

Reimbursement Models to Promote Evidence Generation and Innovation for Genomic Tests

National Institutes of Health
Bethesda, Maryland
October 24th, 2012

Workshop Summary

On October 24, 2012, the National Human Genome Research Institute (NHGRI) and the Center for Medical Technology Policy (CMTP) convened a workshop to explore innovative ways in which genomics-based tests could be covered by public and private payers while generating evidence of the test's impact on medical outcomes, and to develop an action plan enabling future reimbursement of such tests and large-scale sequencing. The workshop was structured around exploration of four case studies followed by discussions focused on developing an actionable "reimbursement policy" strategy for genetic and genomic tests. In attendance were representatives from several stakeholder communities, including government, public and private payers of health insurance, manufacturers of genetic diagnostic tests, and academia.

Introductory Remarks

NHGRI Director **Eric Green, M.D., Ph.D.** began the meeting by noting that we are well poised to meet the goal of genomic medicine, but need a clear path to realize that goal. To identify the barriers to genomic medicine and develop strategies for their removal, NHGRI created the Genomic Medicine Working Group (GMWG). The GMWG determined that ensuring genetic and genomic diagnostic tests are covered and reimbursed by insurance providers is central to the goal of implementing genomic medicine. A critical challenge to genomic medicine is how we bridge the evidence gap necessary to pave the way for coverage and reimbursement of genetic tests. This workshop was convened as an opportunity for both learning about and organizing ways to answer that fundamental question.

Sean Tunis, M.D., President and CEO of the Center for Medical Technology Policy (CMTP), expanded upon Dr. Green's remarks with a discussion of the "clinical utility problem." Dr. Tunis stated that demonstrating the clinical utility of a genetic or genomic test is the major bottleneck in establishing coverage and reimbursement. Further complicating this issue is that different payers have different standards for what data demonstrate clinical utility and that many of those standards require rigorous and time consuming clinical trials. Dr. Tunis urged that we approach coverage decision-making with the recognition that evidence will, over time, reduce uncertainty regarding the usefulness of a test. He encouraged the group to identify practical models that allow coverage of genetic and genomic tests while clinical utility data are being generated.

The moderator for the workshop, **Marc S. Williams, M.D.**, Director of the Genomic Medicine Institute at Geisinger Health System and a member of the GMWG, asked workshop participants to keep the following goal in mind:

To develop a plan for future application of refined and novel reimbursement policy tools to evaluate the clinical utility, and the actual effect on the care of patients, of genomics-based tests. Through a series of case analysis exercises, develop a “reimbursement policy” strategy that 1) facilitates the collection of clinical and resource utilization data pertaining to genomics-based tests, 2) informs payer and developer decision-making in a manner that balances the need for methodological rigor, and 3) incorporates the lessons learned from prior initiatives.

Summary of Presentations

United HealthCare (UHC)/Genomic Health (GH) Performance-based Risk Sharing Agreement for OncotypeDX coverage

- **Steven Richardson, M.D., M.Sc., Director, Medical Affairs, Genomic Health, Inc.**
- **Daniel Trodden, Director, Managed Care, Genomic Health, Inc.**

In 2007, United Healthcare (UHC) agreed to pay for a gene-expression profiling test, OncotypeDX by Genomic Health (GH), designed to quantify the likelihood of disease recurrence in women with breast cancer and to predict whether adjuvant chemotherapy would be beneficial as part of a Performance-based Risk Sharing Agreement (PBRSA). Under this approach, UHC agreed to pay for the test in breast cancer patients who met certain criteria (node negative, tumor less than 5cm, and estrogen receptor positive) while the PBRSA stipulated that the patient’s risk score be reported to UHC for further analysis. GH hypothesized that physicians would use test results in treatment decisions that would lead to a more optimal use of chemotherapy. Both parties agreed to measure chemotherapy usage in accordance with the test results and adjust the terms of the agreement after a defined period of time, if necessary.

The speakers emphasized that the agreement between UHC and GH developed from dialog between the two companies, which allowed each to understand the other’s needs and to build trust. Through this conversation, they were also able to set up a unique data sharing agreement that allowed UHC to determine if doctors were prescribing chemotherapy in accordance with test results. Furthermore, GH engaged in physician education (*i.e.*, the laboratory would communicate with physicians who ordered the test inappropriately).

Workshop participants explored how the data sharing agreement between GH and UHC could be generalized, particularly because there are numerous legal and ethical issues surrounding confidential patient health record and genomic information data sharing. Workshop participants agreed that an analysis of the issues surrounding sharing of these types of data would be exceedingly helpful to inform future agreements.

