Abstract #2575

# *The NantOmics Pharmacogenomics Test: a panomic approach to pharmacogenomics screening.*


CONTRIBUTING RESEARCHERS

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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 pharmacogenomics 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 and somatic 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 1,879 CLIA patients.
- Clinical panel comprised of 31 pharmacogenomic markers related to 16 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).

| Drugs | Gene | Clinical Implications |
|---|---|---|
| Tamoxifen | CYP2D6 | Lower endoxifen concentration, increased likelihood of recurrence |
| Lapatinib | HLA-DRB1 HLA-DQA1 | Increased risk of hepatotoxicity |
| Fluorouracil, Capecitabine, Tegafur | DPYD | Increased risk of severe or life threatening adverse events |
| Belinostat, Irinotecan, Nilotinib, Pazopanib | UGT1A1 | Increased risk of toxicities, neutropenia, hyperbilirubinemia, hyperbilirubinemia (respectively) |
| Rasburicase, Dabrafenib | G6PD | Increased risk of hemolytic anemia |
| Tacrolimus | CYP3A5 | Normal metabolizers may fail to reach target dose |
| Mercaptopurine | NUDT15 | Increased risk of myelotoxicity (leukopenia or neutropenia) |
| Azathioprine, Mercaptopurine, Thioguanine | TPMT | Increased risk of myelosupression and potentially fatal toxicities |
| Eltrombopag Olamine | F5 | Increased risk of thromboembolism |

## RESULTS

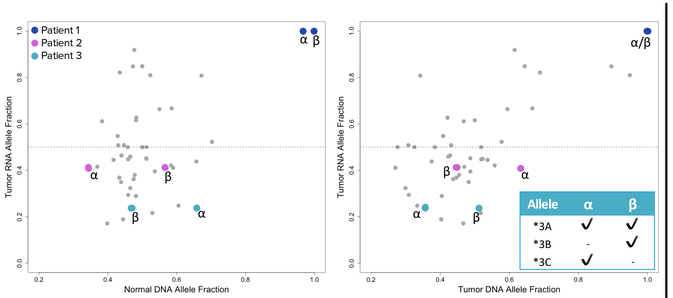
Observed allele frequencies correspond to known population frequencies

| Gene | Allele | Frequency | Population Frequency |
|---|---|---|---|
| CYP3A5 | *3 | 85.74% | 85-95% |
| CYP3A5 | *6 | 0.43% | 1.19% |
| CYP2D6 | *10 | 4.23% | [2.5-42.4]% |
| TPMT | *3A | 5.69% | 4.50% |
| TPMT | *3B | 5.53% | 2.75% |
| TPMT | *3C | 7.08% | 3.67% |
| TPMT | *2 | 0.16% | 0.14% |
| F5 | rs6025 | 2.13% | 2.15% |
| DPYD | *2A | 0.48% | 0.58% |
| DPYD | rs67376798 | 0.48% | 0.29% |
| G6PD | Mediterranean | 1.22% | 0.24% |
| G6PD | A- | 1.12% | 1.13% |
| NUDT15 | *3 | 1.44% | 2.62% |
| NUDT15 | *4 | 0.08% | 0.24% |

