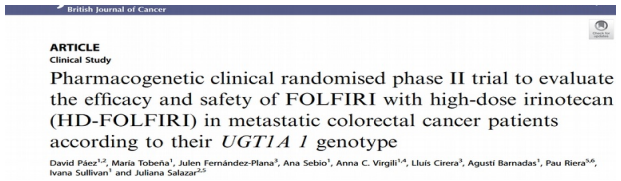
Genotype-Driven Phase I Study of Irinotecan Administered in Combination With Fluorouracil/Leucovorin in Patients With Metastatic Colorectal Cancer

Giuseppe Toffoli, Erika Cecchin, Giampiero Gasparini, Mario D'Andrea, Giuseppe Azzarello, Umberto Basso, Enrico Mini, Sergio Pessa, Elena De Mattia, Giovanni Lo Re, Angela Buonadonna, Stefania Nobili,


A genotype-directed phase I–IV dose-finding study of irinotecan in combination with fluorouracil/leucovorin as first-line treatment in advanced colorectal cancer

E Marcuello[1,4], D Páez[1,4], L Paré[2], J Salazar[2,3], A Sebio[1], E del Rio[2] and M Baiget*[,2]

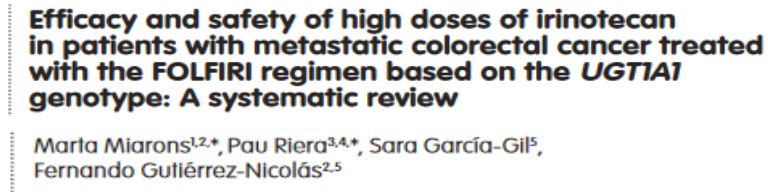
[1]Medical Oncology, Universitat Autònoma de Barcelona, Pare Claret 167, Barcelona 08025, Spain; [2]Genetics Departments, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Pare Claret 167, Barcelona 08025, Spain; [3]U-705 CIBERER, Barcelona, Spain


British Journal of Cancer

ARTICLE
Clinical Study

Pharmacogenetic clinical randomised phase II trial to evaluate the efficacy and safety of FOLFIRI with high-dose irinotecan (HD-FOLFIRI) in metastatic colorectal cancer patients according to their *UGT1A 1* genotype

David Páez[1,2], María Tobeña[1], Julen Fernández-Plana[3], Ana Sebio[1], Anna C. Virgili[1,4], Lluís Cirera[3], Agustí Barnadas[3], Pau Riera[5,6], Ivana Sullivan[1] and Juliana Salazar[2,5]


**Efficacy and safety of high doses of irinotecan in patients with metastatic colorectal cancer treated with the FOLFIRI regimen based on the *UGT1A1* genotype: A systematic review**

Marta Miarons[1,2,*], Pau Riera[3,4,*], Sara García-Gil[5], Fernando Gutiérrez-Nicolás[2,5]

