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REVIEW ARTICLE

Current insight on irinotecan dose adjustment in advanced colorectal cancers based on pharmacogenetic studies: an updated review

Sanambar Sadighi, Pouyan Shaker, Mohammad Ali Shafiee[1]*

[1]General Internal Medicine Department, University Health Network, Toronto University

*Mohammad.Shafiee@uhn.ca

ABSTRACT

Despite advancements in colorectal cancer screening and treatment, the occurrence, severity, and mortality rates have consistently risen among younger patients. Precision medicine aims to personalize cytotoxic drug dosages, such as irinotecan, by considering the pharmacogenetic specificity of glucuronidation backgrounds. Our search, focused on recent developments (2020-2024) in categorizing Uridine 5'-diphosphate-glucuronosyltransferase (UGT)1A1 variants related to irinotecan's safety, effectiveness, and cost-benefit in metastatic colorectal cancer patients identified 32 relevant clinical studies and recent reviews from 296 abstracts in PubMed and PubMed Central databases. This updated review emphasizes racial disparities in the incidence and essential variants influencing irinotecan's activated metabolite (SN-38). While UGT1A1*28 homozygosity is the primary cause of toxicity in North America, Europe, and a Middle Asian country, *UGT1A1*6* is the prominent variant responsible in East Asian countries. Despite various methods employed for dose adjustment based on pharmacogenomic findings, individualization of the dose has been associated with reduced toxicity, improved response, and enhanced patient survival. The recommended irinotecan dose in the FOLFIRI regimen can be variable between 120mg/m2 to 350 mg/m2 based on the UGT1A1 genotype variant. Moreover, this approach appears to be cost-effective, as suggested by European and Chinese studies.

Introduction

According to the 2023 Global Cancer Observatory (GLOBOCAN)[1] report, colorectal cancer (CRC) stands as the second leading cause of cancer-related fatalities in Western countries and the percentage of cases occurring in individuals under 55 years old has risen from 11% in 1995 to 20% in 2019. Colorectal cancer poses the greatest risk among gastrointestinal cancers worldwide, constituting 38.5% and 28.2% of the overall lifetime risks for developing and dying of gastrointestinal cancers globally[2]. The regions with the highest lifetime risk of developing colon cancer include Australia and New Zealand, as well as Southern Europe[2]. There has been an annual increase ranging from 0.5% to 3% in those under 50 years old and in Native Americans under 65 years old, highlighting significant age and racial disparities in incidence and mortality [1]. Disparities are also observed in examining people's susceptibility to the toxicity of anti-cancer drugs, particularly notable for medications like irinotecan with a narrow therapeutic range[3]. Previous clinical investigations focusing on the application of irinotecan have predominantly centered on European and North American patients. However, in recent years, there has been a significant increase in clinical studies involving East Asian patients[4-6]. It is important to highlight a notable difference in the exploration of pharmacogenetic studies on irinotecan metabolism between high-income and middle-low-income countries[7].

The management of Irinotecan-induced toxicities poses a persistent obstacle to achieving optimal treatment outcomes and determining appropriate dosing schedules for cancer patients[8]. Despite the common practice of dosing chemotherapy regimens based on patient-specific factors such as body surface area or weight, these protocols are frequently complicated by the development of severe or life-threatening conditions in 35% to 40% of Irinotecan recipients[7].

Precision medicine involves customizing treatment based on an individual's genetic background. In the field of oncology, pharmacogenomic studies have advanced rapidly including incorporating drug metabolism to optimize drug dosages. To improve safety in chemotherapy regimens that include UGT1A1-irinotecan, pharmacogenetic dosing recommendations have been provided[9-10]. Concerning UGT1A1, while the FDA and EMA do not mandate pre-treatment genotyping, they recommend initiating dose reductions for patients homozygous for UGT1A1*28[11-12]. Despite the existence of guidelines and scientific support for the advantages of pharmacogenetic testing, the routine integration of pretreatment testing for these enzyme genes in clinical settings is not widely practiced.

