Retrospective and Prospective Clinical Studies of *DPYD* Pharmacogenetics Within an Institutional Genetics Data Repository

Daniel L Hertz[1,2], PharmD, PhD; Amy L Pasternak[1], PharmD; Javier Granados[1], PharmD; N. Lynn Henry[2], MD, PhD,
[1]Department of Clinical Pharmacy, University of Michigan College of Pharmacy, Ann Arbor, Michigan, USA; [2]University of Michigan Rogel Cancer Center, Ann Arbor, Michigan, USA

Background: Pre-treatment genetic testing for validated *DPYD* variants (i.e., *DPYD*2A, DPYD*13, DPYD p.Asp949Val, DPYD HapB3*) reduces severe fluoropyrimidine toxicity. Additional *DPYD* variants, including *DPYD p.Y186C*, have been identified but their association with toxicity has not been demonstrated. Additionally, *DPYD* testing only recently became standard of care in the United States, leaving many patients at risk for preventable toxicity. The objectives of this study were to use the Michigan Genomics Initiative institutional genetic data repository to investigate the association of uncommon *DPYD* polymorphisms with fluoropyrimidine toxicity and demonstrate the feasibility of using existing research-only data to identify *DPYD* variant carriers for confirmatory clinical testing prior to treatment.
Methods: Toxicity data was retrospectively collected from adult patients treated with standard doses of fluoropyrimidines for the retrospective association study. The primary toxicity endpoint was grade ≥3 toxicity or treatment modification due to toxicity in the first two cycles. Uncommon variants were analyzed in aggregate, excluding patients carrying any of the four validated variants. The prospective study used automated electronic medical record screening to identify Michigan Genomics Initiative participants who carried validated *DPYD* variants who were scheduled to receive fluoropyrimidines, to trigger confirmatory clinical testing.
Results: In the retrospective analysis of 799 patients who did not carry a validated variant, carriers of an uncommon variant (1.1% of patients) had significantly higher risk of toxicity than non-carriers (66.7% vs. 23.7%; adjusted odds ratio=7.36; 95% CI 1.75–38.2; p=0.009). The prospective study passively screened 2959 MGI participants who carried a validated *DPYD* variant. A rectal cancer patient planning to start fluoropyrimidine-containing chemotherapy underwent clinical testing that confirmed a *DPYD* c.1129-5923C>G (HapB3) variant and dosing was adjusted based on clinical guidelines.
Conclusions: This study demonstrated that an institutional genetic data repository can be used to identify uncommon *DPYD* variants that increase toxicity risk and identify *DPYD* carriers for clinical testing prior to fluoropyrimidine treatment.