ASHP Best Practices Award

Real-world Clinical Impact of an In-house Dihydropyrimidine Dehydrogenase (*DPYD*) Genotyping Test on Fluoropyrimidine Dosing and Toxicity at a Multisite Cancer Center

Sarah A. Morris, PharmD; D. Grace Nguyen, PharmD, BCPS; Donald C. Moore, PharmD, BCPS, BCOP, DPLA, FCCP; Sarah L. Hanson, PharmD, BCOP; Chris Larck, PharmD, BCOP, CPP; Karine Eboli Lopes, MS; Alicia Hamilton, BS; Simeon Owuor Kwange, MS; Nury Steuerwald, PhD, HCLD (ABB); James Symanowski, PhD; Laura Musselwhite, MD; Kunal C. Kadakia, MD; Brinda Koya, MD; Seungjean Chai, MD; Kwabena Osei-Boateng, MD; Sini Kalapurakal, MD; Jimmy Hwang, MD; Jai N. Patel, PharmD, BCOP, CPP

Atrium Health Levine Cancer
Charlotte, North Carolina

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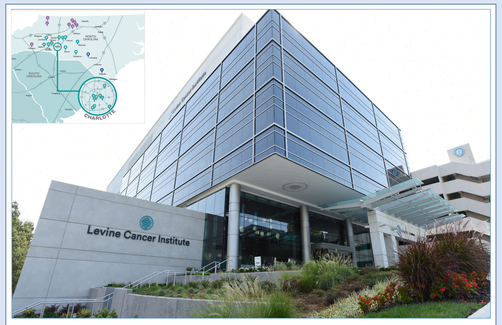
Authors have nothing to disclose.



Introduction

Levine Cancer

- Community-Academic Hybrid Model Cancer Center
- Care locations across North Carolina and South Carolina
- >18,000 new patients with cancer treated/year

Department of Pharmacy

- 60 full time outpatient hematology/oncology pharmacists embedded in most clinic locations

Department of Cancer Pharmacology & Pharmacogenomics (PGx)

- 3 pharmacists with fellowship/residency PGx training
- PGx laboratory with director (PhD), molecular biologists, research associates, and technicians

DPYD Testing Program Purpose

- One-third of patients develop severe toxicities with fluoropyrimidines (FPs), including 5-fluorouracil (5-FU) and capecitabine
- Toxicities can be partly due to genetic variations in *DPYD*, which encodes for DPD, the catabolic enzyme responsible for the inactivation of FPs
- *DPYD* variant carriers had a 4-fold higher risk of FP-related toxicity and a 25-fold higher risk of treatment-related mortality compared to non-carriers

DPYD Testing Program Goal

- Improve patient safety by mitigating FP-related toxicities through identification of *DPYD* variant carriers and genotype-guided dose reductions

Description of the Program

Phase 1: Identify and address barriers

Barrier	Actions
Lack of education/awareness of clinical utility	Presentations at section meetings Role specific presentations (e.g. nurse, pharmacists)
Lack of support for universal testing from the FDA and national oncology organizations (e.g., NCCN)	Universal testing SOP supported by LCI leadership Support/data from international organizations (e.g. EMA)
Prolonged turnaround time	Developed in-house genotype test using buccal swab and SOP for rapid turnaround of results to clinic
Cost of test to patient	Obtained institutional and external grant funding
Limited clinical decision support	Provide dose recommendations directly to oncologist Develop interruptive alerts in the EMR

Figure 1. Key barriers identified by stakeholders to implementing universal *DPYD* genotyping and actions taken by Levine Cancer to address these barriers

Phase 2: Pilot *DPYD* testing program

- Clinical *DPYD* genotyping test established and available to those starting (pre-treatment testing) or continuing (reactive testing) FP-based chemotherapy

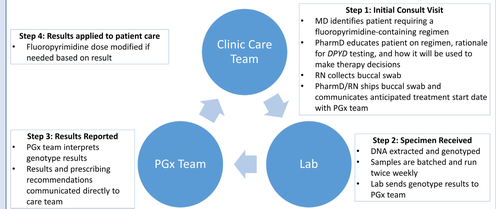
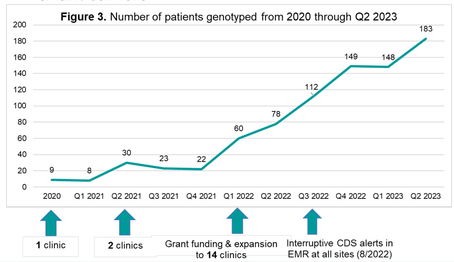


Figure 2. Multidisciplinary *DPYD* genotyping workflow

Phase 3: Expansion to all clinics and clinical decision support (CDS) integration

- Test results entered as discrete data in electronic medical record (EMR)
- Alerts embedded within chemotherapy order sets
  - Pre-test alerts: prompt test ordering for patients without DPYD results
  - Post-test alerts: prompt dose modification for *DPYD* variant carriers