The objective of this research is to provide up-to-date information on genomic testing for UGT1A1 before initiating irinotecan treatment. The aim is to tailor the dosage based on peer-reviewed literature, ensuring a safe and effective treatment strategy. Additionally, the study aims to investigate the cost-effectiveness of UGT1A1 genomic testing as a promising approach to precision medicine in adapting cancer treatment.

Combination regimens of irinotecan

Despite the utilization of various chemotherapy protocols involving irinotecan in the treatment of different solid tumors, a primary chemotherapy combination for metastatic colorectal cancer

(mCRC) is FOLFIRI. FOLFIRI regimen comprising of 400 mg/m^2 bolus IV on day one and 2400 mg/m^2 IV on day two of 5-fluorouracil, 200 mg/m^2 leucovorin, and 180 mg/m^2 irinotecan currently serves as first-line treatment for mCRC for patients who have undergone adjuvant oxaliplatin-based chemotherapy within the past 12 months or have experienced oxaliplatin-related neuropathy. It demonstrated an objective response rate of 40% and median progression-free survival (PFS) of 7 months[13]. Moreover, FOLFIRI is employed in combination with Vascular Endothelial Growth Factor (VEGF) inhibitors[14-16] such as bevacizumab and regorafenib and Epidermal Growth Factor Receptor (EGFR) inhibitors like cetuximab and panitumumab. A recent advancement in cancer chemotherapy is the development of Antibody Drug Conjugates (ADCs). While topoisomerase 1 inhibitors have gained approval for various carcinomas through clinical exploration, ongoing clinical development is focusing on targeting approaches to deliver drugs (chemotherapy payload) specifically to tumors by using a monoclonal antibody as Antibody Drug Conjugates (ADCs)[17]. Currently, under investigation or approved for the treatment of colorectal cancer, three ADCs incorporate the active metabolite of irinotecan (SN-38) or its derivative as the chemotherapy payload. These ADCs, namely labetuzumab govitecan, sacituzumab govitecan, and trastuzumab deruxtican[18-20], have also been subject to reports of dose adjustment for their chemotherapy payload.

Pharmacogenetics, irinotecan dose, and toxicity

Adverse events related to CPT11 not only negatively impact patient safety and quality of life but may also compromise the effectiveness of the treatment due to dose reduction or interruption. The elevated risk of toxicity is attributed, in part, to genetic variations in the uridine diphosphate-glucuronosyltransferase isoform 1A1 (UGT1A1) gene, which encodes the enzymes responsible for metabolizing irinotecan. Therefore, integrating pharmacogenetics in oncology is crucial for effectively managing the treatment of patients receiving this drug[21].

Dose-limiting toxicities (DLT) with irinotecan are neutropenia and delayed diarrhea. Historically, cases of fatal toxicity have been documented with Irinotecan at doses exceeding 250mg/m2[3,9]. Nevertheless, researchers revealed significant toxicity even in mCRC patients treated with moderate doses (180mg/m2)[3]. Additional investigations highlight the unpredictable and severe nature of Irinotecan toxicity, indicating an elevated risk of adverse effects in patients receiving medium doses, especially those with UGT1A1*28 homozygosity[22,23]. It is essential to emphasize that this concern becomes particularly significant and potentially life-threatening when employing medium to high doses of Irinotecan (180-350mg/m2) in homozygote patients[24]. According to Tsai and colleagues,[24] homozygous patients (*28/*28) could receive a reduced dose (i.e., 120 mg/m2) with favorable clinical outcomes and toxicity profiles. The results of the Hulshof [25] multicenter study on dose reduction for homozygotes (Table 1) were compared with a historical cohort of UGT1A1 homozygotes treated with the full dose and with UGT1A1 wild or heterozygote types who received the full dose in the study. Out of the 350 patients evaluated, 31 (8.9%) were recognized as UGT1A1 homozygotes and received a median 30% dose reduction.

In this subgroup, the incidence of febrile neutropenia was 6.5%, in contrast to the 24% observed in the historical group (P <0.04) and consistent with the incidence in UGT1A1 heterozygotes treated with the full dose.