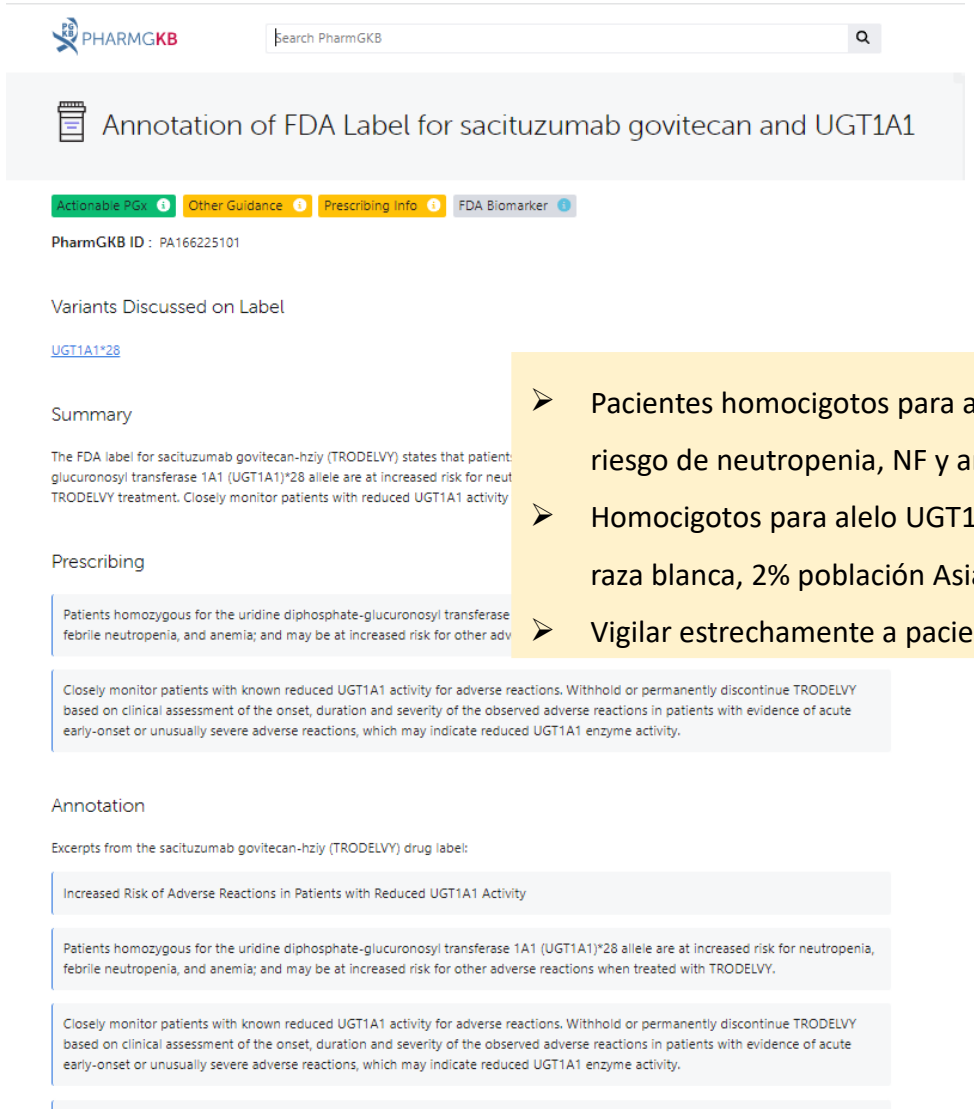
- Pacientes con genotipo wild-type (*1/*1) y *1/*28 (metabolizadores intermedios) toleran dosis de hasta 370 mg/m² y 310 mg/m² respectivamente → 180 mg/m² de irinotecan (Folfiri) es considerablemente menor que la dosis tolerada en estos grupos de pacientes

- Escalado de dosis con Folfiri según genotipo UGT1A1 (incluidos pac homocigotos *28). Las DMT de irinotecan en pacientes con genotipo *28/*28 fueron un 30% menores que las estándar de 180 mg/m²

- Folfiri estándar vs Folfiri-Altas dosis (irinotecan 300 mg/m² para *1/*1, 260 mg/m² para *1/*28. No diferencias en toxicidades graves (22,5% vs 20,5%). Tasa de respuesta significativamente superiores en pacientes tratados con Folfiri-Altas dosis (67,5% vs 43,6%). No diferencias en PFS (mPFS 8,2 vs 8,6 m)

- Dosis >180 mg/m² son bien toleradas por la mayoría de pacientes (UGT1A!*1/*1 y *1/*28). Estudios favorables al aumento de dosis en términos de TRO y SLP

# UGT1A1 – Sacituzumab govitecan


PHARMGKB

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Annotation of FDA Label for sacituzumab govitecan and UGT1A1

Actionable PGx | Other Guidance | Prescribing Info | FDA Biomarker

**PharmGKB ID :** PA166225101

Variants Discussed on Label

UGT1A1*28

Summary

The FDA label for sacituzumab govitecan-hziy (TRODELVY) states that patients glucuronosyl transferase 1A1 (UGT1A1)*28 allele are at increased risk for neut TRODELVY treatment. Closely monitor patients with reduced UGT1A1 activity

Prescribing

Patients homozygous for the uridine diphosphate-glucuronosyl transferase febrile neutropenia, and anemia; and may be at increased risk for other adv

Closely monitor patients with known reduced UGT1A1 activity for adverse reactions. Withhold or permanently discontinue TRODELVY based on clinical assessment of the onset, duration and severity of the observed adverse reactions in patients with evidence of acute early-onset or unusually severe adverse reactions, which may indicate reduced UGT1A1 enzyme activity.