Workshop participants noted that although the GH/UHC study was not a randomized clinical trial (RCT), UHC was nevertheless willing to pay for the test while data were being collected as part of the PBRSA.

Palmetto GBA's Molecular Diagnostics Services Program (MoDx) and the Pervenio Lung RS Assay

- **Becke Turner, R.N., MoDx Program Manager, Palmetto GBA**

A major hurdle in reimbursing genetic tests stems from the way these tests are coded. Currently, genetic tests are billed with a series of method-based [Current Procedural Terminology](#) (CPT) codes that do not uniquely identify which test is being performed. This lack of transparency is a barrier to payment as payers cannot specifically identify which genetic test is ordered and performed. They do not know the clinical indication (and hence medical necessity) for an ordered test, and cannot determine whether payment for the test is within the terms of their coverage policy or if test is even medically appropriate.

Palmetto GBA, a Medicare contractor, developed the [MoDx program](#) to systematically catalog and determine coverage for genetic tests. For each genetic test, the MoDx program identifies and assigns it a unique identification number, determines if Medicare coverage for the test is appropriate, and establishes rates of reimbursement. For new tests, MoDx performs a technical assessment (TA) to determine whether the test meets coverage requirements.

For its TAs, MoDx requires that test developers submit evidence demonstrating the analytical validity, clinical validity, and clinical utility for each diagnostic test. MoDx will accept a number of different forms of evidence demonstrating clinical utility, each weighted differently: published peer-reviewed articles, RCTs or other well-designed controlled trials, cohort and case study analysis, and articles that are "accepted for publication." Throughout the TA process, Palmetto communicates extensively with the test developer. Positive TAs will be published and coverage will be determined. If the TA is negative, MoDx will explain why to the developer. In the case of the Pervenio Lung RS prognostic test for a subset of lung cancer, MoDx determined that there is insufficient evidence to demonstrate the clinical utility of the test at this time. Palmetto is open to a "Coverage with Evidence Development" scheme as an alternative to TA denial for tests like Pervenio Lung RS, but test developers will have to fund the evidence development themselves.

In her remarks, Ms. Turner echoed the points made previously by GH, emphasizing a role for labs in physician education. Palmetto believes that labs should educate physicians at the point of test ordering since physicians often order tests incorrectly.

Workshop participants noted that it was innovative for a Medicare local contractor to implement this program and wondered whether it could be applied nationally. Furthermore, they felt the MoDx program could be a model approach for determining coverage of genomic tests, due to the rigor of the TA process. However, other workshop participants believed that private payers would not be interested in funding TAs.

The Center for Medicare and Medicaid Services' Coverage with Evidence Development (CED) for Pharmacogenomic Testing for Warfarin

- **Jeffrey Roche, M.D., M.P.H., Medical Officer, Coverage and Analysis Group, Centers for Medicare and Medicaid Services**

- **An Pang Chieng, M.D., Principal Investigator, WARFARIN Study, Iverson Genetics**

Coverage with Evidence Development (CED) allows health insurers to offer payment for promising treatments while the effectiveness of the treatment is being assessed. In 2009, The Centers for Medicare and Medicaid Services (CMS) issued a Medicare national coverage decision to support a CED for pharmacogenomic testing in the use of warfarin. The decision covered testing for Medicare enrollees participating in clinical trials that examine the effectiveness of genetic testing in adjusting warfarin dosage.

Warfarin, a commonly prescribed anticoagulant, is difficult to dose initially due to a narrow therapeutic index and numerous clinical and environmental factors that affect appropriate dose. Genetic variation in two genes (*CYP2C9* and *VKORC1*) contributes as much as 40% to the variability in stable warfarin dose between patients. Genetic testing is available to help guide administration of the drug. CMS has determined that, while there is insufficient evidence to clearly establish the test's clinical utility, there is sufficient data to indicate that its use may improve clinical outcomes. CMS therefore instituted a policy of coverage for the test for patients enrolled in clinical trials as part of a "coverage with evidence development" policy. One such clinical trial is the Warfarin Adverse Event Reduction For Adults Receiving Genetic Testing at Therapy Initiation (WARFARIN) trial sponsored by Iverson Genetics.

The WARFARIN study began in 2011 and has since enrolled 491 patients. Iverson Genetics developed a 3-step process with a 24-hour turnaround time from the collection of blood to reporting of the genetic test results to the doctor, as follows: (1) a doctor decides to enroll a patient in the study, collects a blood sample, and overnights the blood to Iverson Genetics via UPS; (2) the sample is genotyped on the same day it is received; and (3) the genotyping results are reported back to the doctor's office on the same day as sample receipt.

