JAMA Network Open

Invited Commentary | Pharmacy and Clinical Pharmacology

Pharmacogenomics in Oncology—Running Out of Excuses for Slow Adoption

Howard L. McLeod, PharmD; D. Grace Nguyen, PharmD, BCPS

+ Related article

Author affiliations and article information are listed at the end of this article.

A hallmark of cancer drug therapies has been the major impact of treatment-related toxic effects, challenging the palliative and even curative goals of these interventions. Severe toxic effects can impede patients from completing their treatment courses at the target dose, potentially leading to hospitalizations and even fatalities, while also adversely affecting quality of life and increasing health care costs. This has been especially true in gastrointestinal cancers, where the fluoropyrimidines (intravenous fluorouracil and its oral prodrug capecitabine) and irinotecan are the mainstay chemotherapies. Approximately 80% of an administered fluoropyrimidine is inactivated by dihydropyrimidine dehydrogenase (DPD), which is encoded by the *DPYD* gene. Pharmacogenomics (PGx) studies have found that patients with reduced or no function alleles in *DPYD* have increased risk for severe or fatal toxic effects when receiving standard doses of fluoropyrimidines. Similarly, uridine diphosphate glucuronosyltransferase isoform 1A1 (UGT1A1) is the enzyme that converts the active metabolite of irinotecan (SN-38) to the inactive SN-38 glucuronide. Patients with reduced function alleles in the *UGT1A1* gene are also at risk for toxic effects with standard-dose irinotecan.[1] Pretreatment *DPYD/UGT1A1* genetic testing before initiating fluoropyrimidine and irinotecan enables the identification of at-risk patients and initial dose reductions in these patients to mitigate the risk of toxic effects. Nonetheless, there remains apprehension to adopt this otherwise logical patient safety strategy into routine care, primarily due to concerns regarding test availability, cost, lessening of treatment efficacy, and guideline recommendations.

First, genotyping tests for *DPYD* and *UGT1A1* have become more widely available through both specialty and reference laboratories. Some offer multigene panel testing, providing a more cost-effective option. Second, the cost of genotyping testing has decreased over the years and is covered by many insurance plans, including Medicare, in 28 states that follow MolDX policies. This expense is a fraction of the cost associated with an intensive care unit stay due to toxic effects that could be avoided with PGx-guided prescribing. Moreover, it was shown that *DPYD*-guided fluoropyrimidine dosing does not negatively impact progression-free survival and overall survival in *DPYD* variant carriers treated with a reduced dose compared with patients with *DPYD* wild-type receiving the full dose.[2] Clinical studies have shown that *UGT1A1*-guided irinotecan dosing did not compromise efficacy and was cost-effective.[1,3] Food and Drug Administration–approved drug labels recommend considering *UGT1A1* testing for irinotecan and *DPYD* testing for fluorouracil and capecitabine, and PGx advocates continue to push for the inclusion of testing recommendations in oncology guidelines.[4] While some challenges remain with the implementation of PGx-guided therapy, several leading academic and community centers have incorporated *DPYD* and/or *UGT1A1* testing as part of their standard of care.[5,6] The use of *DPYD* to avoid severe or fatal toxic effects is now part of international clinical guidelines and was added to the US Veterans Administration Oncology Clinical Pathways.[7]

The article by Roncato et al[8] addresses several critical gaps for routine implementation of *DPYD* and *UGT1A1* testing in clinical practice, in particular, conduct of a randomized clinical trial, demonstration of a significant reduction in toxic effects, and absence of impairment of survival outcome. This work performed an analysis of patients with cancer who were treated as part of the larger, practice-changing Pre-Emptive Pharmacogenomic Testing for Preventing Adverse Drug Reactions randomized clinical trial.[9] The subset focused on patients receiving a fluoropyrimidine and/or irinotecan to treat gastrointestinal cancer, with the control arm receiving standard dosing and management, while the intervention arm received reduced dosing per the Dutch Pharmacogenetics Working Group guideline that focused on *DPYD* and/or *UGT1A1* genotype status.

While the study was multicenter, all centers were in Italy and most patients were of European ancestry, which may introduce some nuances with generalizability. Among patients with actionable genotypes, patients in the PGx arm had a 90% lower risk of clinically relevant toxic effects compared with those in the control arm (OR, 0.1; $P = .04$), with carriers in the control arm experiencing a 4-fold higher incidence of hospitalization. In addition, the toxic effect costs for carriers in the control arm were 91-fold higher than for noncarriers in the same arm and carriers and noncarriers in the PGx arm. Treatment intensity slightly favored the PGx-informed treatment arm in patients with risk variants. Moreover, the 3-year overall survival was not significantly different between the 2 arms. These findings further reduce the excuses for the slow adoption of PGx-guided cancer therapy.

