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Expanding Evidence Leads to New Pharmacogenomics Payer Coverage

Philip E. Empey, PharmD, PhD[1], **Victoria M. Pratt, PhD**[2], **James M. Hoffman, PharmD, MS**[3,4], **Kelly E. Caudle, PharmD, PhD**[4], **Teri E. Klein, PhD**[5]

[1]Department of Pharmacy and Therapeutics, University of Pittsburgh, Pittsburgh, PA. USA

[2]Department of Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, IN, USA

[3]Office of Quality & Patient Care, St. Jude Children's Research Hospital, Memphis, Tennessee, USA

[4]Department of Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, Tennessee, USA

[5]Department of Biomedical Data Science and Medicine, Stanford University, Stanford, California, USA

In Dr. Francis Collins' 2001 testimony to Congress, he heralded advances in genetics with The Human Genome Project. He imagined testing "being used to tailor medicines to fit individual genetic profiles, since drugs that are effective in some people are less effective in others and, in some, cause severe side effects." It has been nearly 20 years and finally, this promise of pharmacogenomics is becoming a reality through increasing clinical implementation and recent significant milestones in payer coverage.

A wealth of evidence drives implementation

Genetic determinants of pharmacokinetics and pharmacodynamics are increasingly understood as evidenced by the >23,000 drug/gene-variant annotations curated in the PharmGKB (www.pharmgkb.org). Importantly, over the past decade, the Clinical Pharmacogenetics Implementation Consortium (CPIC;www.cpicpgx.org), has published >25 peer-reviewed guidelines involving >50 drugs to facilitate the translation of pharmacogenomic data into actionable prescribing algorithms.[1]

While genotype-phenotype discovery continues, focus on implementation science is expanding to prove the value of testing, overcome implementation barriers, and move pharmacogenomics into the clinic. Institutions within NHGRI's *Implementing Genomics in Practice (IGNITE)* network have deployed testing clinically and are conducting pragmatic clinical trials to evaluate clinical utility. NIH's *All of Us research program* has similarly recognized the value of pharmacogenomics and has prioritized the return of these results to

Corresponding author: Philip E. Empey, PharmD, PhD; 335 Sutherland Dr., 205 Salk Pavilion, Pittsburgh, PA 15261; Tel: (412) 648-7219; Fax: (412) 624-8175; pempey@pitt.edu.

its one million participants. Moreover, because of the lifelong reusability of germline test results that are shared by many drugs, pharmacogenomic testing done in advance of prescribing is strategic. Indeed, several health systems such as University of Pittsburgh Medical Center, St. Jude Children's Research Hospital, and Vanderbilt University Medical Center have invested in large, population-scale, preemptive testing programs.

New payer coverage milestones set to expand testing

The cost of pharmacogenomic testing can be as low as a few hundred dollars and is often cost-effective.[2] However, reimbursement has lagged as payers seek to understand variable test offerings, clinical utility, and economics. Few tests are reliably covered and payers have been critical of the multi-gene testing panels commonly offered by laboratories.[3]

Importantly, the US payer landscape for pharmacogenomic test reimbursement is improving. In 2012, the AMA created unique current procedure terminology codes to facilitate documentation, and consequently billing, for some single gene tests.[4] In 2019, the United Health Group instituted new coverage for testing that guides antidepressant and antipsychotic prescribing in some settings. This was significant because the largest US private payer declared that the use of "pharmacogenetic multi-gene panels to guide therapy decisions is proven and medically necessary" citing studies showing cost savings and improvement in outcomes.

In August 2020, expanded coverage arrived for Medicare patients through new Molecular Diagnostic Services (MolDx) local coverage determinations (LCDs).[5] MolDx is an influential program involving four of the seven Medicare Administrative Contractors (MACs) whose mission is to establish coverage and reimbursement for molecular diagnostic tests. The LCDs add new coverage stating "pharmacogenomic tests are indicated when medications are being considered for use (or already being administered) that are medically necessary, appropriate, and approved for use in the patient's condition and are known to have a gene(s)-drug interaction that has been demonstrated to be clinically actionable as defined by the FDA (pharmacogenomic information required for safe drug administration) or CPIC guidelines."[5]

There are several important features of this decision that make it a significant milestone. First, the coverage is defined broadly. The LCD does not limit coverage to specific genes/drugs. Instead, it recognizes the CPIC evidence grades as well as FDA labeling. Clinically actionable gene/drug pairs are defined as CPIC level A (when genetic information should be used to change prescribing) or B (when genetic information could be used to change prescribing because alternative therapies/dosing are extremely likely to be as effective and as safe as non-genetically based dosing).[6] Supplemental Figure 1 lists >50 actionable gene/drug pairs that are included in a CPIC guideline that will be covered under this new LCD. These drugs span many therapeutic classes and are commonly prescribed across medical specialties. Second, coverage includes both single gene and multi-gene tests. Panel tests are covered if more than one gene on the panel is considered reasonable and necessary for the safe use of a medication or if multiple drugs are being considered. Third, testing is not considered reasonable solely because a patient has a particular diagnosis; non-genetic factors

must also be considered in selecting drug therapy. Finally, the LCD does not support combinatorial tests that use proprietary commercial algorithms to make treatment recommendations stating that independent evidence establishing their validity and utility is needed over the results provided by single and multi-gene pharmacogenomic tests.