Table 1-Characteristics of recent studies

First Author	Country	Year	Study Design	Number of patients	Treatment	Outcome
Ginzac	France	2023	prospective phase-II, multicentre, non-randomized trial	34	FOLFIRI	severe toxicities (defned as grade 4 neutropenia, grades 3 and 4 febrile neutropenia or grade 4 diarrhoea
Tsai	Taiwan	2023	retrospective observational study	25	FOLFIRI + bevacizumab Or FOLFOXIRI + bevacizumab	progression-free survival, Overal Survival, adverse events
Hulshof	the Netherlands	2022	prospective, multicentre, non-randomised	Total =350 (UGT1A1 PM = 31, UGT1A1 IM = 158 UGT1A1 EM = 161)	FOLFIRINOX,FOLFIRI, FOLFIRI, Irinotecan,	Febrile neutropenia, diarrhea
Li	China	2022	Prospective cohort	107	FOLFIR I/xeliri/ CPT-11 for colorectal cancer; IP/CPT-11 for lung cancer; CPT-11 single dr ug± Apatinib for gastr ic cancer; CPT-11 for cholangiopancreatic cancer	Adverse reaction spectrum to CPT-11 in panneoplastic and colorectal cancer patients
Tsai	Taiwan	2020	multicenter, randomised, controlled, open-label trial	221	FOLFIRI plus bevacizumab	progressionfree survival (PFS), overall response rate (ORR), disease control rate (DCR), overall survival (OS), AEs and metastasectomy rate
Paez	Spain	2019	RCT phase II trial	79 (HD-FOLFIRI group = 40, control group = 39)	HD-FOLFIRI	Neutropenia, diarrhea, asthenia

To assess the influence of UGT1A1 heterozygous mutations on the adverse reactions associated with CPT-11, Li Y et al.[5] conducted a study involving 107 patients with either UGT1A1 heterozygous mutations or the wild type (Table 1). There were no significant differences in efficacy and prognosis among patients with different genotypes and those treated with either reduced CPT-11 dosage or the standard dosages. Notably, results from

Chen and colleagues for Irinotecan 180 mg/m2 showed that grades 3–4 neutropenia occurred in 15% of patients with wild-type UGT1A1 (1*/1*) and 30.8% of patients with a heterozygous UGT1A1 genotype (1*/28*)[4]. Li Q[6] et al examined the spectrum of adverse reactions observed in patients with heterozygous mutations in UGT1A1*6 and UGT1A1*28. Logistic regression analysis revealed an association between the presence of vomiting and mucositis and the UGT1A1*28 heterozygous mutation. Meanwhile, the severity of vomiting, diarrhea, and neutropenia showed a correlation with the UGT1A1*6 heterozygous state. Despite the dosage remaining unchanged between the wild-type and heterozygote groups, there was a higher incidence of toxicity in the heterozygote variant group of patients.

In a randomized phase II trial conducted by Paez[26] et al., the experimental group with UGT1A1*1/*1 patients received an irinotecan dose of 300 mg/m2, while *1/*28 patients received 260 mg/m2; in the control group, the dose was 180 mg/m2. Objective response rates for the higher dose group were significantly better. No disparities in survival outcomes were observed. The authors concluded there were no differences in grades 3–4 toxicities between the control group (180 mg/m2) and the high-dose group (300 mg/m2 for 1*/1* and 260 mg/m2 for 1*/28*). Ginzac A et al.[27] in a phase II clinical trial as first-line treatment for mCRC, adapted Irinotecan dose on the basis of UGT1A1 polymorphisms: *1/*1 (370 mg/m^2); *1/*28 (310 mg/m^2), and *28/*28 (180 mg/m^2). The OS in the *1/*1 cohort surpassed that in the *1/*28 cohort, with durations of 36 and 27 months, respectively. This study indicates that mCRC patients undergoing FOLFIRI treatment can endure a higher irinotecan dose than the standard (>180 mg/m2) based on their UGT1A1 genotype without experiencing elevated toxicities. Upon reviewing the results from the mentioned studies, it appears there are inconsistent findings regarding the differences in response and survival of patients with heterozygous and wild-type variants of UGT1A1. Additionally, the heterozygous group may require a lower CPT11 dose, as demonstrated in the clinical trial conducted by Paez et al.