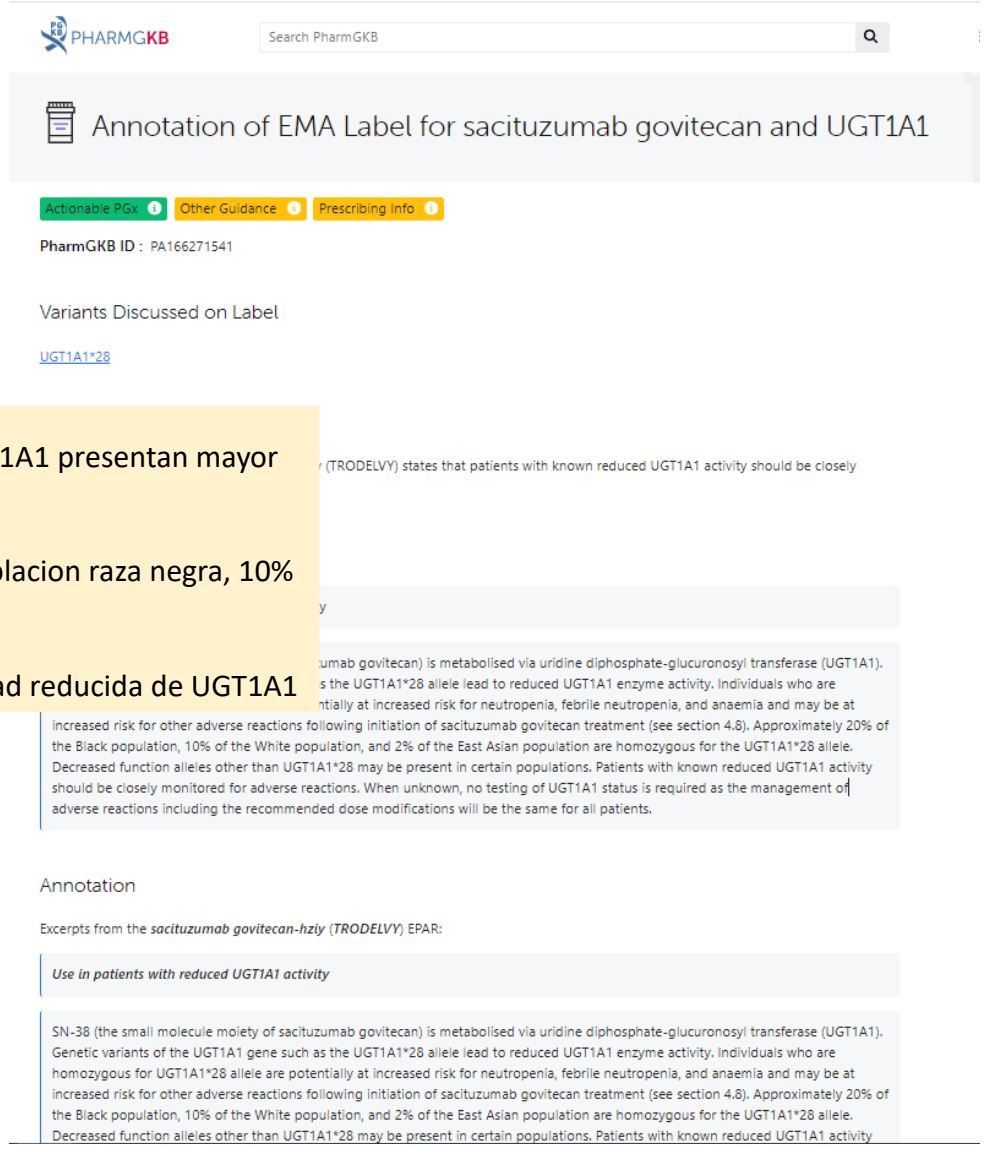
Annotation

Excerpts from the sacituzumab govitecan-hziy (TRODELVY) drug label:

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.

Closely monitor patients with known reduced UGT1A1 activity for adverse reactions. Withhold or permanently discontinue TRODELVY based on clinical assessment of the onset, duration and severity of the observed adverse reactions in patients with evidence of acute early-onset or unusually severe adverse reactions, which may indicate reduced UGT1A1 enzyme activity.