Meeting participants discussed the types of end-points that CMS considers when making coverage decisions. CMS favors end-points directly tied to patient outcomes, but not other factors – such as examining whether pharmacogenomic testing increases efficiencies in healthcare delivery (*e.g.* decreasing the number of tests a patient needs to reach the right dose).

Meeting participants noted that a CED-approach appears to be useful in warfarin dosing, but it may not be as appropriate to demonstrate the clinical utility of tests that require longer periods of follow-up (*e.g.* OncotypeDX).

Finally, meeting participants discussed who should pay for evidence development. Dr. Chieng noted that Iverson Genetics receives a small CMS reimbursement for the test, but no support to defray the costs that Iverson pays to sponsor an expensive RCT. Attendees noted that diagnostic companies do not typically have the funds to invest in demonstrating clinical utility of a test, especially if the reimbursement received for a test is low. Representatives of the payer community noted that payers are often reluctant to fund the research.

Medco Health Solutions, Inc. /Mayo Clinic Pharmacogenomic Testing for Warfarin Dosage Effectiveness Study

- **Robert Epstein, M.D., M.S., Formerly of Medco Health**
- **Russell Teagarden, Ph.D., Formerly of Medco Health**

In 2007, the Mayo Clinic and Medco Health Solutions Inc. (Medco) initiated a prospective study to evaluate how genetic testing during the first six months of warfarin treatment affected the rate of patient hospitalizations due to bleeding or thromboembolism. This study was unique in that it was the first large-scale, prospective, comparative effectiveness study conducted in usual care settings. While there had been smaller prospective studies suggesting a clinical benefit of pharmacogenomic testing to guide warfarin dosing decisions, clinical adoption of genetic testing had been slow due to a lack of evidence demonstrating an improvement in clinical outcomes, such as bleeding or thromboembolism. The study was managed by Medco, which enrolled patients from its prescription benefit plans and analyzed their medical and pharmacy claims data. Medco identified all new patients starting warfarin prescriptions, contacted the prescribing physician to inform them about genetic testing, and then worked with patient directly to facilitate testing. The study found that patients undergoing genetic testing had a 27% reduction in hospitalizations for bleeding or thromboembolism as compared with a historical control group. The testing itself was performed by the Mayo Clinic using an assay developed by Luminex Molecular Diagnostics (Luminex). Testing was provided free of charge to patients enrolled in the study.

In this study, the hospitalizations rates for patients undergoing genotyping to guide warfarin dosing were compared with hospitalization rates of a historical group. Enrollees came from over 200 individual payers over a 4 year period. Legal concerns barred the use of an RCT in this circumstance, because payers cannot deny a benefit to a portion of their membership, but offer it to others. Meeting attendees noted this and suggested a policy analysis of the legal issues surrounding the various trial designs discussed during the workshop.

Teagarden and Epstein emphasized that lab-doctor contact is an appropriate point of contact for physician education. Medco used an algorithm that notified the lab if a doctor ordered the test incorrectly or used the wrong requisition forms. They noted that many doctors have either never ordered a test or do not order tests appropriately.

Themes Emerging from the Discussion

- A major bottleneck in establishing reimbursement policies for genetic tests is the demonstration of the clinical utility. Further complicating this issue is the fact that there is not a consensus among payers about the evidence thresholds required to demonstrate clinical utility. Given that there are many genomics-based tests where the evidence of clinical utility is very limited, it is important to set research priorities.
- The case studies demonstrate that there are instances where payers will accept clinical utility data other than RCTs, and that payers sometimes recognize the promise of genomics-based tests in the absence of RCTs.
- The role of communication, trust-building, and data sharing between payers and test developers is an essential component of a successful coverage agreement. On data-sharing, the legal and

privacy issues that need to be considered can be complex. Workshop participants decided that a detailed analysis of the laws surrounding data sharing among payers, test developers, and researchers would be informative for crafting of future coverage agreements and developing the evidence base for genomic medicine. Also, if payer data *can* be used, its informational content will be greatly improved by the MoDx initiative, especially if different payers use the same codes across the country (as well as the incoming updated CPT codes for genetic tests).

