Abstract #180123404

# *The NantOmics Pharmacogenomics Test: multi-omic screening of 2,489 oncology patients*


## CONTRIBUTING AUTHORS

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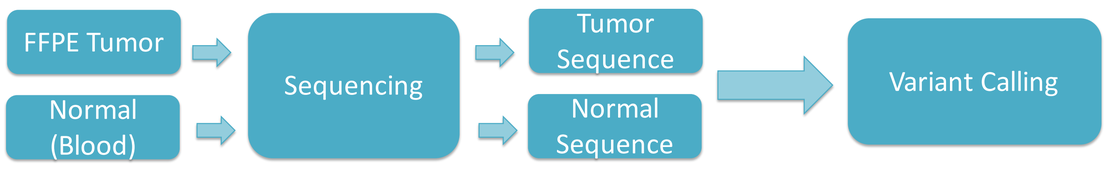
## BACKGROUND

- Pharmacogenomics can be used to tailor therapies to patient genotypes to reduce adverse drug events, improve outcomes, and reduce treatment costs.
- Many oncology drugs have pharmacogenomic warnings on their FDA labels, yet pharmacogenomics screening is not routinely employed in clinical practice.
- The increased accessibility of next generation sequencing (NGS) enables introduction of comprehensive pharmacogenomics screening to oncology patients.
- We screen for germline variants to determine how an oncology patient will respond to potential therapies in a clinical setting.



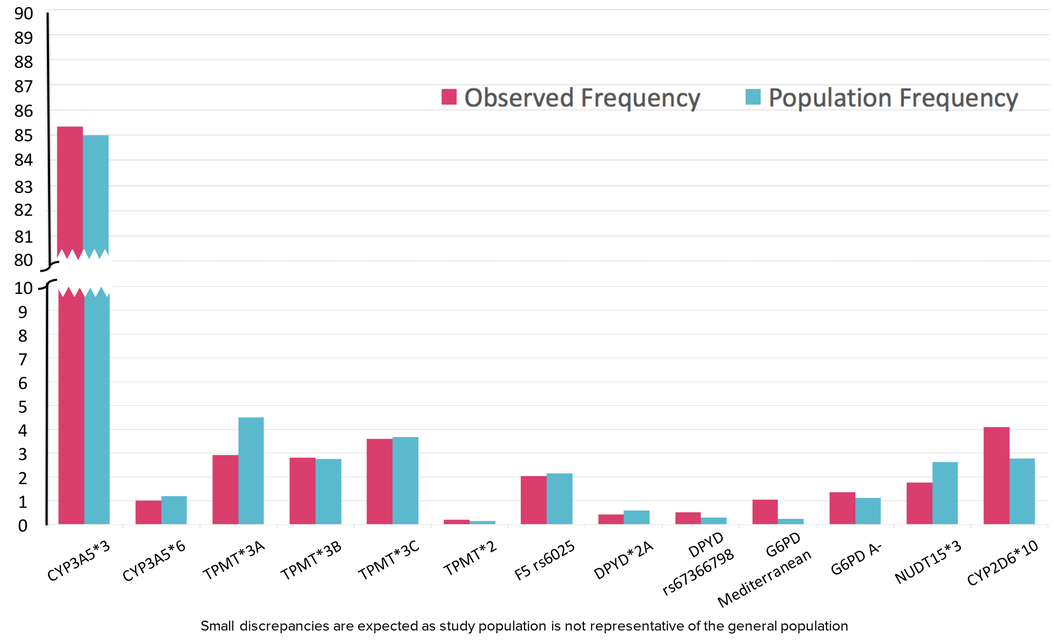

## METHODS

- Whole genome and whole exome sequencing data from FFPE tumors and matched normal samples of 2,489 CLIA patients.
- Clinical panel comprised of 29 pharmacogenomic markers related to 15 oncology drugs from FDA labels and CPIC guidelines.
- Validation was performed on a cohort of patients previously genotyped by an independent CLIA-validated PCR-based panel and the CDC genetic testing reference materials (GeT-RM).

| Gene | Alleles | Drugs |
|---|---|---|
| CYP3A5 | *3, *6, *7 | Tacrolimus |
| TPMT | *2, *3A, *3B, *3C, *4 | Azathioprine, Mercaptopurine, Thioguanine |
| F5 | rs6025 | Eltrombopag Olamine |
| DPYD | *2A, *3, *4, *5, *6, *7, *8, *9A, *9B, *10, *11, *12, *13, rs67376798 | Fluorouracil, Capecitabine, Tegafur |
| UGT1A1 | *28 | Belinostat, Irinotecan, Nilotinib, Pazopanib |
| G6PD | Mediterranean, A-202A/376G | Rasburicase, Dabrafenib |
| NUDT15 | *2, *3 | Azathioprine, Mercaptopurine, Thioguanine |
| CYP2D6 | *10 | Tamoxifen |

