SOMATO PUBLICATIONS ISSN: 2643-2609

Annals of Gastroenterology and Digestive Disorders

Review Article Open Access

# Pharmacogenomic Profiling of DPYD and UGT1A1 Variants and Prediction of Chemotherapy Toxicity in Patients with Advanced Colorectal Cancer: A Review

**Nikolaos Papadopoulos[1*], Camille Rousseau[2] and Jan Vermeulen[3]**

[1]Department of Medical Oncology, National and Kapodistrian University of Athens, Athens, Greece

[2]Department of Clinical Pharmacology, University of Bordeaux, Bordeaux, France

[3]Department of Human Genetics, Radboud University, Nijmegen, Netherlands

***Correspondence to: Nikolaos Papadopoulos, Department of Medical Oncology, National and Kapodistrian University of Athens, Athens, Greece**

**Received: 14 January 2026; Accepted: 2 April 2026; Published: 9 July 2026**

**Volume: 9; Issue: 1; ISSN: 2643-2609**



## Abstract

*Fluoropyrimidines and irinotecan carry a narrow therapeutic margin, and a minority of patients are genetically unable to clear them. Both vulnerabilities are detectable by a pre-treatment blood test. The evidence for acting on the DPYD result is now strong enough that the remaining questions are about the size of the dose reduction rather than whether to test.*

***Objectives:*** *To review the published evidence on DPYD and UGT1A1 genotyping before chemotherapy for advanced colorectal cancer: which variants matter, how much toxicity they confer, what genotype-guided dosing achieves, and where the current dose recommendations fall short.*

***Material and Methods:*** *Narrative review of prospective genotyping studies, pharmacogenetic cohorts, meta-analyses and consensus dosing guidance indexed in PubMed and the major oncology and pharmacology journals. Studies were eligible if they reported the association between a DPYD or UGT1A1 variant and chemotherapy toxicity, or the outcome of genotype-guided dosing, in a defined population. No new patient data were generated; every estimate quoted is one published by the original investigators.*

***Results:*** *Severe fluoropyrimidine toxicity occurs in up to 30 per cent of treated patients. In a prospective study applying genotype-guided dose reduction, the relative risk of severe toxicity in DPYD*2A carriers fell to 1.31 (95% CI 0.63-2.73) from 2.87 (2.14-3.86) in a historical full-dose cohort, and no severe toxicity occurred in c.1679T>G carriers against a historical risk of 4.30 (2.10-8.80). The reduction was not uniformly sufficient: a 50 per cent reduction lowered severe toxicity in c.1905+1G>A carriers from 73 to 18 per cent, while a 25 per cent reduction left residual rates of 39 per cent in c.1236G>A and 47 per cent in c.2846A>T carriers. For irinotecan, UGT1A1*28 homozygosity carried an odds ratio for neutropenia of 4.79 (3.28-7.01) against wild type, and febrile neutropenia occurred in 18.2 per cent of homozygotes against 1.5 per cent of wild-type patients.*

***Conclusion:*** *DPYD genotyping before fluoropyrimidine treatment is supported by prospective evidence and should be routine. The dose reductions currently recommended are adequate for the loss-of-function alleles and demonstrably insufficient for the two reduced-function alleles. UGT1A1 testing has a weaker evidence base, with a clear toxicity association but limited prospective evidence that upfront dose reduction improves outcome.*

***Abbreviations:*** *DPD – Dihydropyrimidine Dehydrogenase, DPYD – Dihydropyrimidine Dehydrogenase Gene, UGT1A1 – UDP Glucuronosyltransferase 1A1, 5-FU – Fluorouracil, SN-38 – Active Metabolite of Irinotecan, CRC – Colorectal Cancer, RR – Relative Risk, OR – Odds Ratio, CTCAE – Common Terminology Criteria for Adverse Events, CPIC – Clinical Pharmacogenetics Implementation Consortium, DPWG – Dutch Pharmacogenetics Working Group, AUC – Area Under the Concentration Curve.*

**Keywords:** *DPYD; UGT1A1; Fluoropyrimidine; Irinotecan; Pharmacogenomics*

## Introduction

Fluoropyrimidines and irinotecan remain the backbone of systemic treatment in advanced colorectal cancer, and both are limited by toxicity rather than by efficacy. Severe fluoropyrimidine-related adverse events occur in up to 30 per cent of treated patients, and most of that excess is attributable to reduced activity of dihydropyrimidine dehydrogenase, the enzyme that clears more than 80 per cent of administered fluorouracil [1]. Irinotecan toxicity is similarly concentrated in patients with impaired glucuronidation of its active metabolite [2,3].

