PharmacoDx
Pharmacogenetic Testing

Overview:
Pharmacogenetic testing analyzes specific genetic variants to better understand how a person may respond to certain medications (Weinshilboum et al., 2017). The choice and dose of medications are largely determined based on population data; however significant variation in drug response exists. Some of this variation can be attributed to genetic variants in genes associated with drug metabolism and response (Van Driest et al., 2014). On average, about 50-75% of individuals prescribed a particular medication will have the intended response (Spear et al., 2001). Pharmacogenetic testing may be useful to avoid adverse drug reactions (ADRs) as well as the chance that a medication or dose won't work well, which may be cost-effectively beneficial for patient care (Verbelen et al., 2017).

Over 90% of people who undergo panel-based pharmacogenetic testing are expected to have a clinically actionable result (Van Driest et al., 2014; Dunnenberger et al., 2015). Evidence suggests that chance of clinical actionability may vary in people of different ancestries (Van Driest et al., 2014; Dunnenberger et al., 2015).

PharmacoDx is a comprehensive pharmacogenetics panel including over 100 genetic variants involved in drug metabolism, transport, or response. The panel is designed to help providers select the choice and dose of medications that are most likely to be effective and least likely to cause side effects.

Description:
PharmacoDx targets sequence variants in genes known to contribute to drug metabolism and response and for which there is evidence of clinical utility. PharmacoDx provides information on the anticipated response to medications commonly prescribed to treat pain, psychiatric disorders, cardiovascular disease, gastrointestinal conditions, neurological conditions, cancer, and other medical conditions (see details below). PharmacoDx offers evidenced-based suggestions for medication management to guide drug selection and dosing.

PharmacoDx can be performed preemptively, prior to the prescribing of medication, so that results are available to guide initial medication selection and dosing (Relling et al., 2011; Dunnenberger et al., 2015). PharmacoDx can also be used to guide drug therapy for conditions that fail to respond to initial treatment or to aid in the selection of medication in an effort to decrease the chance of ADRs.

Results Reporting:
Each PharmacoDx report includes:

- Anticipated response to specific medications
- Prescribing guidance based on anticipated response
- A detailed summary of the available evidence behind prescribing guidance
- Interpretation for metabolic status for genes involved in drug metabolism
- Patient genotype for each sequenced variant

Medications Addressed with PharmacoDx:

- Antiarrhythmics
- Anticoagulants
- Antidepressants
- Antidiabetics
- Antiepileptics
- Antihypertensives
- Antipsychotics
- Benzodiazepines
- Chemotherapeutics
- Corticosteroids
- General Anesthetics
- Antivirals/Antiretrovirals
- Immunosuppressants
- Muscle Relaxants
- NSAIDS
- Opioids
- Platelet Aggregation Inhibitors
- Proton Pump Inhibitors
- Statins
- Stimulants

Resources for Clinical Applications and Use:
Evidence-based dosing guidelines are available to assist providers in applying pharmacogenetic test results to prescribing decisions. (Relling et al., 2011; Whirl-Carrillo et al., 2012; Swen et al., 2008; 2011; FDA 2017). Pharmacogenetic guidelines are freely available and frequently updated.

Pharmacogenetic information is included in FDA drug labeling for over 100 medications, including several medications with black box warnings of ADRs in patients with specific genetic changes. FDA labeling for these medications often includes specific actions that can be taken based on genetic information. A table of pharmacogenetic biomarkers in drug labeling may be found at fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm.

The Clinical Pharmacogenetics Implementation Consortium (CPIC) offers objective, evidence-based dosing guidelines for many medications (Relling et al., 2011). All guidelines are published in PubMed and available on cpicpgx.org or guideline.gov.

The Pharmacogenetic Knowledge Database houses information about pharmacogenetics, including clinically actionable dosing guidelines for many medications (Whirl-Carrillo et al., 2012). These guidelines and other information are available on pharmgkb.org.

Example Prescribing Applications:

Gene	Medications	Clinical Implications
CYP2C9 and VKORC1	Warfarin	**Poor Metabolizers**: Increased risk of bleeding during therapy. Lower doses to achieve appropriate levels of anticoagulation and more time to achieve a stable INR is recommended
CYP2C19	Citalopram, Escitalopram	**Ultrarapid Metabolizers**: Risk of reduced response. Consider alternative drug **Poor Metabolizers**: Increased risk of side effects. Consider alternative drug
CYP2C19	Sertraline	**Poor Metabolizers**: Increased risk of side effects. Consider alternative drug
CYP2C19	Clopidogrel	**Ultrarapid Metabolizers**: Risk of increased platelet inhibition, decreased residual platelet aggregation, and bleeding complications. Prescribe as directed, monitor for adverse reactions **Poor Metabolizers**: Increased risk of adverse cardiovascular events. Select alternative drug
CYP2D6	Paroxetine	**Ultrarapid Metabolizers**: Risk of reduced response. Consider alternative drug **Poor Metabolizers**: Increased risk of side effects. Consider alternative drug
CYP2D6	Codeine, Tramadol, Hydrocodone, Oxycodone	**Ultrarapid Metabolizers**: Increased risk of drug toxicity. Consider alternative analgesics **Poor Metabolizer**: Risk of insufficient pain relief. Consider alternative analgesics

