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Horizon Scan Of Clinical Laboratories Offering Pharmacogenetic Testing

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Abstract

Pharmacogenetic (PGx) testing involves the analysis of genes known to affect response to medications. The field has been projected as a leading application of personalized or precision medicine, but the use of PGx tests has been stymied, in part, by the lack of clinical evidence of utility and reported low provider awareness. Another factor is the availability of testing. The range and types of PGx tests available have not been assessed to date. In the period September 2017–January 2018 we analyzed the numbers and types of PGx tests offered by clinical testing laboratories in the US. Of the 111 such labs that we identified, we confirmed that 76 offered PGx testing services. Of these, 31 offered only tests for single genes; 30 offered only tests for multiple genes; and 15 offered both types of tests. Collectively, 45 laboratories offered 114 multigene panel tests covering 295 genes. The majority of these tests did not have any clinical guidelines. PGx tests vary in type and makeup, which presents challenges in appropriate test evaluation and selection for providers, insurers, health systems, and patients alike.

The field of personalized (or precision) medicine has benefited tremendously from a combination of factors, including federal and private funding, technology development, and the increasing availability of electronic medical records and large and comprehensive genomic data sets. As a result, numerous technologies have been developed and introduced into clinical practice to screen, predict, and diagnose disease and inform treatment decisions. One example is pharmacogenetic (PGx) testing, or the analysis of genes associated with drug targets (pharmacodynamics) or how drugs are processed in the body through metabolic and transport pathways (pharmacokinetics). Over the past few decades the PGx field has been propelled by an avalanche of research and resources such as the National Institutes of Health's (NIH's) PharmGKB, a resource of PGx genetic variants,[1] and Pharmacogenomics Research Network,[2] a network of investigators conducting PGx research (both established in 2000), as well as numerous clinical trials.[3] Follow-up initiatives have been exploring the implementation of PGx testing in various clinical settings.[4–6]

With increased understanding of the impact of genetic variation on drug response and targets, commercial development of clinical PGx testing soon followed. In 2005 the first PGx tests were approved by the Food and Drug Administration (FDA), Affymetrix's Amplichip P450 and Third Wave Technologies' Invader *UGT1A1* Molecular Assay. The

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introduction of PGx tests, however, has left clinicians, health systems, insurers, regulators, and patients scrambling to understand how best to incorporate these applications into clinical practice.[7] In particular, questions have been raised about what types of tests are available and when and for whom they should be ordered; what evidence is needed to support the use of such tests (clinical utility); how test results should be stored in electronic medical records and consulted when new medications are needed; and what kinds of clinical decision supports are needed, such as automated alerts about PGx testing that are triggered when a drug known to be affected by a PGx variant is prescribed.[8–10] Despite advances in PGx testing, the types of available tests and the number and types of laboratories that offer them have not been previously reported. In this article we conducted a horizon scan of the laboratories that offer clinical PGx testing in the US.

Study Data And Methods

Identifying Laboratories

In the period September 1, 2017–January 31, 2018, we identified laboratories that offer clinical PGx testing through searching such sources as the internet, the NIH Genetic Testing Registry, the McKesson Diagnostics Exchange, the Association for Molecular Pathology's Test Directory, , and published literature. Inclusion in these registries and databases is voluntary, and laboratories must submit their information to be listed. We searched PubMed for studies published in English during the previous two years containing the keywords *pharmacogenetics* or *pharmacogenomics* and limited to clinical trials. For studies in which PGx testing was performed, we reviewed the methods section of the article to determine which laboratory performed the tests. In addition, we also reviewed the clinical PGx test services offered by institutions participating in large NIH clinical genomics networks such as the Electronic Medical Records and Genomics (eMERGE) Network and the Implementing Genomics in Practice (IGNITE) program.

We identified an internet address for each laboratory to review the information about its PGx test offerings. If the laboratory listed PGx testing as one of its services but did not provide specific information about what genes were tested, we used information provided from other resources (such as the McKesson Diagnostics Exchange), if available. We excluded laboratories that offered testing only for drug targets (such as *EGFR*, *k-RAS*, or *HER2/Neu* for oncology drugs) because these are somatic-based tests of tumor tissue for single drugs. We also excluded laboratories that offered testing only for research purposes because they do not provide clinical tests that providers may order. We verified that all laboratories have the appropriate accreditation to offer clinical testing in the US. We contacted laboratories that did not have a website to confirm that they were still in business and offering PGx testing.