What distinguishes these two from most sources of chemotherapy toxicity is that the vulnerability is inherited, identifiable before the first dose, and correctable by adjusting that

dose. The relevant variants in DPYD and UGT1A1 were characterised more than two decades ago [3,4,5], and the question since has been whether pre-treatment genotyping changes outcomes rather than merely predicting them.

For DPYD that question has been answered prospectively [1], and consensus guidance now recommends testing before fluoropyrimidine exposure [6]. For UGT1A1 the position is less settled: the association with neutropenia is robust and reproducible [7,8,9], but evidence that acting on it improves anything is thinner [2].

This review sets out what each variant confers, what genotype-guided dosing has achieved, and where the recommended reductions have proved inadequate.

## Material and Methods

**Search strategy:** PubMed and the archives of the major oncology, clinical pharmacology and pharmacogenetics journals were searched for studies of DPYD and UGT1A1 genotyping in colorectal cancer. Search terms combined DPYD, dihydropyrimidine dehydrogenase, UGT1A1 and glucuronosyltransferase with fluoropyrimidine, fluorouracil, capecitabine, irinotecan, toxicity, neutropenia, genotype-guided dosing and dose reduction. Reference lists of retrieved trials and guidance documents were screened by hand.

**Eligibility:** Studies were included if they reported an association between a defined DPYD or UGT1A1 variant and chemotherapy toxicity, the outcome of prospective genotype-guided dosing, or consensus dosing recommendations. Studies in mixed tumour types are included where they provide the best available prospective evidence and are identified as such. Pharmacokinetic studies are cited where they explain a clinical observation.

**Data extraction and handling:** Design, sample size, variants genotyped, dose adjustment applied, toxicity grading system and reported effect estimates with confidence intervals were extracted as published. Variants are named at nucleotide level throughout, because star-allele nomenclature is inconsistently applied across this literature. No pooling or re-analysis was performed and no patient-level data were obtained. Figures 1 to 4 and Tables 1 and 2 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

## Results

**Which DPYD variants matter:** Four variants have established functional and clinical validity: the loss-of-function alleles DPYD*2A (c.1905+1G>A) and DPYD*13 (c.1679T>G), and the reduced-function alleles c.2846A>T and c.1236G>A, the last also known as HapB3 [1,6]. Together these occur in roughly 3 to 8 per cent of people of European ancestry, which is high enough that pre-emptive genotyping identifies a substantial at-risk group [6,10]. Many further variants alter enzyme activity in vitro but are too rare to have been characterised clinically [6].

**What genotype-guided dosing achieves:** The pivotal evidence comes from a prospective study in which patients were genotyped for all four variants before treatment. Heterozygous carriers received an initial dose reduction of 50 per cent for the loss-of-function alleles and 25 per cent for the reduced-function alleles, and wild-type patients received standard dosing. Toxicity was compared against a historical cohort of carriers treated at full dose [1].

The relative risk of severe toxicity fell from 2.87 (95% CI 2.14-3.86) to 1.31 (0.63-2.73) in DPYD*2A carriers, and from 4.30 (2.10-8.80) to no observed severe toxicity in c.1679T>G carriers (Figure 1) [1]. Earlier prospective work screening for DPYD*2A alone had reduced severe toxicity in carriers from 73 to 28 per cent, close to the 23 per cent seen in non-carriers on full dose [11]. Pharmacokinetic analysis confirmed that reduced-dose carriers achieved drug exposure comparable to non-carriers on standard dose, so the reduction did not amount to undertreatment [1].