- A major theme of the discussion was physician education. Many workshop participants noted that physician knowledge of genetics and genomics is often not current enough to deal with recent advances in genomic medicine. There is significant concern that physicians do not know when it is appropriate to order tests and what to do with the result, which can threaten the ultimate clinical utility of a test, regardless of the test's value in expert hands. Several stakeholder groups had taken or recommended steps to provide physician education. Genomic Health laboratory staff contacted doctors when they inappropriately ordered OncotypeDX testing. Additionally, Medco staff in the Medco/Mayo case contacted doctors when they listed the wrong test requisition number. Furthermore, Palmetto representatives emphasized the roles that labs can play in physician education: ensuring appropriate test use and assisting with test interpretation.
- Medicare has statutory limitations that prevent some genomics-based tests from being covered. For instance, Medicare cannot cover services to identify disease risk or confirm a diagnosis. It may be possible for whole genome sequencing to be covered by Medicare, but a clear use needs to be defined that is “reasonable and necessary” for the Medicare population.
- Participants in the workshop also discussed what end-points are analyzed in these types of agreements. It may be useful for studies to include measures beyond classic health outcomes. For example, the Medco/Mayo study assessed hospitalization rates following test-based warfarin dosing and the UHC/Genomic Health study assessed referral rates for chemotherapy.
- Identifying sufficient sources of funding for clinical utility research remains a challenge. Attendees identified that it is challenging for test developers to fund the research necessary to demonstrate clinical utility of a test and subsequently enjoy a sufficient return on the investment. However, it was further observed that private payers are not likely to fund the research demonstrating the clinical utility of tests. As a complicating factor, it was also noted that different payers all require different levels of evidence necessary to provide coverage. NIH and the Patient-Centered Outcomes Research Institute are possible sources of funding, but they are unlikely to be able to meet all the research needs. It is therefore important to seek new ways in which such research could be conducted to minimize the burdens.

Recommended Action Items

- (1) **Issue a White Paper on innovative ways to couple coverage and reimbursement with evidence development.** The paper should define the barriers and drivers surrounding coverage and reimbursement of genetic tests for various types of tests (predictive vs. diagnostic). The paper should summarize models that have worked in the past; the legal issues at play in each coverage

model; how payers and test developers can establish and build trust; what levels and types of evidence are necessary for payers to cover tests; and what kinds of study endpoints are required.

- (2) **Develop criteria for prioritizing tests for coupling evidence generation with coverage and reimbursement.** This action item aims to identify opportunities to fill unmet clinical needs and to match study designs with indications.
- (3) **Undertake an analysis of the legal and policy issues affecting data sharing.** This policy analysis should aim to identify ways in which academia, payers and/or test developers can share clinical and claims data in a “safe harbor” environment to advance the evidence development necessary for coverage of genetic/genomic tests.
- (4) **Define a private infrastructure model to conduct clinical utility research.** This research should define the infrastructure necessary to facilitate data collection, reduce the costs of clinical trials, and establish a collaborative network.
- (5) **Research physician ordering of genetic tests and the actions taken based upon those tests.** This research will determine how best to standardize “companion services” workflow so that doctors order the correct genetic test for a given circumstance and that labs communicate the information necessary to ensure that doctors take the correct action in response to test results.

Invited Participants:

An Pang Chieng, M.D., Principal Investigator, WARFARIN Study, Iverson Genetics

Rex Chisholm, Ph.D., Professor of Medical Genetics, Northwestern University

Robert Epstein, M.D., M.S., Formerly of Medco Health

Muin Khoury, M.D., Ph.D., Director, Office of Public Health and Genomics, CDC

Robert McCormack, Ph.D., Director of Technology Assessment, Veridex

P. Pearl O’Rourke, M.D., Director, Human Research Affairs, Partners HealthCare Systems, Inc.

Steven Richardson, M.D., M.Sc., Director, Medical Affairs, Genomic Health, Inc.

Jeffrey Roche, M.D., M.P.H., Medical Officer, Coverage and Analysis Group, CMS

Alan Rosenberg, M.D., V.P., Medical Policy, Technology Assessment and Credentialing, WellPoint, Inc.

J. Russell Teagarden, Ph.D., Formerly of Medco Health

Daniel Trodden, Director, Managed Care, Genomic Health, Inc.

Becke Turner, R.N., MoDx Program Manager, Palmetto GBA

Richard Wenstrup, M.D., Chief Medical Officer, Myriad Genetic Laboratories

Marc S. Williams, M.D., Director, Genomic Medicine Institute, Geisinger Health System

NHGRI Participants:

Alice Bailey, Scientific Program Analyst

Eric D. Green, M.D., Ph.D., Director

Laura M. Koontz, Ph.D., Genetics and Public Policy Fellow

Eugene R. Passamani, M.D., Consultant

Laura Lyman Rodriguez, Ph.D., Director, Division of Policy, Communications, and Education

Derek T. Scholes, Ph.D., Chief, Policy and Program Analysis Branch

CMTP Participants:

Pat Deverka, M.D., M.S., Senior Research Director

Tania Dutta, M.S., M.P.P., Research Associate

Stuart Spector, M.B.A., Chief Operating Officer

Sean R. Tunis, M.D., M.Sc., President and Chief Executive Officer