The PharmacoScan™ Array: Performance Across Biological Specimens

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Background

Preemptive genotyping of relevant pharmacogenetic (PGx) genes and HLA typing for known associations with drug metabolism and hypersensitivity enables a clinician to provide a patient with an optimized treatment regimen by maximizing drug efficacy and limiting adverse reactions. There are over 300 actionable genetic variants with dosing guidelines on FDA-approved medications (1). These drugs span a wide range of categories from pain management to cancer, impacting a significant percentage of prescription medication (e.g. codeine, warfarin, allopurinol) (1-3).

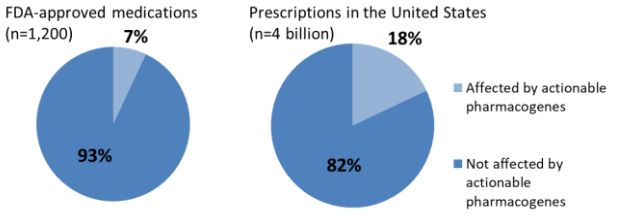

Figure 1. Percentage of medications and prescriptions affected by genotyping of actionable pharmacogenes. Relling & Evans, *Nature*, 2015

High risk genotypes vary in frequency between different ethnicities , with certain high risk alleles being common in some populations (4).

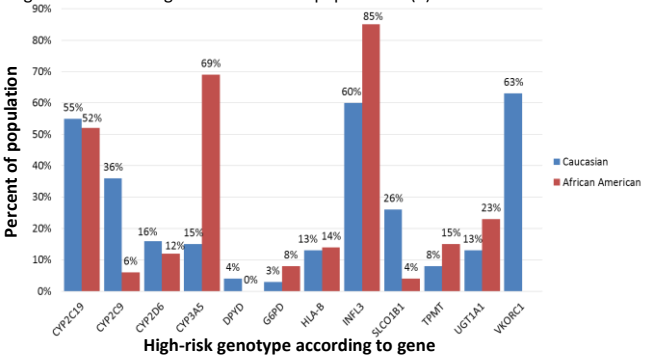

Figure 2. Percentage of individuals predicted to have a high-risk diplotype for 12 PGx relevant genes. Dunnenberger et al., *ARPT*, 2015

Genotype analysis of clinically actionable PGx genes allows for personalized drug selection and dosing. The accuracy and reproducibility of testing platforms is critical to accurately predict phenotype. In this study we determined whether the PharmacoScan™ (pScan) array **(4,627 ADME markers in 1,191 genes + copy number (CN) analysis on a subset of genes),** can be reliably utilized to genotype DNA originating from different biological specimens. **Table 1** shows a subset of the PGx relevant genes included on the array.

CPIC genes	Haplotype calling genes				Copy number genes
CFTR	CDA	CYP2E1	GSTM1	TPMT	CYP2A6
CYP2C9	CYP19A1	CYP2F1	GSTP1	UGT1A10	CYP2D6
CYP2C19	CYP1A1	CYP2J2	GSTT1	UGT1A1	GSTM1
CYP2D6	CYP1A2	CYP2S1	NAT1	UGT1A3	GSTT1
CYP3A5	CYP1B1	CYP3A43	NAT2	UGT1A4	UGT2B17
DPYD	CYP2A13	CYP3A4	PTGIS	UGT1A6	
HLA-B	CYP2A6	CYP3A5	SLC15A2	UGT1A7	
IFNL3	CYP2B6	CYP3A7	SLC22A2	UGT1A8	
SLCO1B1	CYP2C19	CYP4B1	SLCO1B1	UGT1A9	
TPMT	CYP2C8	CYP4F2	SLCO2B1	UGT2B15	
UGT1A1	CYP2C9	DPYD	SULT1A1	UGT2B7	
VKORC1	CYP2D6	FMO2	TBXAS1	VKORC1	

Table 1. A subset of actionable genes genotyped on PharmacoScan™ with haplotype and dosing guidelines.

Methods and Results

Genomic DNA (gDNA) was acquired from:

- Coriell Institute (from LCL cell lines; n= 112); Isolated from liver tissue (n=161), blood (n=20), or saliva (n=20). Analysis was done on the Axiom™ Analysis Suite 3.1.
- Additionally, the blood, saliva and Coriell samples were run on the DMETTM Plus array and received CYP2D6 TaqMan-based CN testing.

All sample types interrogated had passing rates of >95% for all array quality control (QC) metrics.

- Genomic DNA samples from blood, saliva and Coriell demonstrated call rates of 99.85-99.99%, intra-run concordance of 99.65-99.99% and inter-run concordance of 98.88-100%.
- Liver-derived gDNA samples had call rates of 99.67-99.93%.

All samples showed 100% concordance with copy number qPCR results for *CYP2D6*, including *CYP2D6/D7* hybrids; *CYP2D6* genotype calls were consistent with those obtained using TaqMan. Samples showed an average concordance of 99.44% with DMET results.

Table 2 : Intra-run and Inter-run Concordance for PharmacoScan™ Array for blood, saliva and gDNA (Coriell).

	Plates 1 & 2% inter-run Concordance	Plates 1 & 2% intra-run Concordance	Gender Match %	% Copy Number Concordance (9 CNV Locations, 24 Samples)
Average Concordance	99.838	99.986	100.000	99.537
Concordance Range	98.882-100	99.961-100	100.000	88.89-100
Average concordance with in -house extractions	99.918	99.975	100.000	100.000
Average concordance with Coriell controls	99.789	99.997	100.000	99.259

Table 3: Diagnostic Sensitivity Results

Plate/Sample information	% False Negative	%True Positive
Plate 1: Coriell Samples	0.09%	99.91%
Plate 2: Coriell Samples	0.00%	100%
Plate 1: In-house Extracted Samples	0.25%	99.75%
Plate 2: In-house Extracted Samples	0.00%	100%

Table 4: Diagnostic Specificity

Plate/Sample information	% False Positive	% True Negative
Plate 1-Coriell Samples	0.09%	99.91%
Plate 2-Coriell Samples	0.09%	99.91%
Plate 1-In-house extracted Samples	0.00%	100%
Plate 2- In-house extracted Samples	0.00%	100%

Conclusions

Regardless of gDNA origin, samples produced results that meet the array QC requirements. Comparison with 1000 Genomes and DMET results allowed for the determination of the accuracy of the blood, saliva and Coriell samples. Of note, the array accurately detected *CYP2D6* CN variation and *CYP2D6* hybrid or gene conversion arrangements, which is integral for metabolizer status prediction. Downstream inclusion of this data in the EMR will enable clinicians to preemptively make the most informed drug choices and dosing decisions, providing cost effective and better individualized patient care.

References

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