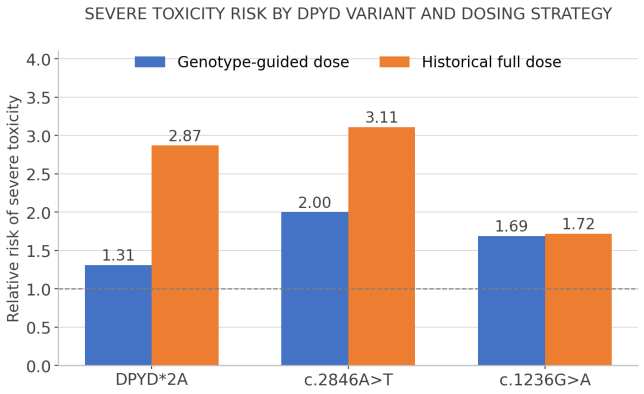


**Figure 1:** Relative risk of severe fluoropyrimidine toxicity under genotype-guided dosing against a historical full-dose cohort [1]

**Where the recommended reduction is not enough:** The same study identified an important asymmetry that is easily lost in summary. A 50 per cent reduction in c.1905+1G>A carriers lowered severe toxicity from 73 to 18 per cent, bringing it close to the background rate. But the 25 per cent reduction applied to the reduced-function alleles left severe toxicity at 39 per cent in c.1236G>A carriers and 47 per cent in c.2846A>T carriers, both well above the rate in non-carriers (Figure 2) [1,12].

The relative risks reflect this: 2.00 (1.19-3.34) against a historical 3.11 (2.25-4.28) for c.2846A>T, and 1.69 (1.18-2.42) against 1.72 (1.22-2.42) for c.1236G>A, the latter representing essentially no improvement [1]. Genotyping these patients and reducing the dose by a quarter therefore identifies the risk without adequately mitigating it, and there is a case for a larger initial reduction with subsequent titration [13].

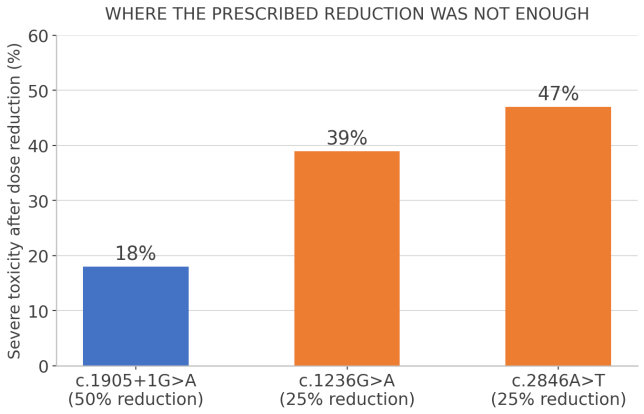


**Figure 2:** Severe toxicity remaining after the prescribed genotype-guided dose reduction, by variant [1,12]

| Study | n | Gene | Principal reported finding |
|---|---|---|---|
| Abigerges et al. 1995 [14] | — | — | Dose-limiting toxicity of irinotecan characterised |
| Ando et al. 2000 [7] | — | UGT1A1 | Polymorphism linked to irinotecan toxicity |
| Kweekel et al. 2008 [2] | 218 | UGT1A1 | Febrile neutropenia 18.2% in TA7 homozygotes |
| Deenen et al. [11] | 2,038 | DPYD | Severe toxicity fell from 73% to 28% with dose reduction |
| Henricks et al. 2018 [1] | 1,103 | DPYD | Guided dosing effective for loss-of-function alleles only |
| García-Alfonso et al. 2022 [13] | — | DPYD | National consensus on pre-treatment genotyping |

**Table 1:** Principal studies reviewed, with the gene examined and the finding as reported by the original investigators

**The evidence behind the four validated alleles:** The clinical validity of the four variants rests on more than the prospective dosing study. An individual patient data meta-analysis established the predictive value of c.1679T>G, c.1236G>A and c.1601G>A for severe fluoropyrimidine toxicity [15], a large capecitabine trial with an accompanying systematic review reached compatible conclusions [16], and an earlier meta-analysis had already established the two best characterised alleles as predictors [17]. Comparative functional analysis in vitro supports the classification of variants into loss- and reduced-function categories [18], and haplotype structure has been shown to modify the apparent effect of two common variants, which explains some inconsistency between earlier association studies [19].

**UGT1A1 and irinotecan:** Irinotecan is a prodrug whose active metabolite SN-38 is inactivated by glucuronidation, and the UGT1A1*28 allele reduces that capacity [3,7,14]. The clinical consequence is dose-limiting neutropenia and diarrhoea. Pooled across sixteen trials in patients of European ancestry, UGT1A1*28 homozygosity carried an odds ratio for neutropenia of 4.79 (95% CI 3.28-7.01) against wild type, and heterozygosity 1.90 (1.44-2.51) (Figure 3) [8]. An earlier prospective study had established the same relationship between UGT1A1 genotype and severe neutropenia risk [20].