PHARMGKB

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Annotation of EMA Label for sacituzumab govitecan and UGT1A1

Actionable PGx | Other Guidance | Prescribing Info

**PharmGKB ID :** PA166271541

Variants Discussed on Label

UGT1A1*28

(TRODELVY) states that patients with known reduced UGT1A1 activity should be closely

umab govitecan) is metabolised via uridine diphosphate-glucuronosyl transferase (UGT1A1). s the UGT1A1*28 allele lead to reduced UGT1A1 enzyme activity. Individuals who are ntially at increased risk for neutropenia, febrile neutropenia, and anaemia and may be at increased risk for other adverse reactions following initiation of sacituzumab govitecan treatment (see section 4.8). Approximately 20% of the Black population, 10% of the White population, and 2% of the East Asian population are homozygous for the UGT1A1*28 allele. Decreased function alleles other than UGT1A1*28 may be present in certain populations. Patients with known reduced UGT1A1 activity should be closely monitored for adverse reactions. When unknown, no testing of UGT1A1 status is required as the management of adverse reactions including the recommended dose modifications will be the same for all patients.

Annotation

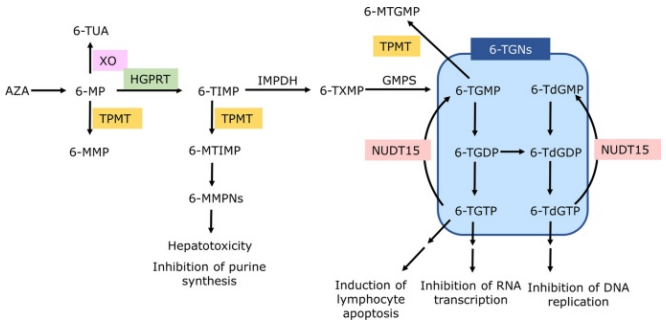
Excerpts from the ***sacituzumab govitecan-hziy*** (***TRODELVY***) EPAR:

***Use in patients with reduced UGT1A1 activity***

SN-38 (the small molecule moiety of sacituzumab govitecan) is metabolised via uridine diphosphate-glucuronosyl transferase (UGT1A1). Genetic variants of the UGT1A1 gene such as the UGT1A1*28 allele lead to reduced UGT1A1 enzyme activity. Individuals who are homozygous for UGT1A1*28 allele are potentially at increased risk for neutropenia, febrile neutropenia, and anaemia and may be at increased risk for other adverse reactions following initiation of sacituzumab govitecan treatment (see section 4.8). Approximately 20% of the Black population, 10% of the White population, and 2% of the East Asian population are homozygous for the UGT1A1*28 allele. Decreased function alleles other than UGT1A1*28 may be present in certain populations. Patients with known reduced UGT1A1 activity

- Pacientes homocigotos para alelo *28 de UGT1A1 presentan mayor riesgo de neutropenia, NF y anemia
- Homocigotos para alelo UGT1A1*28: 20% poblacion raza negra, 10% raza blanca, 2% población Asia oriental
- Vigilar estrechamente a pacientes con actividad reducida de UGT1A1

# TPMT, NUDT15 – Tiopurinas




- Forman parte de esquemas para tratamiento de LLA
- TPMT (tiopurina-S-metiltransferasa) y NUDT15 (Nudix-hidrolasa) inactivan tiopurias
- Variantes no funcionales de TPMT y NUDT15 inducen mielosupresión, a veces con consecuencias muy graves

- TPMT → *2, *3A, *3C
  10-12% portadores heterocigotos
  0.1-0.3% portadores homocigotos
- Polimorfismos NUDT15 (rs11655232) incrementan la toxicidad (tolerancia <10% dosis estándar en homocigotos)

