Implementation of Affymetrix PharmacoScan™ for Comprehensive Preemptive Clinical Pharmacogenetic Testing

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Pharmacogenetics

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).

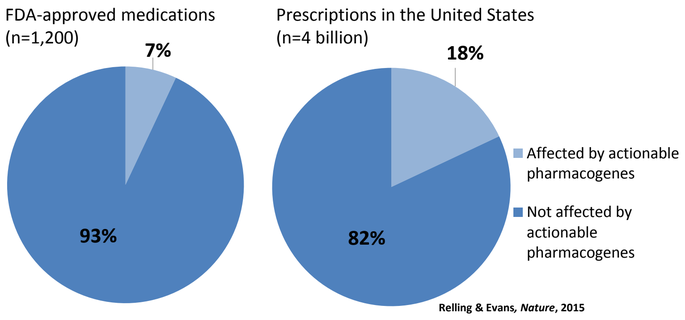

Figure 1. Percentage of medications and prescriptions affected by genotyping of actionable pharmacogenes.

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

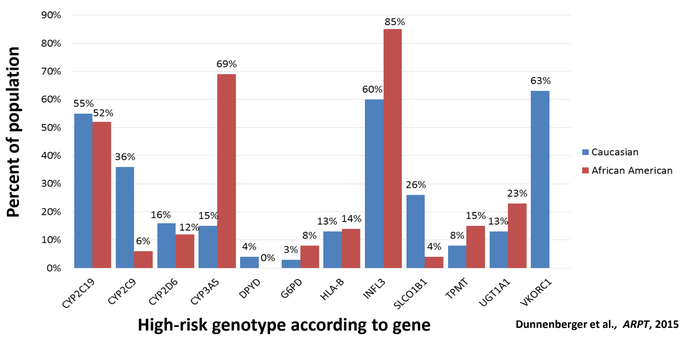

Figure 2. Percentage of individuals predicted to have a high-risk diplotype for 12 PGx relevant genes.

Implementation of preemptive pharmacogenetic testing in combination with phenotypic information allows for personalized drug selection and dosing decisions prior to administration.

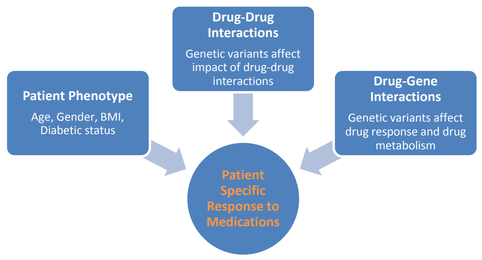

Figure 3. Factors involved in individual patients response to medications.

Comprehensive Pharmacogenetics

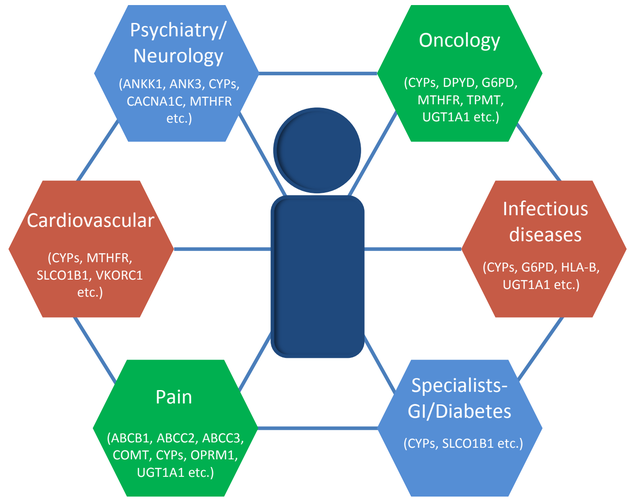

Figure 4. Genes tested on PharmacoScan™ affecting the metabolism of drugs in different clinical categories.

