Check for updates

Integrating pharmacogenetic testing in the management of gastrointestinal cancers.

Darshana Patil, Navin Srivastava, Atreyee Saha, Stefan Schuster, Sachin Apurwa, Dadasaheb B Akolkar, Vineet Datta, Rajan Datar; Datar Cancer Genetics, Nasik, India; Datar Cancer Genetics UK, Guildford, United Kingdom; Datar Cancer Genetics Europe GmbH, Bayreuth, Germany; Datar Cancer Genetics, Nashik, India; Datar Cancer Genetics Limited, Nashik, India; Datar Genetics Limited, Nashik, India

Background: Gastrointestinal cancers are among the most prevalent malignancies, often treated with chemotherapeutic agents whose efficacy and toxicity can be influenced by genetic variations. Pharmacogenetic testing for key metabolic genes, including DPYD, UGT1A1, and G6PD, can guide personalized treatment approaches. **Methods:** We analyzed samples from 3,519 individuals for genotyping using semiconductor-based Next-Generation Sequencing (NGS) technology. High-quality genomic DNA was extracted and subjected to target enrichment via high multiplex PCR amplification using an NGS panel targeting variants of key metabolic genes, including DPYD, G6PD, and UGT1A1. **Results:** For the DPYD gene, 96% of patients were normal metabolizers. However, 4% intermediate and 0.17% individuals had poor metabolizer status. Poor metabolizers possess homozygous non-functional alleles, leading to complete dihydropyrimidine dehydrogenase (DPD) deficiency and increased toxicity risk with fluoropyrimidine drugs like 5-fluorouracil (5-FU), Capecitabine, and Tegafur. Patients with certain homozygous or compound heterozygous variants in the DPYD gene are at increased risk for acute early-onset toxicity and serious, including fatal, adverse reactions due to fluorouracil. 5-FU is not recommended for use in patients known to have certain homozygous or compound heterozygous DPYD variants that result in complete absence of DPD activity. Intermediate metabolizers exhibit approximately 50% reduced DPD activity, necessitating a 50% reduction in starting doses followed by careful titration based on toxicity. UGT1A1 analysis revealed 46% normal, 42% intermediate, and 12% poor metabolizers, affecting Irinotecan metabolism and toxicity risks. Poor metabolizers show decreased UGT1A1 activity, resulting in reduced clearance of Irinotecan and increased risk of dose-limiting toxicities. These patients are also at higher risk for neutropenia, diarrhea, and asthenia, requiring starting dose adjustments. Additionally, they may experience elevated hyperbilirubinemia with treatments like Regorafenib. Recognizing G6PD deficiency in GI cancers can prevent serious complications and ensure safer treatment options. G6PD testing indicated that 98% were homozygous wildtype, 2% heterozygous, and 0.31% homozygous/hemizygous deficient. Patients with homozygous/hemizygous deficient genotype may be at increased risk for drug-induced hemolysis, particularly when treated with Dabrafenib. **Conclusions:** These findings highlight the therapeutic significance of incorporating genetic testing into clinical practice to tailor treatments, enhance drug efficacy, and minimize side effects in GI cancer management. By integrating pharmacogenetic insights, the safety and effectiveness of therapies can be significantly improved, ultimately leading to better patient care in GI oncology. Research Sponsor: None.

Downloaded from ascopubs.org by 90.190.172.18 on October 16, 2026 from 090.190.172.018
Copyright © 2026 American Society of Clinical Oncology. All rights reserved.