A larger synthesis of 30 studies covering 4,471 patients reported the same direction of effect for both neutropenia and diarrhoea across additive, dominant and recessive models [9]. In a colorectal-specific cohort of 218 patients receiving irinotecan, febrile neutropenia occurred in 18.2 per cent of TA7 homozygotes on combination therapy against 6.5 per cent of heterozygotes and 1.5 per cent of wild-type patients (Figure 4) [2].

Two findings from that cohort temper the enthusiasm. Response rates did not differ by genotype, so the allele predicts harm rather than benefit. And homozygotes did not in practice receive lower doses or more frequent reductions than other genotypes, which suggests that knowing the genotype had not translated into prescribing behaviour [2].

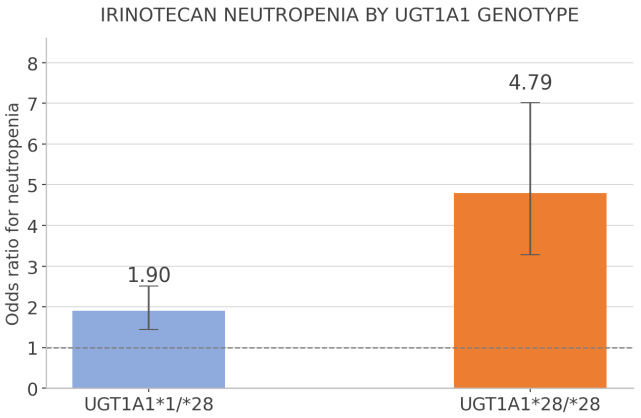


**Figure 3:** Pooled odds ratio for irinotecan-induced neutropenia by UGT1A1 genotype against wild type [8]

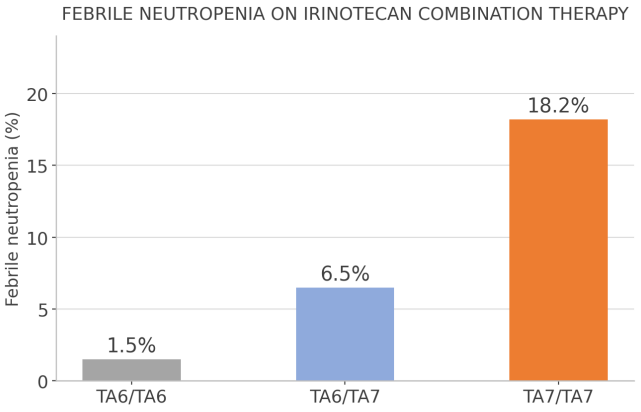


**Figure 4:** Febrile neutropenia by UGT1A1 genotype in 218 patients with metastatic colorectal cancer [2]

| Variant | Effect | Recommended action and its adequacy |
|---|---|---|
| DPYD*2A (c.1905+1G>A) | Loss of function | 50% reduction; toxicity 73% to 18% [1,11] |
| DPYD*13 (c.1679T>G) | Loss of function | 50% reduction; no severe toxicity observed [1] |
| DPYD c.2846A>T | Reduced function | 25% reduction; residual toxicity 47% [1] |
| DPYD c.1236G>A | Reduced function | 25% reduction; residual toxicity 39% [1] |
| UGT1A1*28 homozygous | Reduced glucu ronidation | Association robust; prospective dosing evidence limited [2,8,9] |

**Table 2:** The clinically validated variants, what each confers and whether the recommended dose adjustment is sufficient

## Discussion

The case for DPYD genotyping before fluoropyrimidine treatment is settled in a way that little else in pharmacogenomics is. The evidence is prospective, the intervention is a dose adjustment rather than a change of drug, pharmacokinetic data confirm that carriers on reduced doses achieve comparable exposure, and survival is not compromised [1,11]. Consensus guidance and national recommendations have followed [6,13].

The more interesting finding is the one that qualifies it. The 25 per cent reduction applied to c.2846A>T and c.1236G>A carriers left roughly two fifths of them still experiencing severe toxicity [1]. For c.1236G>A the relative risk under guided dosing, 1.69, was statistically indistinguishable from the historical figure of 1.72, meaning the intervention as delivered achieved essentially nothing

for that group. Reporting a genotyping programme as successful on aggregate obscures a subgroup in which it is not.

