PRECISION MEDICINE ADVISORS

A comparison of commercially available comprehensive pharmacogenomic tests

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INTRODUCTION

The genetic testing landscape has exploded in recent years. With dozens of commercial pharmacogenetic (PGx) tests on the market, selection of which PGx test to order can be challenging for the average health care provider. While PGx tests for single drugs are available, a more cost-effective approach is to test for panels of genes covering multiple drugs. These broad PGx panels are especially useful for pre-emptive PGx testing, where testing is done outside of a medical indication and the results stored in the medical record until needed.

Several factors go into selecting a PGx gene panel test including which genes are on the panel, the variant detection method and scope of variants detected, as well as cost, insurance reimbursement, turn-around-time, ease of use of the report, integration of results into the EHR and other factors. This report addresses the selection of PGx gene panel tests based on the genes on the panel and the variants detected.

BACKGROUND

Among the commercially available comprehensive PGx gene panels, the number of genes on the panels varies considerably, ranging in size from a few genes to several dozen. Many of the test providers tout coverage of a larger number of drugs by these genes as a selling point for their PGx panels. Yet, bigger panels are not always better. The quality of the genes in terms of their clinical validity and utility may be a better metric. Clinical validity refers to the strength of association between the gene and drug response. This includes both the evidence supporting statistical significance and reproducibility of results, as well as the predictive value of the test. Clinical utility refers to whether the test results impact prescribing action (drug avoidance or dosing change). Some gene/drug pairs are supported by strong scientific and clinical evidence of clinical validity while others are not. Some PGx tests have good clinical validity, and yet the results won't change prescribing action.

Two related professional organizations evaluate the clinical validity/utility of PGx tests in the US: The Phamacogenomics Knowledge Base (PharmGKB) evaluates the scientific literature for genetic association between the gene and drug response (clinical validity); The Clinical Pharmacogenetics Implementation Consortium (CPIC) evaluates the gene-drug pair for the strength of evidence supporting prescribing changes (clinical utility).

Both CPIC and PharmGKB provide classification of gene/drug pairs into levels of evidence (Table 1).

For the most clinically valid genes, CPIC and PharmGKB ratings are generally in agreement. Current CPIC guidelines are for genes supported by the highest level of evidence from PharmGKB. With few exceptions, the availability of CPIC guidelines is probably the best indication of clinical validity and utility.

Table 1. Classification Levels from PharmGKB and CPIC

	Level	Meaning
PharmGKB[1]		
	1A, 1B	High evidence of genetic association
	2A, 2B	Moderate evidence of genetic association
	3, 4	Low evidence of genetic association
CPIC[2]		
	A, B	Prescribing action recommended
	C	No prescribing action, but testing common
	D	No prescribing action recommended

The breadth of indications for a given gene panel varies as well. Some panels are limited to drugs within a specific therapeutic area (e.g. cardiology, pain, etc), while others are broader and may be used across therapeutic areas. Many organizations are moving toward broad, preemptive testing of genes across several therapeutic areas. Broad PGx panels are thought to be more useful throughout the patient's lifetime as they are not limited to a certain therapeutic area.

In this report, we analyze the gene composition of commercially available broad PGX panel tests, as well as the specific variants analyzed.

METHODS

Selection of panel tests

To identify commercially available PGx tests, we searched the Concert Genetics database[3] in November 2018 using the term *pharmacogenetic*. Concert maintains the most comprehensive catalog of genetic tests available in the US. We removed panels covering single therapeutic areas as well as those with <10 genes.

Selection of clinically valid genes to benchmark against

We accessed the CPIC website to identify a list of gene/drug pairs that were included in CPIC guidelines, either published, in progress or in review[4]. All genes included in CPIC guideline genes have strong evidence supporting prescribing changes (17 classified with CPIC level 'A', 1 with 'A/B' and 1 with 'B').