Test Methods:

Genomic DNA from the submitted specimen is amplified with primers specific for ABCB1, ABCG2, ADRB1, AGT, CACNA1C, CES1, COMT, CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, DPYD, DRD1, DRD2, DRD3, EDN1, GNB3, GRIK4, HTR1A, HTR2A, HTR2C, IFNL3, KCNIP1, LDLR, MTHFR, NR1H3, OPRM1, RYR1, SLC6A2, SLCO1B1, TPMT & VKORC1 using Nested Patch PCR (Varley, et. al.). Targeted regions are sequenced simultaneously by massively parallel (NextGen) sequencing using an Illumina instrument. Sequences are analyzed using alignment and base call algorithms with Kailos Blue Software for the presence or absence of single nucleotide base changes, insertions and deletions. CYP2D6 duplications and deletions are also detected and used for haplotype calling and interpretation.

References:

Dunnenberger et al. (2015) Annu. Rev. Pharmacol. Toxicol. 55 :89-106 (PMID: 25292429)
Relling et al. (2011) Clin. Pharmacol. Ther. 89 (3):464-7 (PMID: 21270786)
Spear et al. (2001) Trends Mol Med 7 (5):201-4 (PMID: 11325631)
Van Driest et al. (2014) Clin. Pharmacol. Ther. 95 (4):423-31 (PMID: 24253661)
Verbelen et al. (2017) Pharmacogenomics J. 17(5):395-402 (PMID: 28607506)
Weinshilboum et al. (2017) Mayo Clin. Proc. 92 (11):1711-1722 (PMID: 29101939)
Whirl-Carrillo et al. (2012) Clin PharmacolTher 92(4): 41-417 (PMID: 22992668)
Swen et al. (2008) Clin. Pharmacol. Ther. 83 (5):781-7 (PMID: 18253145)
Swen et al. (2011) Clin. Pharmacol. Ther. 89 (5):662-73 (PMID: 21412232)
Table of pharmacogenomic biomarkers in drug labeling. US Food and Drug Administration. https://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm. Accessed November 2017.

PharmacoDx Gene and Variant List:

ABCB1	rs72552267	rs5030862	DRD1	rs3813929	rs28933397
rs1045642	rs72558186	rs72549357	rs4532	rs518147	rs121918594
rs2032582	rs41291556	rs28371706	DRD2	rs6318	rs118192167
rs1128503	rs17884712	rs59421388	rs1079598	IFNL3	rs121918595
rs2235015	rs6413438	rs769258	rs1799732	rs12979860	rs118192170
ABCG2	rs55640102	rs28371725	rs1799978	rs8099917	SLC6A2
rs2231142	rs12248560	rs28371696	rs6277	rs8103142	rs3785143
ADRB1	CYP2C9	rs28371717	DRD3	KCNIP1	rs12708954
rs1801252	rs1799853	CYP3A4	rs167771	rs11739136	SLCO1B1
AGT	rs1057910	rs12721627	rs6280	LDLR	rs4149056
rs5051	rs28371686	rs2242480	rs963468	rs688	rs11045819
rs699	rs9332131	rs12721629	EDN1	MTHFR	rs2306283
CACNA1C	rs7900194	rs4987161	rs5370	rs1801133	rs4149015
rs1051375	rs28371685	rs72552799	GNB3	rs1801131	rs4149081
CES1	rs56165452	rs67784355	rs2301339	NR1H3	TPMT
rs71647871	CYP2D6	rs4986909	rs5443	rs11039149	rs1142345
COMT	Duplication	rs35599367	GRIK4	OPRM1	rs1800584
rs4680	Deletion	rs67666821	rs1954787	rs2281617	rs1800460
CYP1A2	rs16947	CYP3A5	HTR1A	rs510769	rs1800462
rs2069526	rs1135840	rs776746	rs10042486	RYR1	VKORC1
rs2470890	rs35742686	DPYD	rs6295	rs118192161	rs9923231
rs4646425	rs1135824	rs67376798	HTR2A	rs121918592	rs9934438
rs4646427	rs1065852	rs3918290	rs7997012	rs118192162	rs17708472
rs762551	rs3892097	rs55886062	rs9316233	rs118192172	rs2359612
CYP2C19	rs5030655	rs2297595	rs6313	rs118192175	rs7294
rs4244285	rs5030867	rs17376848	rs6311	rs118192163	rs8050894
rs4986893	rs5030865	rs1801159	HTR2C	rs118192176	
rs28399504	rs5030656	rs1801158	rs1414334	rs118192177	
rs56337013	rs5030863	rs115232898	rs3813928	rs121918593	