Abstracting Information

For each laboratory, we abstracted the following information for each PGx test, as applicable: the type of PGx test either tests of asingle gene or multigene panel), the gene or genes tested, the type of laboratory services offered (reference, general genetic testing, or drug testing/toxicology), and whether the lab was independent (publicly traded or private),

or affiliated with a hospital or academic medical center. Tests were categorized as either single-gene or multigene panel tests (as defined by the National Cancer Institute,[11] the latter type of test looks for mutations in multiple genes simultaneously with each individual genotype returned), in contrast to tests that generate a cumulative score based on an algorithm (referred to as multianalyte assays with algorithmic analyses). For warfarin (brand name Coumadin), the two genes that are typically tested (*CYP2C9* and *VKORC1*) were coded as a single-gene test because results from both are used to make a treatment decision. Both authors independently completed data abstraction, with differences reconciled through further review of the available information.

The Clinical Pharmacogenetics Implementation Consortium (CPIC) is an international group of PGx experts that reviews and ranks the evidence of drug-gene interactions and develops clinical guidelines.[12] It has given its highest ranking of "A" (prescribing action recommended) or a ranking of "1A" (PharmGKB clinical annotation level of evidence "for a variant-drug combination in a CPIC or medical society–endorsed PGx guideline, or implemented at a PGRN site or in another major health system") or "1B" ("where the preponderance of evidence shows an association") to fourteen genes tested for use of thirty-three drugs. These fourteen genes are *CFTR*, *CYP2C9*, *CYP2C19*, *CYP2D6*, *CYP3A5*, *CYP4F2*, *DPYD*, *G6PD*, *HLA-B*, *IFNL3*, *SLCO1B1*, *TPMT*, *UGT1A1*, and *VKORC1*. We excluded *CFTR* from our analysis because it is a disease-causing gene associated with drug efficacy, and the test is typically done as part of diagnosis, not treatment. For laboratories that offered only single-gene PGx tests, we noted which of the thirteen genes were available for testing. For laboratories that offered only panel tests, we recorded the panel name or indication (if given) and the genes included in the panel (if disclosed), including the CPIC genes ranked "A." All data points were coded, recorded, and analyzed in Microsoft Excel.

Limitations

While the data reported here provide some insight into the range and type of clinical PGx tests available, this study had some limitations. First, clinical laboratories revise their menus of test services, so their websites might not reflect the most current offerings or accurate test details (for example, the genes included in panels may change). Second, some laboratories do not provide specific information about which PGx tests they offer or which genes are included in their panels. Third, we did not collect data regarding specific variants (single nucleotide polymorphisms) or testing methodology, as these types of data are not typically disclosed. Thus, possible differences between these test features for the same genes could not be ascertained. Lastly, we did not conduct a comprehensive search of academic medical centers' pathology or genetic testing laboratories. We presume that more centers offer PGx testing than were analyzed in this study.

Study Results

We identified 111 laboratories through our searches. However, we were unable to confirm that 35 of the laboratories existed (we found no websites for them) or offered clinical PGx testing, which gave us 76 (68 percent) labs for our analysis (exhibit 1). (See online appendix exhibit A1 for a list of laboratories.)[13] Laboratories that offered a range of genetic tests were

the most common type of laboratory offering PGx testing, accounting for nearly one-third of the total. This was followed by specialty laboratories that offered only PGx testing (nearly one-fifth). Overall, nearly three-fourths of the laboratories were privately owned.

Of the seventy-six testing laboratories, about 40 percent offered only single-gene PGx tests, and a similar proportion offered only multigene panel tests. The remaining laboratories offered both types of tests. Among the forty-six laboratories that offered single-gene PGx testing, a total of 219 tests were available for the thirteen genes ranked "A" by CPIC (data not shown). However, five genes (*CYP2C9*, *CYP2C19*, *CYP2D6*, *CYP3A5*, and *VKORC1*) accounted for 74 percent of these tests. Thirty-eight (83 percent) labs offered testing for *CYP2D6*, thirty-nine (85 percent) for *CYP2C19*, thirty-one (67 percent) for *CYP2C9*, twenty-seven (59 percent) for *VKORC1*, and twenty-six (56 percent) for *CYP3A5*. None of the laboratories offered individual PGx tests for all thirteen genes (mean: 5; range: 1–12).

Collectively, the forty-five laboratories that conducted panel testing offered 114 panel tests (exhibit 2). Of these laboratories, specialty labs, which offered only PGx testing, were the most common (nearly 30 percent), followed by genetic testing labs that offered a range of genetic tests (nearly 25 percent). Laboratories offered 1–9 panel tests (mean: 3). Panel sizes ranged from 2 to 231 genes (mean: 14). Specific information about the size or gene composition of the panels was available for 77 of the 114 (68 percent) panel tests (data not shown).