To assess the relevance of a given pharmacogene to the average patient population, we cross-referenced the list of CPIC genes with a list of the 200 most commonly prescribed drugs from 2016[5].

[1] PharmGKB Levels: https://www.pharmgkb.org/page/clinAnnLevels
[2] CPIC Levels: https://cpicpgx.org/prioritization/#cpicLevels
[3] Concert Genetics: https://app.concertgenetics.com/apps/search/#/
[4] CPIC guidelines: https://cpicpgx.org/prioritization-of-cpic-guidelines/
[5] Commonly prescribed drugs: https://clincalc.com/DrugStats/

Evaluation of variants detected by each lab

We obtained information about specific variants detected by each lab by accessing their sample reports and test literature from their websites. In some cases, direct communication with the lab was necessary. Comparisons were made only for the three most important genes: CYP2D6, CYP2C9 and CYP2C19.

Allele frequencies and activities (whether the variant results in an increase, decrease or loss (null) of activity) were obtained from the PharmGKB website[6]. Allele frequencies are presented in PharmGKB broken down by ethnic group. Since frequencies can vary substantially by ethnic group, we selected the maximum allele frequency reported (MaxAF) in any given ethnic group. MaxAF does not represent the overall population allele frequency (which would be the weighted average of all populations and thus be lower). Rare variants (MaxAF<.01) were not included in comparisons, nor were alleles whose function was uncertain.

RESULTS

Number and type of available PGx panel tests

A search of the Concert Genetics database revealed 104 products in 9 categories (Table 2). Most categories were for narrow indications, either single genes or single therapeutic areas. The largest category was 'Pharmacogenetic Panel Tests' with 52 products.

Table 2. Test Categories and Number of PGx Products in Concert Genetics Database

Test Category	# of Products
Attention Deficit Hyperactivity Disorder PGx Panel Tests	2
CFH Targeted Mutation Analysis Tests	6
Newborn Diagnostic Targeted Panel Tests	9
Pharmacogenetic Neuropsychiatric Panel Tests	19
PGx Cytochrome P450 Panel Tests	22
TPMT Typing (Thiopurine Medications) Tests	36
CYP2D6 Targeted Mutation Analysis Tests	37
CYP2C19 Targeted Mutation Analysis Tests	43
Pharmacogenetic Panel Tests	52

Evaluation of the 52 products in the PGx Panel Tests category revealed many for single therapeutic areas (e.g. hematology panel, PgxPsych, etc). The most common therapeutic areas included pain, oncology and cardiology. After removing these tests from consideration, there were 17 remaining.

Selection of clinically valid genes to benchmark against

Nineteen genes have CPIC guidelines (16 published; 1 in review; 2 in progress) (Table 3). All but two CPIC guideline genes had strong evidence of clinical validity (PharmGKB level 1A or 1B). Two CPIC guideline genes, RYR1 and CACNA1S, had low evidence of clinical validity (PharmGKB level 3), but according to PharmGKB these are being revised (personal communication).

[6] PharmGKB allele frequencies and activities: https://www.pharmgkb.org/page/pgxGeneRef

Table 3. Genes with Greatest Clinical Validity/Utility

Genes	PharmGKB Level	CPIC guidelines	CPIC class
CYP2C9	1A	Published	A
CYP2C19	1A	Published	A
CYP2D6	1A	Published	A
CYP3A5	1A	Published	A
VKORC1	1A	Published	A
SLCO1B1	1A	Published	A
TPMT	1A	Published	A
DYPD	1A	Published	A
IFNL3	1A	Published	A
CYP2B6	1B	in progress	B
HLA-B	1A	Published	A
CFTR	1A	Published	A
G6PD	1A	Published	A
CYP4F2	1A	Published	A
HLA-A	1A	Published	A
UGT1A1	1A	Published	A
NUDT15	1B	Published	A/B
RYR1	3	in review	A
CACNA1S	3	in review	A

Among all genes with evidence of clinical validity (PharmGKB Level 1), all but two are the subject of CPIC reviews. The two remaining PharmGKB evidence Level 1B genes without CPIC guidelines are ANKK1 and XPC.

