



COMMENT

Expanding evidence leads to new pharmacogenomics payer coverage

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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 the National Human Genome Research Institute (NHGRI)'s Implementing Genomics in Practice (IGNITE) network have deployed testing clinically and are conducting pragmatic clinical trials to evaluate clinical utility. The National Institutes of Health (NIH)'s All of Us research program has similarly recognized the value of pharmacogenomics and has prioritized the return of these results to 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, pre-emptive 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 multigene testing panels commonly offered by laboratories.³

Importantly, the US payer landscape for pharmacogenomic test reimbursement is improving.

In 2012, the American Medical Association (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 multigene 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 nongenetically 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 multigene 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; nongenetic 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

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evidence establishing their validity and utility is needed over the results provided by single and multigene pharmacogenomic tests.

THE PATH FORWARD

This new payer coverage will likely increase access to, and the use of, pharmacogenomic testing as data from 2013 to 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 toward 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 MoDx (Palmetto GBA, Noridian Healthcare Solutions, Wisconsin Physician Services Insurance Corporation and CGS Administrators), just 44% (15 million) of all Medicare beneficiaries (34 million) are impacted.⁸ The Centers for Medicare & Medicaid Services have 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 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 for 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, an 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, the Table of Pharmacogenetic Associations was published by the FDA. While the agency acknowledges it is not complete, it 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 as well as for clinicians 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.

Received: 28 September 2020; Revised: 2 February 2021; Accepted: 2 February 2021;

Published online: 24 February 2021

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COMPETING INTERESTS

P.E.E. is a Co-Investigator on Implementing Genomics in Practice (IGNITE) project grant (U01 HG010245) and has provided consultative services for CIPHEROME. V.M.P. reports the following: the Indiana University School of Medicine

Pharmacogenomics Laboratory is a fee-for-service clinical laboratory that offers clinical pharmacogenetic testing. V.M.P. is supported by the IGNITE project grants (U01 HG007762 and HG010245) and is on the clinical advisory board of Avalon Healthcare Solutions. J.M.H. is a Co-Investigator for CPIC (NIH/NHGRI U24HG010135). K.E.C. is the Co-Principal Investigator for CPIC (NIH/NHGRI U24HG010135). T.E.K. is the Co-Principal Investigator for the PharmGKB (NIH/NHGRI/NICHD U24 HG010615), CPIC (NIH/NHGRI U24HG010135) and PharmCAT (NIH/NHGRI U24 HG010862). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41436-021-01117-w>.

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