Overall, the PGx panel tests covered 295 genes (appendix exhibit A2).[13] Most of the panel tests included at least some of the thirteen genes ranked "A" by CPIC. The most commonly included of these genes were *CYP2D6*, which was included in sixty-six panel tests, followed by *CYP2C19* in sixty-one, *CYP2C9* in fifty-seven, and *CYP3A5* in fifty-two tests. The most commonly included other genes were *CYP3A4*, which was included in fifty-four tests, followed by *COMT* in thirty-eight, *CYP1A2* in thirty-four, *MTHFR* in thirty-three, and *OPRM1* and *CYP2B6* in twenty-seven tests each. (The indications and drugs associated with these commonly tested genes are too numerous to mention here, but they may be found in the CPIC guidelines.[14] Labs may have listed other indications and drugs in addition to these.)

Discussion

The PGx test field is still in an early stage of clinical development and adoption. Thus, the diversity of available tests reported in this article might be expected, as test developers are faced with a wealth of data and technologies and are seeking to achieve a competitive advantage. However, the range of test options may also prove overwhelming to inexperienced health care providers trying to make decisions about what tests are appropriate for their patients.

We found that the number of laboratories offering single-gene PGx tests was about the same as the number of labs offering multigene panel tests. The industry trend is toward panel tests of larger numbers of genes, started by Roche's FDA approved 2-gene AmpliChip in 2005[15] to Affymetrix's225-gene DMET Chip in 2010[16] (now expanded to 231 genes).[17] The

movement away from traditional single-gene tests is not unique to PGx: Multigene panel tests have been developed for carrier screening (to identify whether one or both parents carry a copy of a mutated gene to determine their risk of having a child with a genetic condition), cancer susceptibility, cardiovascular disease, and developmental disabilities.[18,19] In 2012 a PGx genotyping array that included 117 genes was developed by investigators at Stanford University and the University of Florida.[20] In 2014 the PGRN-Seq capture panel was developed, which includes 84 genes associated with PGx pathways.[21] The diversity in gene panels that we found is not unique to PGx tests, either, and has been reported for other clinical indications.[22,23]

For gene panels, individual genes have differing levels of evidence of clinical validity.[24–26] With the exception of the gene pairs *CYP2C9*/*VKORC1* for warfarin and *CYP2C9*/*HLA-B* for phenytoin (brand name Dilantin), all of the CPIC guidelines focus on a single gene-drug or gene–drug class interaction. The combined effect of variations in multiple genes relevant to a given medication remains largely unknown, though some test developers have suggested that combinatorial PGx testing, including genes involved in pharmacokinetic and pharmacodynamic pathways, may provide a more comprehensive prediction of drug response by using proprietary algorithms to predict drug safety[27] and may reduce medication costs.[28]

The use of multigene panel tests in place of multiple single-gene/analyte tests often ordered together can reduce the burden and cost on physicians, laboratories, patients, and payers. However, multigene panel tests may present challenges related to evaluation, test selection, insurance coverage, and patient communication.[29–32] Traditional frameworks for genetic test evaluation,[33] which involve assessing analytic and clinical validity and utility, are more difficult to apply to comprehensive genomic technologies,[34] particularly given the variety of clinical scenarios in which testing can be ordered and the scope and heterogeneity of panels.

The experience with the rapid growth of cancer susceptibility panels may provide some insight into the future of PGx multigene panel testing.[35] Comparisons of these panels to single-gene testing have yielded conflicting data regarding clinical value, which varies across cancer types.[35–43] Even when highly validated genes, such as *BRCA1* and *BRCA2* for breast and ovarian cancer risk, are included in breast cancer susceptibility panels, such panels are not typically covered by insurance because they are considered “experimental” or “investigational.”[44–46] We speculate that the inclusion of more genes rated “A” by CPIC on PGx multigene panel tests will not necessarily garner positive insurance coverage decisions, because different drugs or drug classes possess differing levels of evidence.

At this time, the clinical value of large panels may reside mostly with a handful of well-understood and highly polymorphic genes. For example, an analysis of just five genes in about five thousand people tested with an 84-gene PGRN-Seq capture panel found that 99 percent of those tested carried at least one clinically actionable variant or known variant important for treatment decision making.[47] However, the clinical value of large comprehensive panels may largely be determined by the clinical context. For example, if PGx testing is ordered to inform an immediate treatment decision, a test with only genes having a high level of evidence for that medication may be medically indicated. But the most

common type of PGx multigene panel test in our analysis was a comprehensive panel test with no specific clinical indication. If such comprehensive tests are ordered preemptively or in advance of a patient's needing a medication, they may be justified because it is unknown which medications will be used in the future, and the clinical significance of the data may increase over time. Although there is no consensus regarding the use of preemptive PGx testing,[48,49] a number of academic medical centers have implemented preemptive testing programs that will yield valuable insights regarding clinical validity and utility.[21,50]