In a real-world historical prospective cohort study conducted by Tsai group[28], patient data with BRAF V600E-mutant metastatic colorectal cancer (mCRC) were examined from a single tertiary hospital. Tsai implemented irinotecan dose escalation based on UGT1A1 polymorphism. The analysis focused on outcomes, toxicities, and oncological results of FOLFIRI with irinotecan dose escalation plus bevacizumab (Table1). A comparison between triplet chemotherapy (TRIBE study[11]) and doublet chemotherapy with irinotecan escalation, guided by UGT1A1 pharmacogenomics, revealed no significant differences in outcomes. Notably, doublet chemotherapy with irinotecan escalation had a less pronounced impact on appetite compared to triplet chemotherapy. Otherwise, toxicity rates were the same.

It is crucial to highlight that employing triplet therapy or escalating doses in combinations with irinotecan results in heightened toxicity compared to the standard doublet therapy, especially in heterozygote and homozygote states. Nevertheless, this approach might be the preferred choice for patients exhibiting a favorable performance status (PS) and the potential for cure, as enhancing response rates could facilitate complete metastasis resection[29]. In a study by Barone and colleagues[30], with a

median follow-up of 56 months, the reported median survival for completely resected liver metastasis was 31.5 months, contrasting with non-resected patients who had a median survival of 24 months. The median time to progression was 14.3 months for all patients and 5.2 months for those who were non-resected.

Cost-effectiveness studies

In a prospective study conducted in the Netherlands, Hulshof et al.[25] examined patients eligible for irinotecan treatment, with a specific focus on the UGT1A1*28 and UGT1A1*93 genotypes before initiating chemotherapy (Table 1). Those identified as homozygous variant carriers underwent an initial 30% dose reduction. A cost analysis revealed that genotype-guided dosing resulted in cost savings, with a reduction of 183 Euros per patient. The authors concluded that UGT1A1 genotype testing should be integrated into clinical treatment guidelines before the initiation of therapy and should be regarded as the standard of care to improve individual patient safety.

Wei X et al.[31] conducted a study on the cost-effectiveness of UGT1A1*6/28 genotyping in comparison to scenarios without genotyping or dose adjustment prior to administering irinotecan in China. They utilized a decision tree model to assess costs and health outcomes, measured in quality-adjusted life years gained. Information on genotype frequencies, neutropenia probabilities under FOLFIRI chemotherapy, and associated direct costs and utilities were sourced from published literature. One-way sensitivity analyses were carried out. The genotyping with dose reduction strategy outperformed all other strategies. In contrast to the no genotyping and genotyping with unchanged dose strategies, it yielded slight increases in quality-adjusted life years (0.0011 and 0.0012) but led to cost reductions of $651.12 and $805.22 per patient, respectively. One-way sensitivity analyses indicated the model's relative robustness. The study concluded that UGT1A16/*28 genotyping was a cost-saving approach for Chinese mCRC patients.

Sukri et al.[32] conducted a systematic review of the cost-effectiveness of implementing pharmacogenomics testing in developing nations. Their analysis covered variants influencing drug responses, encompassing those linked to adverse drug reactions and treatment efficacy. The findings indicated that all pharmacogenomics-guided strategies were cost-effective for managing anticancer drugs (n = 5/5, 100%), such as irinotecan for mCRC. Despite the growing interest in applying pharmacogenomics in East Asian countries, a notable gap was observed in studies evaluating cost-effectiveness in other regions. This gap was particularly evident in African countries and low-income regions in South and Southeast Asian countries.