While many PGx studies have assessed the influence of a single gene or gene variant on a specific drug in isolation, this study examined the clinical effect of prospective multigene pharmacogenetic testing on both toxic effects and efficacy of anticancer therapy, and importantly considered the whole patient as the end point. This study only focused on the 2 genes relevant to gastrointestinal chemotherapy, but it demonstrates an important movement away from academic curiosity of a given gene-drug pair to optimal care in the context of the whole patient. This approach should become the standard for biomarker studies, including those that include PGx relevance. This also opens the broader application of PGx in oncology, optimizing not only the management of chemotherapy, but also medications for pain control, antiemetics, antidepressants, and other aspects of supportive oncology care.[10]

ARTICLE INFORMATION

Published: December 6, 2024. doi:10.1001/jamanetworkopen.2024.49453

Corresponding Author: Howard L. McLeod, PharmD, Center for Precision Medicine, Utah Tech University, 1882 E Joe Cir, St George, UT 84790 (hmcleod1965@gmail.com).

Author Affiliations: Center for Precision Medicine, Utah Tech University, St George (McLeod); Department of Cancer Pharmacology and Pharmacogenomics, Atrium Health Levine Cancer Institute, Charlotte, North Carolina (Nguyen).

Conflict of Interest Disclosures: None reported.

REFERENCES

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

2. Knikman JE, Wilting TA, Lopez-Yurda M, et al. Survival of patients with cancer with *DPYD* variant alleles and dose-individualized fluoropyrimidine therapy-a matched-pair analysis. *J Clin Oncol*. 2023;41(35):5411-5421. doi:10.1200/JCO.22.02780

3. Catenacci DVT, Chase L, Lomnicki S, et al. Evaluation of the association of perioperative *UGT1A1* genotype-dosed FOLFIRINOX with margin-negative resection rates and pathologic response grades among patients with locally advanced gastroesophageal adenocarcinoma: a phase 2 clinical trial. *JAMA Netw Open*. 2020;3(2):e1921290. doi:10.1001/jamanetworkopen.2019.21290

4. Baker SD, Bates SE, Brooks GA, et al. *DPYD* testing: time to put patient safety first. *J Clin Oncol*. 2023;41(15):2701-2705. doi:10.1200/JCO.22.02364

5. Jacobson JO, Rompelman G, Chen A, et al. Design and implementation of an opt-out, end-to-end, preemptive *DPYD* testing program for patients planned for a systemic fluoropyrimidine. *JCO Oncol Pract*. 2024;20(8):1115-1122. doi:10.1200/OP.23.00776

6. Nguyen DG, Morris SA, Hamilton A, et al. Real-world impact of an in-house dihydropyrimidine dehydrogenase (*DPYD*) genotype test on fluoropyrimidine dosing, toxicities, and hospitalizations at a multisite cancer center. *JCO Precis Oncol*. 2024;8:e2300623. doi:10.1200/PO.23.00623

7. Amstutz U, Henricks LM, Offer SM, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing: 2017 update. *Clin Pharmacol Ther*. 2018;103(2):210-216. doi:10.1002/cpt.911

8. Roncato R, Bignucolo A, Peruzzi E, et al. Clinical benefits and utility of pretherapeutic *DPYD* and *UGT1A1* testing in gastrointestinal cancer: a secondary analysis of the PREPARE randomized clinical trial. *JAMA Netw Open*. 2024;7(12):e2449441. doi:10.1001/jamanetworkopen.2024.49441

9. Swen JJ, van der Wouden CH, Manson LE, et al; Ubiquitous Pharmacogenomics Consortium. A 12-gene pharmacogenetic panel to prevent adverse drug reactions: an open-label, multicentre, controlled, cluster-randomised crossover implementation study. *Lancet*. 2023;401(10374):347-356. doi:10.1016/S0140-6736(22)01841-4

10. Patel JN, Wiebe LA, Dunnenberger HM, McLeod HL. Value of supportive care pharmacogenomics in oncology practice. *Oncologist*. 2018;23(8):956-964. doi:10.1634/theoncologist.2017-0599