Some CPIC guidelines are for commonly prescribed drugs like simvastatin, while others are for uncommonly prescribed drugs like ivacaftor, used to treat cystic fibrosis. The 200 most commonly prescribed drugs include several with CPIC guidelines. Eight of the 19 CPIC guideline genes are for drugs among the top 200 most commonly prescribed. These include the following genes and drugs (Table 4):

Table 4. CPIC Genes and Drugs among the Top 200 Most Commonly Prescribed

Gene	Drugs
CYP2C19	sertraline, citalopram, excitalopram, clopidogrel, amitriptyline, omeprazole, esomeprazole
CYP2C9	warfarin, diclofena, celecoxib
CYP2D6	methylphenidate, paroxetine, amitriptyline, ondansetron, nortriptyline
CYP4F2	warfarin
SLCO1B1	simvastatin
HLA-B	allopurinol, carbamazepine
VKORC1	warfarin
HLA-A	carbamazepine

Evaluation of broad commercial PGx panels

Panels ranged in size from five genes to 59. None of the panels included all 19 CPIC guideline genes. The six largest panels included the greatest number of CPIC guideline genes. The remainder of the analyses are based on these six panels.

Table 5 shows the coverage of CPIC guideline genes in the six largest panels. Lab1 has the largest coverage of CPIC guideline genes (16/19), followed by Lab5 (15/19).

Table 5. Coverage of CPIC Guideline Genes in Six Commercial PGx Panel Tests

Genes	Lab1	Lab2	Lab3	Lab4	Lab5	Lab6
# panel genes	59	50	38	34	28	26
# CPIC genes	16	14	12	10	15	14
CYP2C9	x	x	x	x	x	x
CYP2C19	x	x	x	x	x	x
CYP2D6	x	x	x	x	x	x
VKORC1	x	x	x	x	x	x
SLCO1B1	x	x	x	x	x	x
HLA-B	x	x			x	x
HLA-A	x				x	x
CYP4F2	x	x			x	x
CYP3A5	x	x	x	x	x	x
TPMT	x	x	x	x	x	x
DYPD	x	x	x	x	x	x
IFNL3		x	x	x	x	x
CYP2B6	x	x			x	x
CFTR	x		x			
G6PD	x	x				
UGT1A1	x	x			x	
NUDT15	x				x	
RYR1			x	x		
CACNA1S			x			

The first eight genes (highlighted in blue) are the genes associated with commonly used drugs. Three labs covered all eight CPIC guideline genes for common drugs (Lab1, Lab5 and Lab6). Reasons for lack of coverage of CPIC-guided genes include: being newer (HLA-A) or not yet published guidelines (RYR1, CACNA1S); uncommon drugs (CFTR); a shift in prescribing of drug (IFNL3); or difficult assays (G6PD)[7].

Besides the genes covered under CPIC guidelines, each panel included a number of other genes not covered by guidelines. Some of these genes may be supported by other guidelines, like those from the the Dutch Pharmacogenomics Working Group (DPWG); However, many of the non-CPIC

[7] Robinson, KM et al. Pharmacogenomics J. 2018 Sep 12

genes tend to have either moderate or low amount of evidence supporting their association with drug response, or low to moderate evidence in favor of changing prescribing behavior. Examples of these genes include KIF6, TYMS, LDLR and PTGS1 (all with CPIC level D – *no prescribing action recommended*). Some genes like KCN1P1 are not even rated by CPIC or PharmGKB.