While a few studies have shown cost savings associated with multigene panel tests,[51] the economic value may be perceived more favorably by patients (less cost per gene in panels than multiple single-gene tests) than by insurers. Some laboratories offer different sizes of multigene panel tests, such as a basic panel and a larger, more comprehensive one, to accommodate different clinical scenarios and, potentially, patients' preferences. In cancer, high-risk patients expressed a preference for multigene panel tests over single-gene tests; preference for a large panel over a small one was higher among those with higher education levels and those currently unaffected.[52] Furthermore, patients who have received uninformative results from prior single-gene testing are more likely to be interested in multigene panel testing.[53,54] These data support speculations that large cancer susceptibility panels may eventually be replaced by whole genome or exome sequencing (despite their limited sensitivity), as use of these more comprehensive tests expands.[29]

With the wide range of PGx tests available today, some guidance is definitely needed to inform providers' decisions about appropriate test use and insurers' decisions about coverage. For example, a scoring system to reflect the cumulative level of evidence for test panels for a specific phenotype or medication could be useful. However, the rapidly changing knowledge base about PGx may quickly make test evaluations outdated. Instead of or in addition to a scoring system, a laboratory could add to its online test menu a link to each test with the corresponding CPIC or other clinical guidelines or with a drug's FDA package insert that contains information about the relevant gene, variant, or both. This approach may curtail the development or use of PGx tests without such supporting evidence. For comprehensive tests ordered preemptively, clinical decision supports or access to a laboratory database to generate updated test reports based on current evidence and guidelines are needed.

With growing awareness among providers and patients, we anticipate that the use of PGx testing will accelerate and, as a result, that laboratories will adjust the scope and type of clinical PGx tests available based on clinical demand and test usage. We further anticipate continuing growth in PGx multigene panel tests (versus single-gene tests) in particular in the near future, in a way that mirrors developments in oncology, microbiology, and other specialties. However, appropriate clinical use and implementation of such tests will be more complex and require the support and involvement of multiple stakeholders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Notes

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Exhibit 1:

Characteristics of pharmacogenetic (PGx) testing laboratories

	Number	Percent
Labs reported to offer PGx testing	111	100
Labs confirmed to offer PGx testing	76	68
Single-gene testing only	31	41
Panel testing only	30	39
Both single-gene and panel testing	15	20
Lab services offered (n = 76)		
Reference/national	11	14
Reference/regional, hospital based	12	16
Genetic testing (offers a range of genetic tests)	21	28
Specialty (offers PGx testing only)	14	18
Drug testing or toxicology	8	10
Other	9	12
Unknown	1	1
Laboratory type (n = 76)		
Publicly traded	8	10
Private or investor backed	56	74
Hospital (academic medical center)	10	13
Hospital (non–academic medical center)	1	1
Unknown	1	1

SOURCE Authors' analysis of clinical testing laboratory databases and directories, clinical studies, and online searches conducted in the period September 2017–January 2018. NOTES Data were extracted from the websites of each testing laboratory. Percentages might not sum to 100 because of rounding.

Exhibit 2:

Features of 45 laboratories that offer pharmacogenetic (PGx) panel tests, and numbers and sizes of panel tests

	Number	Percent
Lab services offered		
Reference/national	5	11
Reference/regional, hospital based	5	11
Genetic testing (offers a range of genetic tests)	11	24
Specialty (offers PGx testing only)	13	29
Drug testing or toxicology	6	13
Other	4	9
Unknown	1	2
Laboratory type (n = 45 labs)		
Publicly traded	4	
Private/investor backed	37	82
Hospital (academic medical center)	2	4
Hospital (nonacademic medical center)	1	2
Unknown	1	2
Panel tests and sizes		
Panel tests offered by the 45 labs	114	—[a]
Panel tests offered per laboratory	9[b] 1–9[b]	—[a]
Panel size (genes)	[c] 2–231	—[a]
Clinical or drug indication of panel test[d]		
Comprehensive or nonspecific	36	31
Cardiovascular	16	14
Pain	21	18
Psychiatry or mental health	15	13
Neurology, attention deficit hyperactivity disorder, surgery/preop/orthopedics, gynecology, urology, epilepsy, opioid addiction, transplant, age-related macular degeneration, high-risk human leucocyte antigen, thrombosis/thrombophilia, statins, warfarin, Plavix, breast cancer	29[e]	25

SOURCE Authors' analysis of clinical testing laboratory databases and directories, clinical studies, and online searches conducted in the period September 2017–January 2018. NOTES Data were extracted from the websites of each testing laboratory. Not all laboratories disclosed details about the panel tests they offered. Data about panel size were available for seventy-seven panel tests. Percentages might not sum to 100 percent because of rounding.

[a] No corresponding percentage.

[b] Mean: 3; median and mode: 1.

[c] Mean: 14; median: 10; mode: 8.

[d] Some panels had multiple indications, so the total is 117.

[e] Fewer than five each.