### Two genes at different stages of evidence

UGT1A1 illustrates the gap between association and utility. The link between the *28 allele and neutropenia is among the most reproducible in oncology pharmacogenetics, with a fourfold odds ratio in homozygotes pooled across trials [8,9] and consistent findings in colorectal cohorts [2,7]. What is missing is the equivalent of the DPYD prospective study: a trial in which upfront reduction in high-risk genotypes is shown to reduce toxicity without loss of efficacy.

The observation that homozygotes in routine practice did not receive lower doses despite a known genotype [2] points at the deeper implementation problem. A test result that does not change prescribing changes nothing, and the barrier there is not evidence but workflow.

### Study limitations

The limitations belong to the underlying literature. The pivotal DPYD study compared genotype-guided dosing against a historical cohort derived from a published meta-analysis rather than a concurrent randomised control group, which leaves open the influence of changes in supportive care over time [1]. Its population included several tumour types rather than colorectal cancer alone [1,11]. Variant frequencies and therefore the yield of testing differ substantially by ancestry, and the four validated alleles were characterised principally in European populations, so performance elsewhere is uncertain [6,10]. UGT1A1 meta-analyses pool studies using different irinotecan doses and combination regimens, and toxicity risk is dose-dependent [8,9,14]. Toxicity grading criteria changed across the period covered by the included studies.

Two gaps deserve naming. No randomised trial has compared a larger initial reduction against the current 25 per cent in reduced-function allele carriers, which is the question the prospective data most clearly raise [1,12]. And no study reviewed here reports whether phenotypic testing of enzyme activity adds to genotyping in patients who prove intolerant despite a wild-type result.

## Conclusion

Pre-treatment DPYD genotyping is one of the few pharmacogenomic interventions supported by prospective evidence that it reduces harm, and it should be routine before fluoropyrimidine exposure in advanced colorectal cancer. The recommended reductions are adequate for the two loss-of-function alleles and demonstrably inadequate for the two reduced-function alleles, where between 39 and 47 per cent of carriers still experienced severe toxicity. UGT1A1*28 has a robust and reproducible association with irinotecan neutropenia, with a fourfold increase in homozygotes, but lacks the prospective dosing evidence that would make testing actionable in the same way. Reporting variant-specific rather than aggregate outcomes is what would move both forward.

## Acknowledgements

Our thanks are owed to the trial groups and genotyping consortia whose published data underpin this review.

## Funding

No money from any funder, commercial partner or charity went into the writing of this review.

## Conflict of Interest

Competing interests: none, for any of the authors.

## Ethics Statement

The article looks only at findings that have already been published. It recruited nobody and opened no new patient record, so no ethics submission was called for.

## References

1. Henricks LM, Lunenburg CATC, de Man FM, Meulendijks D, Frederix GWJ, Kienhuis E, et al. "DPYD genotype-guided dose individualisation of fluoropyrimidine therapy in patients with cancer: a prospective safety analysis". Lancet Oncol 19(2018):1459-1467.
2. Kweekel DM, Gelderblom H, Van der Straaten T, Antonini NF, Punt CJA, Guchelaar HJ. "UGT1A1*28 genotype and irinotecan dosage in patients with metastatic colorectal cancer: a Dutch Colorectal Cancer Group study". Br J Cancer 99(2008):275-282.
3. Ando Y, Saka H, Asai G, Sugiura S, Shimokata K, Kamataki T. "UGT1A1 genotypes and glucuronidation of SN-38, the active metabolite of irinotecan". Ann Oncol 9(1998):845-847.
4. van Kuilenburg ABP, Haasjes J, Richel DJ, Zoetekouw L, Van Lenthe H, De Abreu RA, et al. "Clinical implications of dihydropyrimidine dehydrogenase (DPD) deficiency in patients with severe 5-fluorouracil-associated toxicity: identification of new mutations in the DPD gene". Clin Cancer Res 6(2000):4705-4712.
5. van Kuilenburg ABP, Meinsma R, Zoetekouw L, Van Gennip AH. "High prevalence of the IVS14+1G>A mutation in the dihydropyrimidine dehydrogenase gene of patients with severe 5-fluorouracil-associated toxicity". Pharmacogenetics 12(2002):555-558.
6. Amstutz U, Henricks LM, Offer SM, Barbarino J, Schellens JHM, Swen JJ, et al. "Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing: 2017 update". Clin Pharmacol Ther 103(2018):210-216.
7. Ando Y, Saka H, Ando M, Sawa T, Muro K, Ueoka H, Yokoyama A, Saitoh S, Shimokata K, Hasegawa Y. "Polymorphisms of UDP-glucuronosyltransferase gene and irinotecan toxicity: a pharmacogenetic analysis". Cancer Res 60(2000):6921-6926.
8. Liu X, Cheng D, Kuang Q, Liu G, Xu W. "Association of UGT1A1*28 polymorphisms with irinotecan-induced toxicities in colorectal cancer: a meta-analysis in Caucasians". Pharmacogenomics J 14(2014):120-129.
9. Zhang X, Yin JF, Zhang J, Kong SJ, Zhang HY, Chen XM. "Meta-analysis revisiting the influence of UGT1A1*28 and UGT1A1*6 on irinotecan safety in colorectal cancer patients". Pharmacogenomics 25(2024):439-450.
10. Lunenburg CATC, van der Wouden CH, Nijenhuis M, Crommentuijn-van Rhenen MH, de Boer-Veger NJ, Buunk AM, et al. "Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene-drug interaction of DPYD and fluoropyrimidines". Eur J Hum Genet 28(2020):508-517.
11. Deenen MJ, Meulendijks D, Cats A, Sechterberger MK, Severens JL, Boot H, et al. "Upfront genotyping of DPYD*2A to individualize fluoropyrimidine therapy: a safety and cost analysis". J Clin Oncol 34(2016):227-234.
12. Henricks LM, Lunenburg CATC, de Man FM, Meulendijks D, Frederix GWJ, Kienhuis E, et al. "A cost analysis of upfront DPYD genotype-guided dose individualisation in fluoropyrimidine-based anticancer therapy". Eur J Cancer 107(2019):60-67.