Figure 1. Proportion of CPIC Genes in Six Commercial PGX Panel Tests

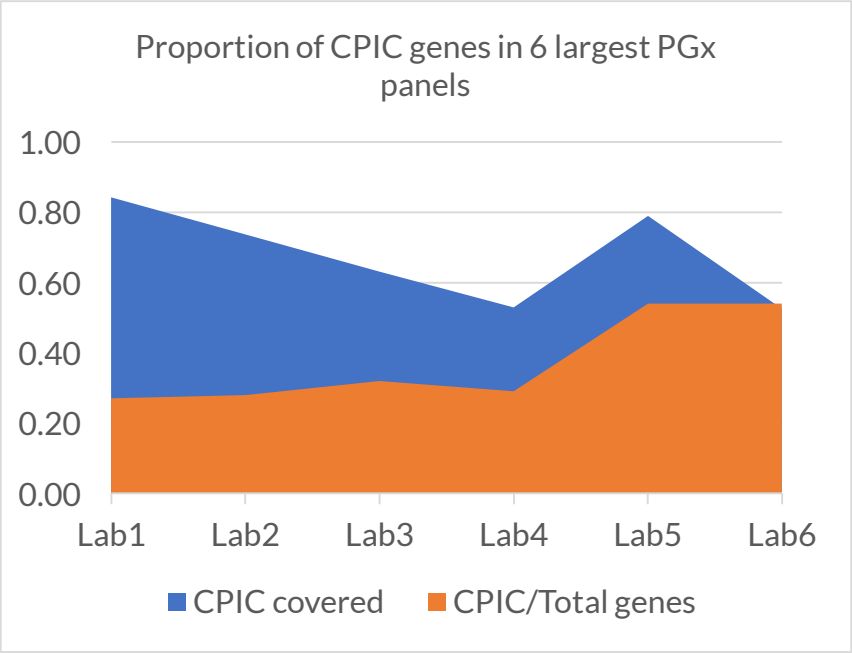

Figure 1 illustrates CPIC coverage by the six largest panels. The blue area shows the amount of coverage of CPI genes. The greatest coverage of CPIC genes by a lab was 16/19 (84%) for Lab1, as stated earlier. The orange area of the graph shows the proportion of all genes on each lab's panel that are CPIC guideline genes. In other words, for Lab1, although it has the best coverage of CPIC guideline genes, these represent only 27% of genes on the panel. The remaining 73% of genes are not supported by CPIC guidelines. Among the six panels evaluated, Lab5 and Lab6 had the highest proportion of clinically valid genes (54%).

Evaluation of variants detected by each lab

Differences were noted in the number of gene variants analyzed by each lab. Each gene has several common functional variants (>1% maximum allele frequency). For example, there are four common variants of CYP2C19, six of CYP2C9 and 13 of CYP2D6. All of these variants result in a change in enzyme activity.

As shown in Table 6, coverage of these variants is not uniform across the top six lab tests. For CYP2C19, only three labs captured the *9 allele, a variant found predominantly in people of African descent. For CYP2D6, only two labs captured *40 (predominant in Africans) and only two captured *36 (predominant in East Asians). Besides common variants, each of these genes has several rare functional variants (<1% prevalence in a single ethnic group). Testing for these provides slightly greater sensitivity (data not shown).

For CYP2D6, all labs were capable of detecting important gene duplication events resulting in increased enzyme activity (1XN and 4XN being the most common in the population).

Coverage of alleles was generally quite good across all labs. Lab2 and Lab5 had the broadest coverage of common alleles (22/23 common alleles), followed by Lab3 (21/23 common alleles).

Table 6. Coverage of common variants of CYP2C19, CYP2C9 and CYP2D6 by top six lab tests.