Pharmacogenomic variants are common across many cancer types

| Cancer Type | # Patients | # With At Least One Variant (%) | # With Potentially Treatment-Altering Variant(s) (%) |
|---|---|---|---|
| Adrenal | 13 | 13 (100%) | 2 (15.4%) |
| Bladder | 30 | 30 (100%) | 3 (10%) |
| Brain | 93 | 91 (97.8%) | 7 (7.5%) |
| Breast | 336 | 317 (94.3%) | 22 (6.5%) |
| Cervical | 16 | 16 (100%) | 2 (12.5%) |
| GI Tract | 573 | 556 (97%) | 41 (7.2%) |
| Kidney | 38 | 37 (97.3%) | 4 (10.5%) |
| Leukemia | 4 | 4 (100%) | 0 (0%) |
| Lung | 149 | 143 (95.9%) | 14 (9.4%) |
| Lymphoma | 12 | 12 (100%) | 1 (8.3%) |
| Melanoma | 37 | 36 (97.3%) | 1 (2.7%) |
| Mesothelioma | 8 | 8 (100%) | 3 (37.5%) |
| Other Cancer | 153 | 148 (96.7%) | 6 (3.9%) |
| Ovarian | 103 | 102 (99%) | 8 (7.8%) |
| Prostate | 51 | 49 (96.1%) | 3 (5.8%) |
| Renal Pelvis and Ureter | 10 | 9 (90%) | 0 (0%) |
| Sarcomas (including Bone) | 161 | 154 (95.6%) | 17 (10.5%) |
| Skin (Non-Melanoma) | 9 | 9 (100%) | 1 (11.1%) |
| Testicular | 6 | 6 (100%) | 1 (16.7%) |
| Thymic | 17 | 17 (100%) | 1 (5.8%) |
| Unknown Primary | 29 | 28 (96.5%) | 1 (3.4%) |
| Uterine (Endometrial) | 29 | 27 (93.1%) | 1 (3.4%) |
| Vulvar | 2 | 2 (100%) | 0 (0%) |
| Total | 1879 | 1814 | 139 |
| Percent | | 96.54% | 7.40% |

Preliminary analysis shows RNA allele fraction can be used to infer complex genotypes




The TPMT*3A allele is made up of two SNPs (rs1142345 and rs1800460), which are separately known as *3B (rs1800460) and *3C (rs1142345). Preliminary analysis shows that we can use RNA allele fraction to determine whether the variants are on the same copy of the gene (*3A), or separate (*3B/*3C). Each color represents a patient possessing both variants at the same RNA allele fraction, indicating *3A.

CYP2D6*10 is a common reduced-function haplotype related to tamoxifen-induced toxicities

Candidates for Tamoxifen therapy harboring CYP2D6*10

| Hormone Receptor Status | *10 het | *10 hom |
|---|---|---|
| ER+/PR+ | 10 | 3 |

Our test detects CYP2D6*10 with a sensitivity of 95.3% and specificity of 99%. In unselected breast cancer cases (N=165) 78% were Tamoxifen candidates (i.e. ER/PR positive by IHC). 118 of the 128 HR positive cases were tested for CYP2D6 haplotype. 8 patients (6.78%) had at least one CYP2D6*10 haplotype and were potentially affected by Tamoxifen-induced toxicities.

| Study | Finding |
|---|---|
| Xu, Y. et al. Ann Oncol (2008). | Women with the CYP2D6*10/*10 genotype treated with Tamoxifen had significantly worse disease free survival than *1/*1 or *1/*10 genotype (HR = 4.7, p= 0.04) |
| Schroth, W. et al. J Clin Oncol (2007) | Tamoxifen treated patients with CYP2D6 *4, *5, *10, *41 had more recurrence and shorter relapse-free periods (HR = 2.24, p=0.02) and worse event free survival (HR = 1.89, p=0.02) compared to carriers of functional alleles. |
| Teh, LK. et al. AAPS J (2012). | Patients carrying CYP2D6*10/*10 have showed higher risks of developing recurrence and metastasis than patients with *1/*10 and *1/*1 genotypes (OR = 13.14, p= 0.004) |

## CONCLUSIONS

- Most patients (>96%) had at least one variant screened for in our pharmacogenomics panel covering 16 commonly used drugs including 5-FU, Lapatinib, and Tamoxifen.
- Of those, a surprising percentage had variants with the potential to change treatment due to severe or life-threatening implications.
- CYP2D6*10 haplotype was found in nearly 7% of patients with HR+ breast cancer.
- Our results underscore the need for pharmacogenomics screening for all patients undergoing cancer treatment.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## CONTACT

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## REFERENCES


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2.FDA labels: https://www.accessdata.fda.gov/scripts/cder/daf/
3.gnomAD: http://gnomad.broadinstitute.org