13. García-Alfonso P, Saiz-Rodríguez M, Mondéjar R, Salazar J, Páez D, Borobia AM, et al. "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". Clin Transl Oncol 24(2022):483-494.
14. Abigerges D, Chabot GG, Armand JP, Herait P, Gouyette A, Gandia D. "Phase I and pharmacologic studies of the camptothecin analog irinotecan administered every 3 weeks in cancer patients". J Clin Oncol 13(1995):210-221.
15. Meulendijks D, Henricks LM, Sonke GS, Deenen MJ, Froehlich TK, Amstutz U, et al. "Clinical relevance of DPYD variants c.1679T>G, c.1236G>A/HapB3, and c.1601G>A as predictors of severe fluoropyrimidine-associated toxicity: a systematic review and meta-analysis of individual patient data". Lancet Oncol 16(2015):1639-1650.
16. Rosmarin D, Palles C, Church D, Domingo E, Jones A, Johnstone E, et al. "Genetic markers of toxicity from capecitabine and other fluorouracil-based regimens: investigation in the QUASAR2 study, systematic review, and meta-analysis". J Clin Oncol 32(2014):1031-1039.
17. Terrazzino S, Cargnin S, Del Re M, Danesi R, Canonico PL, Genazzani AA. "DPYD IVS14+1G>A and 2846A>T genotyping for the prediction of severe fluoropyrimidine-related toxicity: a meta-analysis". Pharmacogenomics 14(2013):1255-1272.
18. Offer SM, Fossum CC, Wegner NJ, Stuflesser AJ, Butterfield GL, Diasio RB. "Comparative functional analysis of DPYD variants of potential clinical relevance to dihydropyrimidine dehydrogenase activity". Cancer Res 74(2014):2545-2554.
19. Hamzic S, Schaerer D, Offer SM, Meulendijks D, Nakas C, Diasio RB, et al. "Haplotype structure defines effects of common DPYD variants c.85T>C (rs1801265) and c.496A>G (rs2297595) on dihydropyrimidine dehydrogenase activity: implication for 5-fluorouracil toxicity". Br J Clin Pharmacol 87(2021):3234-3243.
20. Innocenti F, Undevia SD, Iyer L, Chen PX, Das S, Kocherginsky M, et al. "Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict the risk of severe neutropenia of irinotecan". J Clin Oncol 22(2004):1382-1388.

**Citation:** Papadopoulos N, Rousseau C, Vermeulen J. "Pharmacogenomic Profiling of DPYD and UGT1A1 Variants and Prediction of Chemotherapy Toxicity in Patients with Advanced Colorectal Cancer: A Review." Ann Gastroenterol Dig Disord (2026) Volume 9, Issue 1 doi: 10.5281/zenodo.22207570