Prevalence of Incidental Findings in Pharmacogenomic Panel Testing

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Introduction

- Pharmacogenomic (PGx) testing can guide medication management across many disease states[1]
  - PGx variation can impact medication efficacy and/or tolerability
  - PGx panels can include genes such as: *CYP2C9, CYP2C19, CYP2D6, CYP3A5, DPYD, G6PD, NUDT15, RYR1, SLCO1B1, TPMT, UGT1A1, VKORC1*
- Genes commonly included on PGx panels can have overlap with medication management implications and disease risk[2]
  - PGx genes can have overlapping disease risk or a disease state risk associated with medication use (Table 1) that may require additional education or testing
- To determine the proportion of patients that may warrant additional education regarding the overlapping disease risk and drug-gene interaction, an analysis was conducted to determine the prevalence of these disease risk variants after PGx panel testing

Table 1. PGx Genes with Potential Disease Risk

Gene	Potential Disease Risk Example(s)	PGx Risk Examples[3]
CACNA1S	Malignant hyperthermia*	Malignant hyperthermia associated with desflurane, isoflurane, sevoflurane, succinylcholine
DPYD	Dihydropyrimidine dehydrogenase deficiency	Toxicity associated with capecitabine, fluorouracil
G6PD	Acute or chronic hemolytic anemia	Hemolytic anemia associated with dapsone, pegloticase, rasburicase, tafenoquine
MT-RNR1	Hearing loss	Aminoglycoside induced hearing loss associated with amikacin, gentamicin, streptomycin, tobramycin
RYR1	Myopathies, malignant hyperthermia*	Malignant hyperthermia associated with desflurane, isoflurane, sevoflurane, succinylcholine
UGT1A1	Gilbert syndrome	Toxicity associated with irinotecan, atazanavir, belinostat

*Malignment hyperthermia associated only with medication use

Methods

- Retrospective review of 4063 consecutive PGx panel results
- Genes with overlapping disease risk were included in this assessment: *CACNA1S, DPYD, G6PD, MT-RNR1, RYR1, and UGT1A1*
- Results were assessed to determine the rate of individuals carrying variants with implications for disease risk or from a family planning perspective (Table 2)
- Descriptive statistics were conducted to determine the prevalence

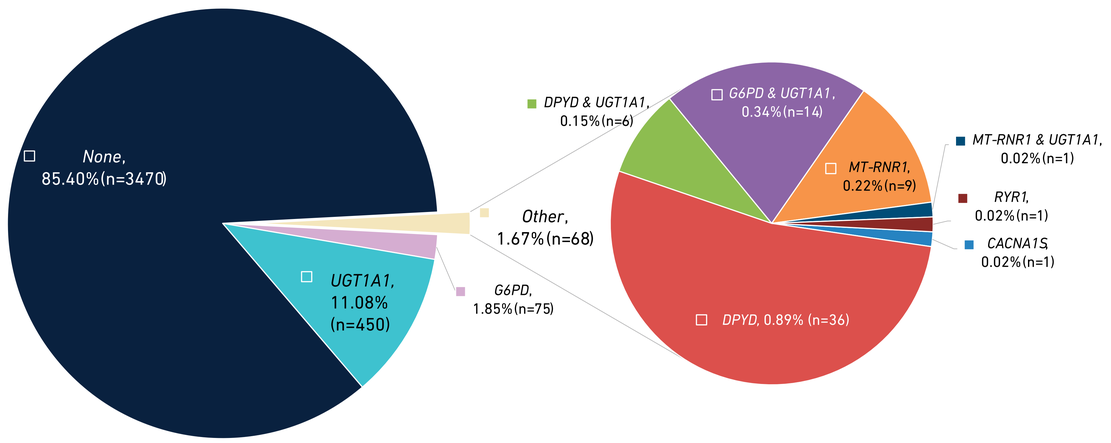
Table 2. Variants With Potential Disease Risk or Family Planning Implications

Gene	Variants / Phenotypes Assessed
CACNA1S	Malignant Hyperthermia Susceptible
DPYD	Carriers of variants with Activity Score = 0
G6PD	Deficient, Deficient with CNSHA, Variable
MT-RNR1	m.1555A>G, m.1494C>T, m.1095T>C
RYR1	Malignant Hyperthermia Susceptible
UGT1A1	*6/*6, *6/*28, *28/*28

Results

- Analysis included retrospective PGx results from 4063 individuals (Figure 1)
  - Majority of patients did not carry a disease risk variation (85.4%, n=3470)
  - Most common disease risk variation were *UGT1A1* diplotypes associated with Gilbert Syndrome (11.6%, n=471)
  - A small number of patients carried two disease risk variants (0.5%, n=21)
  - Most rare variations were with *RYR1* & *CACNA1S*, which reflects expected population frequencies

Figure 1. Number of Individuals Carrying Disease Risk Variants by Gene



Patient and Provider Education Considerations for Incidental Findings:

- Implications of the relevant disease risk and any recommended follow-up testing or care coordination such as with medical genetics.
- Examples:
  - Discuss implications and medical management considerations associated with malignant hyperthermia susceptibility including implications for family members
  - Potential follow-up testing with karyotype to clarify possible chromosomal difference if heterozygous result with *G6PD* and assigned male at birth patient
  - Family planning considerations for findings e.g. *DPYD* non-functional variations, malignant hyperthermia susceptibility
  - Relevant dietary considerations for *G6PD* deficiency

Conclusions

- Nearly 15% of patients with PGx testing results had an incidental finding relating to disease risk although the majority were for Gilbert Syndrome
  - Gilbert syndrome is a benign condition not requiring treatment action itself
  - Less common variations in remaining genes may have more complex management or counseling nuance
  - A small number of patients had multiple disease risk variants that could be missed by more targeted testing suggestive of benefits of panel testing
- Patients may benefit from additional education or counseling regarding the disease risk implication of PGx incidental findings
- More awareness is needed in the field of PGx to ensure education focuses not only on drug-gene interactions but also potential disease risk findings
- Considerations should be made within the field to ensure adequate provider and patient education for potential disease risk findings

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References:

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