The present review has notable shortcomings. Firstly, there is inconsistency in the irinotecan starting doses administered and adjustments for various UGT1A1 genetic variants, categorized as normal, intermediate, and poor metabolizers, across different studies. While Asian researchers often opt for escalating doses, their Western counterparts tend to prefer fixed doses or 30% reductions for poor metabolizers[26,33]. Apart from UGT1A1*28 and UGT1A1*93 which exhibit a significant correlation with irinotecan-induced toxicity in Caucasians, polymorphisms that have been

less thoroughly investigated, including UGT1A*6, as well as polymorphisms in drug transporters such as ABCB1, ABCC5, ABCC2, ABCG1, and SLCO1B1, may also serve valuable in predicting toxicity[31]. Our study boasts a notable strength in its inclusion of the latest peer-reviewed studies published between 2023 and 2024, which, to the best of our knowledge, represent entirely new additions to the content of a review article. Additionally, this comprehensive review incorporated information on the ethnicity associated with UGT1A1 genotypes. Moreover, our approach involved an unbiased evaluation, presenting the included articles' positive and negative aspects to ensure a fair and balanced review.

Conclusion

Considering the well-established understanding of the mechanisms contributing to response variability and the occurrence of adverse events, particularly in the context of carefully conducted feasibility and cost-saving studies, it appears practical to customize the dosage of irinotecan, from 120mg/m2 to 350mg/m2, according to UGT1A1 polymorphisms, patient characteristics, and the goal of treatment in routine oncology practice for patients with metastatic colorectal cancer.

Future perspective

Integrating quality of life (QOL) assessments reported by patients through instruments such as the European Organization for Research[33] and Treatment or the Functional Assessment of Cancer Therapy[34] could be considered a sensible approach. This strategy is justified through cost-effective analyses and may improve patient satisfaction. Evaluating the impact of CPT11 dose adjustments using a multigene assay could be considered when economically possible. This panel could involve chemotherapy combinations, either with or without the inclusion of new classes of anti-cancer medications individualized specifically for the patient.

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References:

1. Siegel RL, Wagle NS, Cercek A, Smith RA, Jemal A. Colorectal cancer statistics, 2023. CA Cancer J Clin. 2023 May-Jun;73(3):233-254. doi: 10.3322/caac.21772.

2. Wang S, Zheng R, Li J, Zeng H, Li L, Chen R, Sun K, Han B, Bray F, Wei W, He J. Global, regional, and national lifetime risks of developing and dying from gastrointestinal cancers in 185 countries: a population-based systematic analysis of GLOBOCAN. Lancet Gastroenterol Hepatol. 2024 Mar;9(3):229-237. doi: 10.1016/S2468-1253(23)00366-7. Epub 2024 Jan 4. PMID: 38185129; PMCID: PMC10849975.

3. Mhandire DZ, and Goey AKL.The Value of Pharmacogenetics to Reduce Drug-Related Toxicity in Cancer Patients. Mol Diagn Ther. 2022 Mar; 26(2): 137–151.

4. Chen X, Liu L, Guo Z, Liang W, He J, Huang L, et al. UGT1A1 polymorphisms with irinotecan-induced toxicities and treatment outcome in Asians with Lung Cancer: a meta-analysis. Cancer Chemother Pharmacol. 2017;79(6):1109–1117.

5. Li Y, Zheng H, Zhang X, Xi Y, Cheng M, Zhao Y, Wang L and Hua B (2022). UGT1A1 Allele Test Not Only Minimizes the Toxicity But Also Maximizes the Therapeutic Effect of Irinotecan in the Treatment of Colorectal Cancer: A Narrative Review. Front. Oncol. 12:854478.doi: 10.3389/fonc.2022.854478.

6. Li Q, Sun T, Zhang H, Liu W, Xiao Y, Sun H, Yin W, Yao Y, Gu Y, Liu Y, Yi F, Wang Q, Yu J, Cao B, Liang L. Characteristics and Clinical Implication of UGT1A1 Heterozygous Mutation in Tumor. Zhongguo Fei Ai Za Zhi. 2022 Mar 20;25(3):137-146. doi: 10.3779/j.issn.1009-3419.2022.101.07. PMID: 35340156; PMCID: PMC8976199.

7. Roden DM, McLeod HL, Relling MV, Williams MS, Mensah GA, Peterson JF, et al. Pharmacogenomics. Lancet. 2019; 394:521–32.