A drug's metabolism may be affected by gene-gene interactions requiring multiple genes to be tested to give accurate dosing recommendations (e.g. warfarin: VKORC1 and CYP2C9) (1,2). Additionally, patients often require multiple medications. The metabolizer status of the genes involved for each drug can affect how the individual will respond if the drugs are taken together (e.g. codeine and propoxyphene) (5). To accurately determine the appropriate selection and dosing of such drugs, a comprehensive genotyping panel is required.

Clinical Implementation of PharmacoScan™

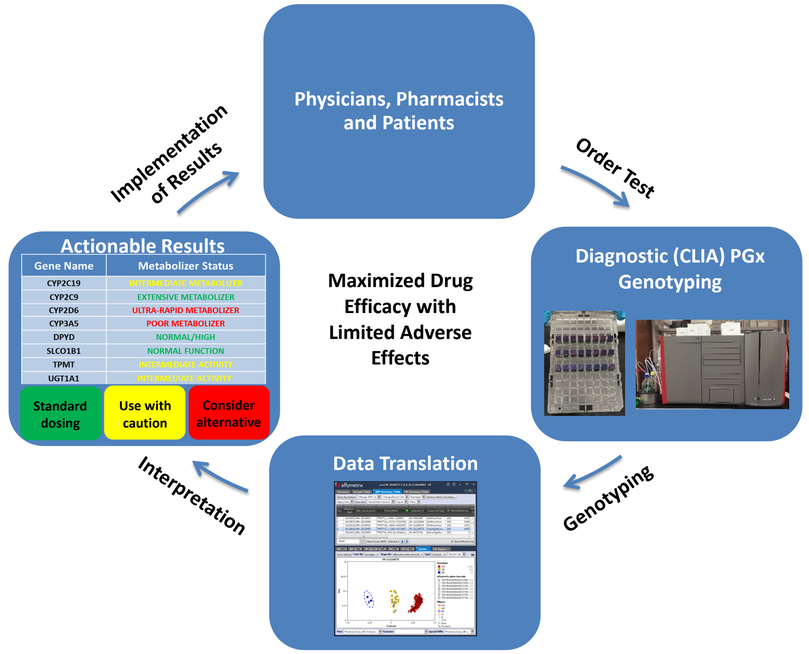

Figure 5. Clinical implementation of Pharmacogenetic testing.

PharmacoScan™ Actionable Genes

Affymetrix's PharmacoScan™ Assay enables genotyping of over 4600 markers in 1191 pharmacogenetic relevant genes in a single test.

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.

PharmacoScan™ Performance

We have tested approximately 5,000 samples on a variety of PGx platforms. To address the need for improved PGx testing, our CLIA certified lab validated the PharmacoScan™ platform for accuracy and the detection of critical PGx variants utilizing the Get-RM sample set (6). We observed high concordance, in particular, in the CPIC and haplotype calling genes.

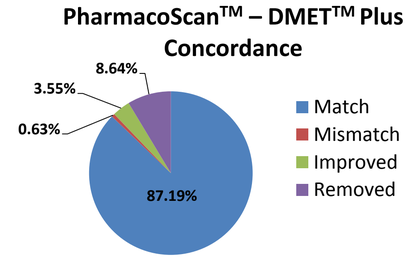

Figure 6. Comparison of genotype calls between PharmacoScan™ and DMET for Coriell Get-RM samples (n=88 samples, for 28 genes).

Conclusion

Data generated on comprehensive platforms can present challenges for interpretation and practical application for both clinicians and patients. As part of our complete diagnostic approach, we developed a workflow to generate quality assured data that is translated in a meaningful and actionable way. In addition to the raw data, we provide translational reports, which include the patient's haplotype-specific metabolizer status based on the CPIC dosing guidelines. 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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4) Dunnenberger et al. Annu Rev Pharmacol Toxicol. 2015;55:89-106
5) Abernethy et al. Br J Clin Pharmacol. 1985;19(1):51-57
6) Pratt et al. J Mol Diagn. 2016;18(1):109-123