**Table 1 Assignment of likely TPMT and NUDT15 phenotypes based on genotypes**

| Likely phenotype[a] | Genotypes | Examples of diplotypes |
|---|---|---|
| Assignment of likely TPMT phenotypes based on genotypes | | |
| Normal metabolizer | An individual carrying two normal function alleles | *1/*1 |
| Intermediate metabolizer | An individual carrying one normal function allele PLUS one no function allele | *1/*2, *1/*3A, *1/*3B, *1/*3C, *1/*4 |
| Possible intermediate metabolizer | An individual carrying one uncertain/unknown function allele PLUS one no function allele | *2/*8, *3A/*7 |
| Poor metabolizer | An individual carrying two no function alleles | *3A/*3A, *2/*3A, *3A/*3C, *3C/*4, *2/*3C, *3A/*4 |
| Indeterminate | An individual carrying two uncertain/unknown function alleles OR one normal function allele plus one uncertain allele function allele | *6/*8 *1/*8 |
| Assignment of likely NUDT15 phenotypes based on genotypes | | |
| Normal metabolizer | An individual carrying two normal function alleles | *1/*1 |
| Intermediate metabolizer | An individual carrying one normal function allele PLUS one no function allele | *1/*2, *1/*3 |
| Possible intermediate metabolizer | An individual carrying one uncertain function allele PLUS one no function allele | *2/*5, *3/*6 |
| Poor metabolizer | An individual carrying two no function alleles | *2/*2, *2/*3, *3/*3 |
| Indeterminate | An individual carrying two uncertain function alleles OR one normal function allele plus one uncertain function allele | *1/*4, *1/*5 *4/*5, *5/*6 |

TPMT, thiopurine methyltransferase. NUDT15, Nudix (Nucleoside Diphosphate Linked Moiety X)-Type Motif 15
[a]See **TPMT and NUDT15 Frequency Table and Diplotype-Phenotype Table**[21–23] for estimates of phenotype frequencies among different ethnic/geographic groups and for a more comprehensive list of predicted metabolizer phenotypes.

https://files.cpicpgx.org/data/guideline/publication/thiopurines/2018/30447069.pdf

# Clinical Pharmacogenetics Implementation Consortium Guideline for Thiopurine Dosing Based on *TPMT* and *NUDT*15 Genotypes: 2018 Update

Mary V. Relling[1], Matthias Schwab[2,3,4], Michelle Whirl-Carrillo[5], Guilherme Suarez-Kurtz[6], Ching-Hon Pui[7], Charles M. Stein[8], Ann M. Moyer[9], William E. Evans[1], Teri E. Klein[4], Federico Guillermo Antillon-Klussmann[10,11], Kelly E. Caudle[1], Motohiro Kato[12], Allen E.J. Yeoh[13,14], Kjeld Schmiegelow[15,16] and Jun J. Yang[1]

**Table 2 Recommended dosing of thiopurines by TPMT phenotype**

| | Mercaptopurine | | | Azathioprine | | Thioguanine | | |
|---|---|---|---|---|---|---|---|---|
| Phenotype | Implications for mercaptopurine and azathioprine phenotypic measures | Dosing recommendations for mercaptopurine | Classification of recommendations | Dosing recommendations for azathioprine | Classification of recommendations | Implications for thioguanine phenotypic measures | Dosing recommendations for thioguanine | Classification of recommendations[b] |
| TPMT normal metabolizer | Lower concentrations of TGN metabolites, higher MeTIMP, this is the "normal" pattern. Normal risk of thiopurine-related leukopenia, neutropenia, myelosuppression. | Start with normal starting dose[a] (e.g., 75 mg/m$^2$/day or 1.5 mg/kg/day) and adjust doses of mercaptopurine (and of any other myelosuppressive therapy) without any special emphasis on mercaptopurine compared with other agents. Allow at least 2 weeks to reach steady-state after each dose adjustment.[4,27,30] | Strong | Start with normal starting dose[a] (e.g., 2–3 mg/kg/day) and adjust doses of azathioprine based on disease-specific guidelines. Allow 2 weeks to reach steady-state after each dose adjustment.[4,30,37] | Strong | Lower concentrations of TGN metabolites, but note that TGN after thioguanine are 5–10 × higher than TGN after mercaptopurine or azathioprine. Normal risk of thiopurine-related leukopenia, neutropenia, myelosuppression. | Start with normal starting dose[a] (e.g., 40–60 mg/m$^2$/day) and adjust doses of thioguanine and of other myelosuppressive therapy without any special emphasis on thioguanine. Allow 2 weeks to reach steady-state after each dose adjustment.[4,18] | Strong |
| TPMT | Moderate to high | Start with reduced starting | Strong | Start with reduced | Strong | Moderate to high | Start with reduced | Moderate |