8. Nelson RS, Seligson ND, Bottiglieri S, Carballido E, Cueto AD, Imanirad I, Levine R, Parker AS, Swain SM, Tillman EM, Hicks JK. *UGT1A1* Guided Cancer Therapy: Review of the Evidence and Considerations for Clinical Implementation. Cancers (Basel). 2021 Mar 29;13(7):1566. doi: 10.3390/cancers13071566.

9. Hulshof EC, Deenen MJ, Guchelaar HJ, *et al.* Pre-therapeutic *UGT1A1*genotyping to reduce the risk of irinotecan-induced severe toxicity: Ready for prime time. Eur J Cancer, 2020, 141: 9-20. doi: 10.1016/j.ejca.2020.09.007

10. Yamazaki S. A retrospective analysis of actionable pharmacogenetic/genomic biomarker language in FDA labels. Clin Transl Sci.. 2021 Jul;14(4):1412-1422. doi: 10.1111/cts.13000.

11. Annotation of EMA Label for irinotecan and UGT1A1file. https://www.pharmgkb.org/labelAnnotation/PA166182952 file. Downloads/Irinotecan_06_21_19_EMA.pdf

12. US Food and Drug Administration (FDA). Guidance for industry: clinical pharmacogenomics: premarket evaluation in early phase clinical studies and recommendations for labeling. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-pharmacogenomics-premarket-evaluation-early-phase-clinical-studies-and-recommendations. Accessed February 19, 2024.

13. Douillard JY, Cunningham D, Roth AD, Navarro M, James RD, Karasek P, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicenter randomized trial. *Lancet.* 2000;355(9209):1041–1047. doi: 10.1016/S0140-6736(00)02034-1.

14. Ma CJ, Chang TK, Tsai HL, Su WC, Huang CW, Yeh YS, Chang YT, Wang JY. Regorafenib plus FOLFIRI with irinotecan dose escalated according to uridine diphosphate glucuronosyltransferase 1A1genotyping in previously treated metastatic colorectal cancer patients: study protocol for a randomized controlled trial. Trials. 2019 Dec 19;20(1):751. doi: 10.1186/s13063-019-3917-z. PMID: 31856912; PMCID: PMC6923824.

15. Cremolini C, Antoniotti C, Rosini D, Lonardi S, Loupakis F, Pietrantonio F, et al. Upfront FOLFIXIRI plus bevacizumab and reintroduction after progression versus mFOLFOX6 plus bevacizumab followed by FOLFIRI plus bevacizumab in the treatment of patients with metastatic colorectal cancer (TRIBE 2): a multicentre, open-label, phase 3, randomized, controlled trial. The Lancet Oncology.2020.21;4:497-507

16. Xu D, Liu Y, Tang W, Xu L, et al. Regorafenib in refractory metastatic colorectal cancer: a multi-center retrospective study. Front. Oncol. 2022; 12:838870. doi: 10.3389/fonc.2022.838870

17. Han S, Lim KS, Blackburn BJ, Yun J, Putnam CW, Bull DA, Won YW. The Potential of Topoisomerase Inhibitor-Based Antibody-Drug Conjugates. Pharmaceutics. 2022 Aug 16; 14(8):1707. doi: 10.3390/pharmaceutics14081707. PMID: 36015333; PMCID: PMC9413092.

18. Alese OB, Christina Wu C, Chapin WJ, Ulanja MB, Zheng-Lin B, Amankwah M, et al. Update on Emerging Therapies for Advanced Colorectal Cancer. American Society of Clinical Oncology Educational Book Volume 43, Number 43 https://doi.org/10.1200/EDBK_389574.

19. NCCN Clinical Practice Guidelines Version 1.2024 Colon Cancer. https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf

20. Benson AB, Venook AP, Al-Hawary MM, et al Rectal cancer, version 2.2022, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 20:1139-1167, 2022

21. Takano M, Sugiyama T. UGT1A1 polymorphisms in cancer: impact on irinotecan treatment. Pharmgenomics Pers Med. 2017 Feb 28;10:61-68. doi: 10.2147/PGPM.S108656. PMID: 28280378; PMCID: PMC5338934.