CYP2C19 # variants	Activity	Max AF	Lab1 3/4	Lab2 4/4	Lab3 4/4	Lab4 4/4	Lab5 3/4	Lab6 4/4
*2	Null	0.54	x	x	x	x	x	x
*17	Increased	0.22	x	x	x	x	x	x
*3	Null	0.15	x	x	x	x	x	x
*9	Decreased	0.04		x	x	x		x

CYP2C9	Activity	Max AF	Lab1 6/6	Lab2 6/6	Lab3 6/6	Lab4 6/6	Lab5 6/6	Lab6 6/6
*2	Decreased	0.13	x	x	x	x	x	x
*3	Decreased	0.10	x	x	x	x	x	x
*8	Decreased	0.07	x	x	x	x	x	x
*11	Decreased	0.03	x	x	x	x	x	x
*5	Decreased	0.01	x	x	x	x	x	x
*6	Null	0.01	x	x	x	x	x	x

CYP2D6	Activity	Max AF	Lab1 10/13	Lab2 12/13	Lab3 11/13	Lab4 11/13	Lab5 13/13	Lab6 12/13
*10	Decreased	0.42	x	x	x	x	x	x
*17	Decreased	0.20	x	x	x	x	x	x
*41	Decreased	0.20	x	x	x	x	x	x
*4	Null	0.18	x	x	x	x	x	x
*29	Decreased	0.09	x	x	x	x	x	x
*5	Null (deletion)	0.06	x	x	x	x	x	x
*12	Null	0.02		x	x	x	x	x
*9	Decreased	0.02	x	x	x	x	x	x
*40	Null	0.02		x			x	
*3	Null	0.01	x	x	x	x	x	x
*36	Null	0.01					x	x
*1XN	Increased	0.12	x	x	x	x	x	x
*4XN	Increased	0.02	x	x	x	x	x	x

SUMMARY

In this report, we analyze the coverage of genes and gene variants among commercially available comprehensive PGx tests. While it's tempting to make a correlation between the size of a gene panel, or the number of drugs covered by those genes, larger gene panels don't necessarily provide more value. We evaluated in detail the six tests with the broadest coverage of CPIC

guideline genes, representing genes with the highest level of evidence supporting both clinical validity and utility. Lab1 and Lab5 had the broadest coverage of CPIC genes.

All of the gene panels evaluated included genes that were not covered by CPIC guidelines. The relationship between the gene and drug is not always supported by sufficent evidence and/or the predictive value of the variant may be small. Moreover, for some genes, there may be evidence supporting an association, but the test may not change prescribing behavior. For these reasons, CPIC guideline-supported genes represent the most clinically valid and useful pharmacogenes to evaluate. The inclusion of other non-CPIC genes can lead to uncertainty in test interpretation and may lack clinical validity and/or utility. Lab5 and Lab6 were the leanest in terms of having the smallest proportion of non-CPIC genes.

The extent to which a test covers the most relevant variants in a gene is an important consideration. Failure to detect commonly occuring functional variants can impact the test's sensitivity, leading to false negative results. In terms of the specific variants analyzed in the three major cytochrome P450 genes, Lab2 and Lab5 had the most comprehensive coverage of the known common functional variants in each of these three genes, but all labs had generally good coverage.

Several of the commercially available comprehensive panels provide good coverage of CPIC-guideline genes as well as the most common functional variants in these genes. In addition, all of the six panels evaluated included non-CPIC guideline genes. These extra genes have the potential to confuse test users who may not be aware of the possible differences in validity of these test results compared to CPIC guideline gene results. Test providers should clearly distinguish guideline-supported genes from others in the test report and provide information on the possible limitations of those results.

More information about each of these labs can be found at their websites:

	Company	**Product**	**Website**
Lab1	Phosphorous	Drug Response Panel	https://www.phosphorus.com/get-started/
Lab2	Admera	PGXONE Plus	https://www.admerahealth.com/pgx/
Lab3	Kailos	PGx Complete	https://www.kailosgenetics.com/targetrich-pgxcomplete
Lab4	GeneDx	PharmacoDx	https://www.genedx.com/test-catalog/available-tests/pharmacodx/
Lab5	OneOme	RightMed	https://oneome.com/rightmed-comprehensive
Lab6	Genelex	Polypharmacy Comprehensive Panel	https://www.genelex.com/test-menu/

