#12119: Frequency of certain germline polymorphisms among ethnicities and adverse drug reaction risk associated with colorectal cancer therapies

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BACKGROUND

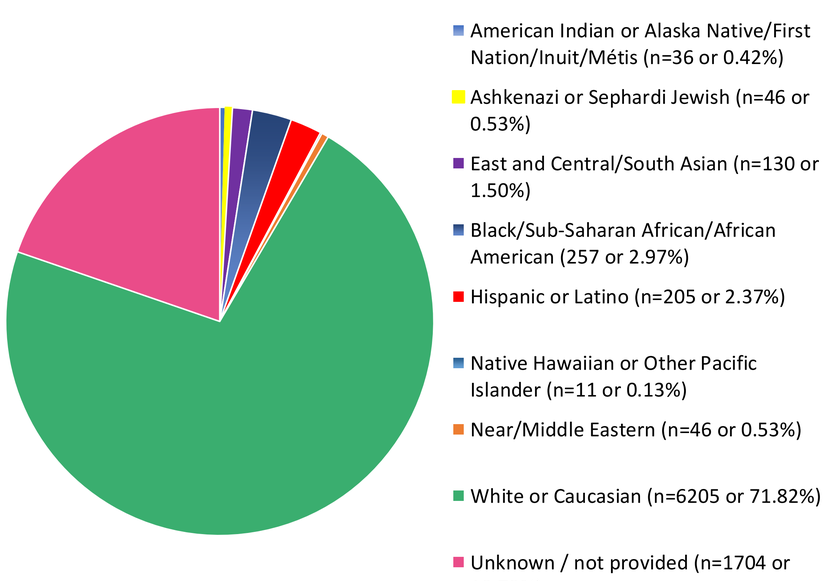
- Fluoropyrimidines (FPs) and irinotecan are common chemotherapy agents used in colorectal cancer regimens.[1,2]
- Severe and life-threatening toxicities from FPs and irinotecan are associated with common germline polymorphisms in the *DPYD* and *UGT1A1* metabolizer genes, respectively.[3]
- Clinically actionable FP dosage recommendations are available from the FDA and Clinical Pharmacogenetics Implementation Consortium (CPIC) for *DPYD* poor metabolizers (PMs) and intermediate metabolizers (IMs).[4,5]
- The FDA also provides clinically actionable irinotecan dosing guidance for *UGT1A1* PMs.[5]
- The frequencies of *DPYD* and *UGT1A1* risk alleles and phenotypes associated with chemotoxicity derived from a large population are reported here.

METHODS

- A retrospective analysis of a **large, diverse population including 8,640 genotyped patient samples** was conducted using the OneOme RightMed® Test. Phenotype and allele carrier frequencies were analyzed and stratified by self-reported race or ethnicity
- *DPYD* alleles: *2A, *13, c.2846A>T, c.557A>G, HapB3
- *UGT1A1* alleles: *6, *28

RESULTS

Figure 1: Sample Population Self-Reported Race or Ethnicity

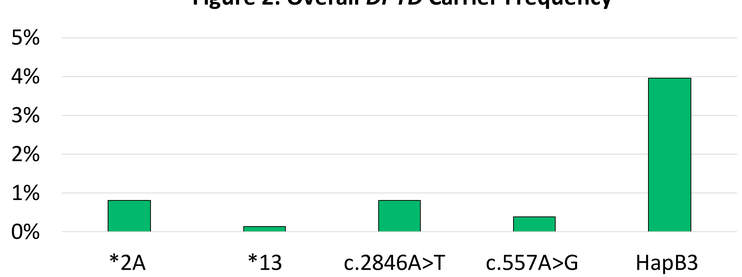


6% Patients at risk for severe/life-threatening **fluoropyrimidine toxicity** due to *DPYD* polymorphisms

56% Patients at risk for severe/life-threatening **irinotecan toxicity** due to *UGT1A1* polymorphisms

RESULTS

Figure 2: Overall *DPYD* Carrier Frequency



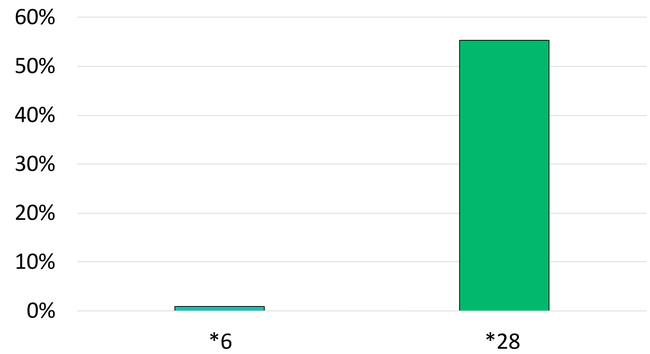
Notable frequencies within self-reported races or ethnicities

- White or Caucasian: **4.42%** HapB3 carriers
- American Indian or Alaska Native/First Nation/Inuit/Métis: **8.33%** HapB3 carriers
- Black/Sub-Saharan African/African American: **2.72%** c.557A>G carriers
- Unknown: **6.10%** with at least 1 variant
- Overall: **6.06%** with at least 1 variant

Overall carrier & clinically actionable phenotype frequency	
DPYD: >/= 1 risk allele	6%
DPYD: clinically actionable phenotypes (PMs, IMs)	6%
UGT1A1: >/= 1 risk allele	56%
UGT1A1: clinically actionable phenotypes (PMs)	12%

RESULTS

Figure 3: Overall *UGT1A1* Carrier Frequency



Notable frequencies within self-reported races or ethnicities:

- East and Central/South Asian: **18.46%** *6 carriers
- Ashkenazi or Sephardi Jewish: **71.74%** *28 carriers
- White or Caucasian: **53.68%** *28 carriers
- Unknown: **60.19%** with at least 1 variant
- Overall: **56.01%** with at least 1 variant

FUTURE DIRECTIONS FOR RESEARCH

- Studies show an association between FP- and irinotecan-induced toxicities, both severe and life-threatening. Further research is needed to determine the impact of pharmacogenomic (PGx)-guided dosing of these agents on clinical outcomes in patients with colorectal and other gastrointestinal cancers.[6,7]

REFERENCES

1. Morris VK, Kennedy EB, Baxter NN, *et al. J Clin Oncol.* 2023;41(3):678-700.
2. Benson AB, Venook AP, Al-Hawary MM, *et al. J Natl Compr Canc Netw.* 2021;19(3):329-59.
3. Cremolini C, Del Re, M, Antoniotti C, *et al. Oncotarget.* 2017;9(8):7859-66.
4. Amstutz U, Henricks LM, Offer SM, *et al. Clin Pharmacol Ther.* 2018;103(2):210-216.
5. Table of Pharmacogenetic Associations. U.S. Food & Drug Administration. October 26, 2022. Accessed Feb 1, 2024. https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations.
6. Knikman JE, Wilting TA, Lopez-Yurda M, *et al. J Clin Oncol.* 2023;41(35):5411-21.
7. Glewis S, Alexander M, Khabib MNH, et al. *Br J Cancer.* 2022;127(1):124-36.

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