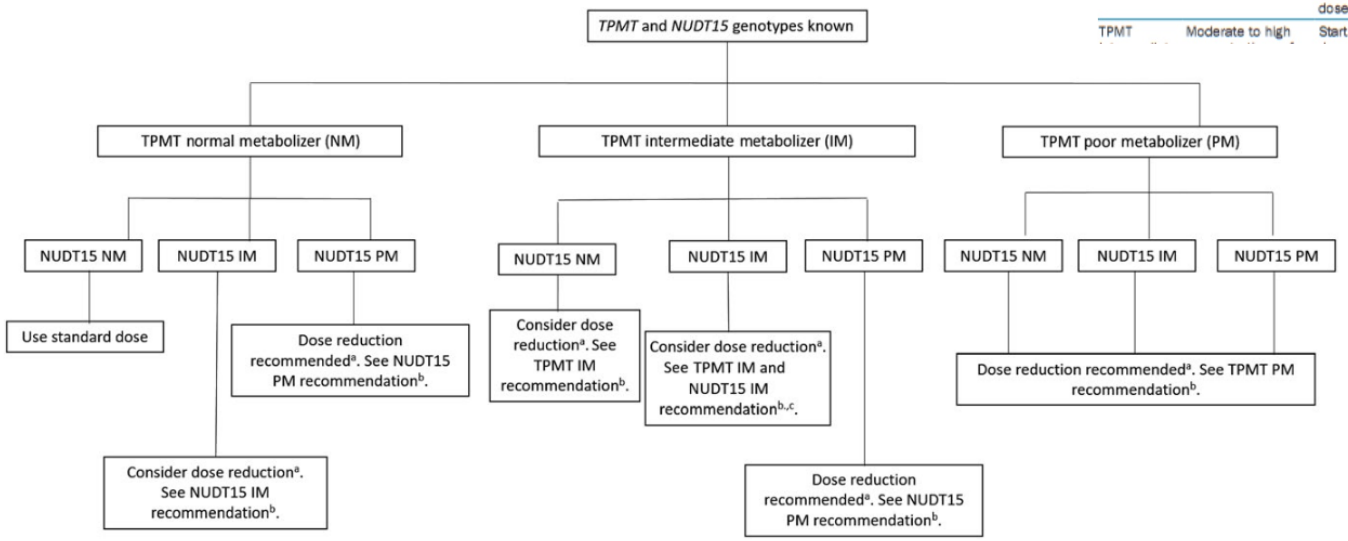



**Figure 2** Recommended starting doses of thiopurines by thiopurine methyltransferase (TPMT) and NUDT15 phenotype. [a]Whether a dose reduction is recommended from the starting dose depends on the level of the standard starting dose; for example, if the standard starting dose of mercaptopurine is 75 mg/m$^2$/day or higher, then a lower starting dose may be considered in intermediate metabolizers and would be recommended in poor metabolizers, whereas if the starting dose is 50 mg/m$^2$/day or lower, a reduced starting dose may not be necessary in intermediate metabolizers. [b]See **Table 2** for recommendation. [c]For patients who are intermediate metabolizers for both TPMT and NUDT15, further dose reduction might be needed compared with those who are only intermediate metabolizers with respect to one gene (*TPMT* or *NUDT15*).

## CPIC® Guideline for Thiopurines and TPMT and NUDT15

Most recent guideline publication:

Clinical Pharmacogenetics Implementation Consortium Guidelines for thiopurine dosing based on *TPMT* and *NUDT15* genotypes: 2018 Update (November 2018)

Updates since publication:

**March 2024:** At the time of guideline publication, the extent of dosage reduction for thiopurines recommended for patients with intermediate metabolism for both TPMT and NUDT15 was unclear. A recent publication (PMID: 38230823) found that these individuals need a substantial dose reduction to mitigate toxicity in TPMT/NUDT15 IM/IM patients. The recommendation for a TPMT intermediate metabolizer/NUDT15 intermediate metabolizer has been updated for all thiopurines to recommend a starting dose at 20%-50% of normal dosages, depending on the starting dose. See here for updated recommendation tables (azathioprine, mercaptopurine, thioguanine). The pre- and post-tests alert tables have been updated accordingly.

https://files.cpicpgx.org/data/guideline/publication/thiopurines/2018/30447069.pdf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