The path forward

This new payer coverage will likely increase access to, and the use of, pharmacogenomic testing as data from 2013–2017 suggest testing utilization rates are responsive to changes in Medicare coverage policy.[7]

To overcome implementation obstacles and fully capture the value of pharmacogenomic testing we make the following recommendations towards best practices. First, the patchwork of variable state-by-state coverage (Supplemental Figure 1) should be harmonized. Because the new LCDs cover only 28 of 50 states within the individual MAC jurisdictions in MolDx (Palmetto GBA, Noridian Healthcare Solutions, Wisconsin Physician Services Insurance Corporation and CGS Administrators), just 44% (15M) of all Medicare beneficiaries (34M) are impacted[8] The Centers. for Medicare & Medicaid Services has acknowledged the need for increased consistency between MACs and their LCDs. Therefore, a national coverage determination or minimally, mirroring LCDs from Novitas, National Government Services (NGS), and First Coast are necessary to achieve an equitable nationwide standard.

Second, greater standardization of testing and interpretation is critical in order to overcome implementation barriers, make test results interoperable across health care record platforms, and expedite reimbursement. Because the most commonly used targeted genotyping methods interrogate specific variants only, patient results may differ due to differences in variant coverage among testing platforms. While the future increased use of sequencing technologies mitigates this selective testing issue, there remains a need to specify what variants enter reporting pipelines. Similarly, interpretations can vary. Efforts by the Pharmacogene Variation (PharmVar) Consortium, CPIC, and the Association of Molecular Pathology (AMP) to set allele definitions, assign clinical allele function, and establish a minimal set of alleles necessary for quality testing, are forward-thinking solutions.

Third, clarity is needed in the regulatory landscape to expand access to testing. In 2018, after the Food and Drug Administration (FDA) authorized the first direct-to-consumer pharmacogenomic test, a FDA Safety Communication broadly warned against the use of genetic tests with unapproved claims of predicting medication response.[9] Subsequently, the agency contacted individual laboratories to demand revision of their test reports and/or promotional materials, even issuing a formal warning letter to an institution that did not remove claims regarding specific medications. Overall, these events had a chilling effect on the field as it created uncertainty regarding how laboratories could provide interpretations to satisfy CLIA requirements as well as respond to the FDA enforcement discretion. In response, stakeholder groups including AMP, the American Clinical Laboratory Association, and the National Alliance on Mental Illness responded with strong statements supporting clinical pharmacogenomic testing best practices and its key role to improve patient care. In February 2020, A *Table of Pharmacogenetic Associations* was published by the FDA. While

the agency acknowledges it is not complete, they welcomed feedback from the scientific community, and this level of detail from FDA is an important first step of additional guidance on the use of pharmacogenomic testing.[10] Further, 2020 brought an apparent shift in regulatory approach. The Department of Health and Human Services issued a statement that, the FDA “will not require premarket review of laboratory developed tests ("LDT") absent notice-and-comment rulemaking” [11] This is a signal that the FDA acknowledges the need to modernize their regulation of LDTs. Collaboration within the agency and externally has also expanded with continued relationships between the FDA, CPIC and the PharmGKB, and, with the formation of a new FDA collaborative community for pharmacogenomics. Additional dialogue between regulators and the scientific community will be essential for FDA to fully reflect the established and emerging evidence base for pharmacogenomic testing to improve medication use.

Fourth, practitioner education and point of care clinical decision support are essential to enable precision prescribing. There have been numerous calls for increased genomics education in health sciences curricula and as well as for physicians who are currently in practice. Integration of clinical decision support tools across health care records for clinics, hospitals, pharmacies, and laboratories is also required to fully capitalize on the utility of pharmacogenomic testing that apply throughout a patient’s lifetime.

Finally, implementers and payers must measure downstream clinical outcomes and adherence to the LCD definition of medical necessity. These data drive clinical utility assessments to determine the value and economics of testing. They are also core activities of learning health systems and are needed to apply the evidence framework cited by payers to justify continued reimbursement.[3]

Overall, pharmacogenomics has achieved an important milestone in payer coverage which is likely to increase adoption. With best practices to capture the value of testing and application of new payer reimbursement policies, the promise of precision prescribing can now be realized for many commonly used medications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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