Experience with the Program

Table 1. Demographics

	Total (N=757)
Age (median, range)	63 (22-94)
Sex, male (N, %)	410 (54.2%)
Race (N, %)	
White	559 (73.8%)
Black	146 (19.3%)
Other/Unknown	52 (6.9%)
Hispanic/Latino	32 (4.2%)
Cancer type (N, %)	
Colorectal	348 (46.0%)
Non-colorectal GI	320 (42.3%)
Non-GI/unknown	89 (11.7%)
Stage (N, %)	
0-II	129 (17%)
III	225 (29.7%)
IV	338 (44.6%)
Unknown	65 (8.6%)
ECOG performance status	
0	194 (25.6%)
1	327 (43.2%)
≥ 2	102 (13.4%)
Unknown	134 (17.7%)
Treatment (N, %)	
5-FU based	415 (54.8%)
Capecitabine-based	256 (33.8%)
Monotherapy	225 (29.7%)
Combination regimen	446 (58.9%)
Did not start FP	86 (11.4%)
DPYD genotype (N, %)	
Wild type (*1/*1)	712 (94.1%)
Heterozygous	45 (5.9%)
*1/c.1236G>A (HapB3)	23 (3.0%)
*1/c.2846A>T	8 (1.1%)
*1/c.557A>G	7 (0.9%)
*1/c.1905+1G>A (*2A)	5 (0.7%)
*1/c.1679T>G (*13)	2 (0.3%)

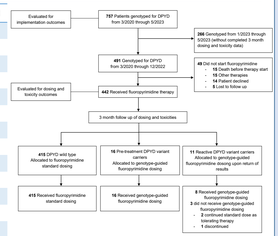


Figure 4. Consort diagram

Table 2. Implementation metrics

Turnaround time (TAT)	Days
Overall TAT (median, IQR)	6 (3-7)
Time from collection-receipt	1 (1-2)
Time from receipt-report	3 (2-6)
Timing of testing	**Patients (N=491)**
Pre-treatment testing (N, %)	621 (82.0%)
DPYD variant carrier rate	**32 (5.2%)**
Resulted by treatment start	561 (90.3%)
Reactive testing (N, %)	136 (18.0%)
DPYD variant carrier rate	**13 (9.6%)**
Collected on start date	59 (43.4%)
FP modifications in carriers	**Carriers (N=45)**
Pre-treatment testing (N, %)	32 (71.1%)
Dose reduced	27 (89.5%)
Not started	5 (15.6%)
Reactive testing (N, %)	13 (28.9%)
Dose reduced	9 (69.2%)
Discontinued	1 (7.7%)
No change	3 (23.1%)

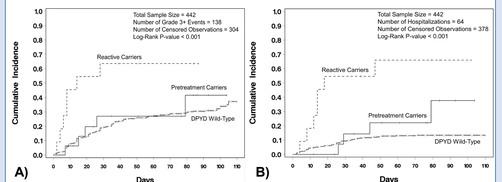


Figure 5. Cumulative Incidence of A) Grade 3+ toxicities and B) Hospitalizations

Table 3. Dose intensity, toxicity and hospitalization rates

	All patients (N=442)	DPYD wild-type (N=415)	Pre-treatment testing carriers (N=16)	Reactive testing carriers (N=11)	p value
Dose intensity, first dose (mean, range)	93.0% [25.9-120.5%]	94.3% [25.9-120.5%]	56.9% [41.9-89.5%]	96.8% [84.9-102.1%]	-
Dose intensity, all cycles (mean, range)[1]	90.3% [34.5-120.1%]	91.9% [34.5-120.1%]	58.1% [40.7-90.1%]	78.2% [56.6-99.4%]	-
FP-related grade 3+ toxicity, N (%)	138 (31.2%)	126 (30.4%)	5 (31.3%)	7 (63.6%)	0.085
Hematological toxicity	66 (14.9%)	62 (14.9%)	1 (6.3%)	3 (27.3%)	0.277
Gastrointestinal toxicity	77 (17.4%)	67 (16.1%)	4 (25%)	6 (54.5%)	0.006
Hand-foot syndrome	7 (1.6%)	7 (1.7%)	0	0	>0.999
Other[2]	2 (0.5%)	2 (0.5%)	0	0	>0.999
FP-related hospitalization, N (%)	64 (14.5%)	53 (12.8%)	4 (25%)	7 (63.6%)	<0.001
FP-related discontinuation, N (%)	41 (9.3%)	37 (8.9%)	3 (18.8%)	1 (9.1%)	0.281

Discussion / Conclusion

Key Findings

- Median TAT: 3 days from sample received to results
- 6% identified as heterozygous carriers
  - Pre-treatment: 5% carrier rate
  - Reactive: 10% carrier rate
- FP dose modified in 100% of pre-treatment carriers who started FP
- *DPYD* genotype-guided dosing
  - Reduced FP-related grade 3+ toxicities in pre-treatment carriers (31%) compared to reactive carriers in the present study (64%) and historical carriers receiving full dose FP (70-75%)
  - Reduced FP-related hospitalizations in pre-treatment carriers (25%) compared to reactive carriers (64%).

Conclusion

- Implementation of a novel pharmacist-led *DPYD* testing program with CDS integration is feasible
- Pre-treatment *DPYD* testing with genotype-guided fluoropyrimidine dosing improves patient safety by mitigating severe toxicities and hospitalizations in *DPYD* variant carriers

Future Directions

- Integrate test ordering in the EMR
- Establish a billing process
- Expand testing across the Advocate Health enterprise
- Conduct a cost-effectiveness analysis
- Discover/validate novel *DPYD* variants using banked samples and further research maximum tolerated doses for each variant

Acknowledgements

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