22. Nielson CM, Bylsma LC, Fryzek JP, Saad HA, Crawford J. Relative dose intensity of chemotherapy and survival in patients with advanced stage solid tumor cancer: a systematic review and meta-analysis. Oncologist. 2021; 26(9):e1609–e1618. doi: 10.1002/onco.13822.

23. Hulshof EC, de With M, de Man FM, Creemers GJ, et al. UGT1A1 genotype-guided dosing of irinotecan: a prospective safety and cost analysis in poor metabolizer patients. *Eur J Cancer.* 2022; 162:148–157. doi: 10.1016/j.ejca.2021.12.009.

24. Emami AH, Sadighi S, Shirkoohi A, Mohagheghi MA. Prediction of Response to Irinotecan and Drug Toxicity Based on Pharmacogenomics Test: A Prospective Case Study in Advanced Colorectal Cancer. *Asian Pac J Cancer Prev,(2017)18 (10), 2803-2807. DOI:10.22034/APJCP.2017.18.10.2803.*

25. Tsai HL, Huang CW, Lin YW, et al. Determination of the UGT1A1 polymorphism as guidance for irinotecan dose escalation in metastatic colorectal cancer treated with first-line bevacizumab and FOLFIRI (PURE FIST). Eur. J. Cancer. 2020;138, 19–29.

26. Páez D, Tobeña M, Fernández-Plana J, et al. 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. *Br J Cancer*. 2019;120(2):190–195. doi: 10.1038/s41416-018-0348

27. Ginzac A, Thivat E, Petorin C, Richard D, Herviou P, Molnar I, Devaud H, Creveaux I, Ferrer F, Authier N, Jary M, Pezet D, Durando X. A phase-II study based on dose adjustment according to UGT1A1 polymorphism: is irinotecan underdosed in first-line FOLFIRI regimen for mCRC? Cancer Chemother Pharmacol. 2024 Mar;93(3):225-236. doi: 10.1007/s00280-023-04603-x. Epub 2023 Nov 7. PMID: 37932443; PMCID: PMC10901933.

28. Tsai HL, Huang CW, Chen Y, et al. Real-World Outcomes of First-Line FOLFIRI Plus Bevacizumab with Irinotecan Dose Escalation versus FOLFOXIRI Plus Bevacizumab in BRAFV600E-Mutant Metastatic Colorectal Cancer: The Preliminary Data from a Single-Center Observational Study. Medicina 2023, 59, 2108. https://doi.org/10.3390/medicina59122108.

29. Barone C, Nuzzo G, Cassano A, et al. Final analysis of colorectal cancer patients treated with irinotecan and 5-fluorouracil plus folinic acid neoadjuvant chemotherapy for unresectable liver metastases. Br J Cancer 2007; 97:1035-9. doi: 10.1038/sj.bjc.6603988.

30. Iwasa S, Muro K, Morita S, et al. Impact of UGT1A1 Genotype on the Efficacy and Safety of Irinotecan-Based Chemotherapy in Metastatic Colorectal Cancer. *Cancer Sci* (2021) 112(11): 4669–78. doi: 10.1111/cas.15092.

31. Wei X, Cai J, Sun H, Li N, Xu C, Zhang G, et al. Cost-effectiveness analysis of UGT1A1*6/*28 genotyping for preventing FOLFIRI-induced severe neutropenia in Chinese colorectal cancer patients. Pharmacogenomics. 2019;20(4):241–9.

32. Sukri A, Salleh MZ, Masimirembwa C, Teh LK. A systematic review on the cost-effectiveness of pharmacogenomics in developing countries: implementation challenges. Pharmacogenomics J. 2022 May;22(3):147-159. doi: 10.1038/s41397-022-00272-w.

33. European Organisation for Research and Treatment (EORTC)—Quality of Life Group. EORTC QLQ-C30. 2021. https://qol.eortc.org/questionnaires/. Accessed 9 Dec 2021.

34. FACIT group. Functional Assessment of Cancer Therapy—General. 2021. https://www.facit.org/measures/FACT-G. Accessed 9 Dec 2021.