## RESULTS

### Observed allele frequencies correspond to known population frequencies

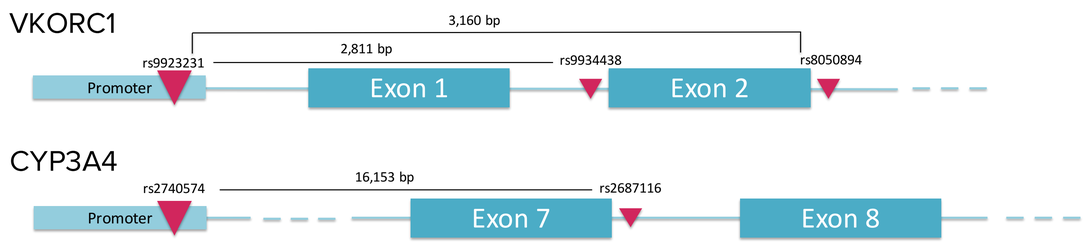



Small discrepancies are expected as study population is not representative of the general population

### Pharmacogenomic variants are common across many cancer types

| Cancer Type | # patients | # with at least one variant (%) | # with potentially treatment-altering variant(s) (%) |
|---|---|---|---|
| Adrenal | 14 | 14 (100%) | 2 (14.2%) |
| Bladder | 41 | 41 (100%) | 6 (14.6%) |
| Bone and Soft Tissue Cancers (including Sarcoma) | 210 | 201 (95.7%) | 21 (10%) |
| Brain | 107 | 105 (98.1%) | 10 (9.3%) |
| Breast | 440 | 417 (94.8%) | 28 (6.3%) |
| Cervical | 29 | 27 (93.1%) | 3 (10.3%) |
| GI | 761 | 737 (96.8%) | 49 (6.4%) |
| Kidney | 43 | 42 (97.6%) | 4 (9.3%) |
| Leukemia | 4 | 4 (100%) | 0 (0%) |
| Lung | 203 | 197 (97.0%) | 17 (8.3%) |
| Lymphoma | 12 | 12 (100%) | 1 (8.3%) |
| Melanoma | 45 | 43 (95.6%) | 3 (6.7%) |
| Mesothelioma | 10 | 10 (100%) | 3 (30%) |
| Myeloma | 3 | 3 (100%) | 1 (33.3%) |
| Other Cancer | 205 | 199 (97.1%) | 10 (4.9%) |
| Ovarian | 143 | 142 (99.3%) | 12 (8.4%) |
| Prostate | 76 | 73 (96.1%) | 7 (9.2%) |
| Renal Pelvis and Ureter Cancers | 16 | 15 (93.8%) | 0 (0%) |
| Skin (Non-Melanoma) | 14 | 14 (100%) | 2 (14.2%) |
| Testicular | 6 | 6 (100%) | 1 (16.6%) |
| Thymic | 18 | 18 (100%) | 2 (11.1%) |
| Unknown Primary | 33 | 32 (96.9%) | 1 (3.0%) |
| Urethral | 1 | 1 (100%) | 0 (0%) |
| Uterine (Endometrial) | 50 | 47 (94.0%) | 3 (6%) |
| Vaginal | 3 | 3 (100%) | 0 (0%) |
| Vulvar | 2 | 2 (100%) | 0 (0%) |
| **Total** | **2489** | **2405 (96.6%)** | **186 (7.4%)** |

### SNPs not detectable by WES may be substituted with SNPs in or near exons




VKORC1 rs9923231 is a promoter variant known to be associated with Warfarin sensitivity. CYP3A4 rs2740574 is a promoter variant associated with docetaxel induced toxicity. Both SNPs are too far (>150 nt) from exon boundaries to be captured by WES, so we look for SNPs found at a similar allele fraction in >90% of patients to serve as substitutes.

| Gene | SNP to be replaced | SNP | Distance of SNP from exon | % Patients with SNP and SNP of interest at similar allele fraction | Known to be in LD w/ SNP of interest [6] |
|---|---|---|---|---|---|
| VKORC1 | rs9923231 | rs9934438 | 136 nt | 96.2% | $r^2$ = 1.0, D' = 1.0 25 populations |
| VKORC1 | rs9923231 | rs8050894 | 124 nt | 93.9% | $r^2$ = 1.0, D' = 1.0 8 populations |
| CYP3A4 | rs2740574 | rs2687116 | 34 nt | 98% | $r^2$ = 1, D' = 1 9 populations |

Further evidence of linkage disequilibrium (LD) of rs9934438 and rs8050894 with rs9923231 can be found in the literature [1, 2].

## CONCLUSIONS

- Most patients (>96%) had at least one variant in our clinical panel
- A surprising amount of patients (7.4%) had a variant with potentially life threatening implications, with these implications being related to a drug commonly used for the cancer type in 1% of patients
- These results underscore the need for routine pharmacogenomic screening


## ACKNOWLEDGEMENTS

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## REFERENCES


1. Owen, R *et al*. Pharmacogenet Genomics 2010.
2. Scott, S *et al*. AJHG 2008.
3. CPIC Guidelines: cpicpgx.org
4. FDA labels: https://www.accessdata.fda.gov/scripts/cder/daf/
5. gnomAD: http://gnomad.broadinstitute.org
6. Ensembl LD calculator: http://grch37.ensembl.org/Homo_sapiens/Tools/LD/



## CONTACT

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