



EVIDENCE, COVERAGE, AND INCENTIVES

A PMC/BIO Solutions Summit

Summary of Proceedings

Omni Shoreham Hotel, Washington, DC

April 17, 2013



Biotechnology
Industry
Organization

Foreword

The Biotechnology Industry Organization (BIO) and the Personalized Medicine Coalition (PMC) have long taken a national leadership role on the need for innovative and forward-looking health care policies that support a transition toward personalized medicine. One of the first and most dramatic examples of a targeted medicine benefitting patients was the controversial therapy Herceptin (trastuzumab). During its development no clear template existed for developing a drug to treat based on an individual's molecular diagnostic profile. Today, past nearly two decades post-U.S. Food and Drug Administration (FDA) approval of Herceptin and its co-developed HercepTest, this diagnostic test and targeted therapy have extended or saved the lives of tens of thousands of women around the world with breast cancers and an overexpressed HER2/neu receptor.

Over the past few years, the long-awaited revolution in diagnostics-targeted medicine has become a reality. The pathway for approval of an *in vitro* diagnostic paired with a drug during a phase III clinical trials is well-established, although what types of evidence is needed to cover, reimburse and adopt a diagnostic is much less defined. For example, separate from a drug approval, molecular panel tests may accurately provide a better molecular classification of disease, diagnose tumors of unknown origin, project the likely prognosis of a patient's cancer, or provide insights into the mechanisms of action of generic drugs or panels of drugs. In all of these cases, the approach to evidence generation for third-party payers' coverage standards still remains unclear.

On April 17, 2013, BIO and the PMC convened a conference entitled, "Evidence, Coverage, and Incentives: A PMC/BIO Solutions Series Summit." The planning committee's vision was that evidence, coverage of tests, and incentives were inextricably related, yet poorly coordinated. In order to improve this situation, the collaboration of many stakeholders would be imperative -- from bench scientists to clinical trials experts and statisticians; evidence reviewers and public policy experts; commercial payers, physicians, patients, and employers. Indeed, the BIO/PMC Summit brought together an audience of over 200 policymakers and stakeholders. The meeting resulted in a vision for a "playbook" that would consolidate best practices and provide guidance both to innovators in the biotechnology industry and to policy and payer experts. This conference report highlights key messages and findings from the Summit, and reflects BIO and PMC's ongoing commitment to pushing forward the national dialog on the transformational impact of personalized medicine. We look forward to continued efforts to develop solutions to critical barriers to the advancement of personalized medicine.

Paul Sheives JD
Director, Diagnostics and Personalized Medicine Policy
Biotechnology Industry Organization

Amy Miller, Ph.D
Vice President, Policy
Personalized Medicine Coalition



Agenda for the Summit and Speakers

Welcome and Introduction	Introduction – James C. Greenwood, President and CEO, Biotechnology Industry Organization • Bruce Quinn, M.D., Ph.D., Senior Health Policy Advisor, Foley Hoag LLP
Introductory Speaker: Challenges facing reimbursement of molecular diagnostics	Reed Tucson, M.D., Managing Director, Tucson Health Connections, Former Executive Vice President and Chief of Medical Affairs, UnitedHealth Group
Panel 1: Evidentiary standards and data requirements for payer coverage	Expert moderator – Kristin Ciriello Pothier, Partner, Health Advances • Jeff Allen, Ph.D., Executive Director, Friends of Cancer Research • Jerry Conway, Vice President of Reimbursement & Payer Strategy, Foundation Medicine • Tamara Syrek Jensen, J.D., Deputy Director, Coverage and Analysis Group, CMS • Matthew Zubiller, Vice President for Decision Management Business, McKesson Corporation
Break	
Panel 2: Becoming the standard of care: Inclusion of new molecular diagnostics into clinical guidelines	Expert Moderator – Gail L. Daubert, J.D., Partner, ReedSmith • Paul Billings, M.D, Ph.D., Chief Medical Officer, Life Technologies • Tadd Lazarus, M.D., Chief Medical Officer/Medical Affairs, QIAGEN • Joan McClure, Vice President of Clinical Information and Publications, National Comprehensive Cancer Network • Steve Shak, M.D., Chief Medical Officer, & Executive Vice President of Research & Development, Genomic Health
Luncheon keynote session: Current Issues in Reimbursement of Molecular Diagnostics at CMS	Introduction – Edward Abrahams, Ph.D., President, Personalized Medicine Coalition • Louis Jacques, M.D., Director, Coverage and Analysis Group, CMS, Interviewed by Bruce Quinn, M.D., Ph.D., Senior Health Policy Advisor, Foley Hoag LLP

Panel 3:

Market Access Issues for Companion Diagnostics: Reimbursement and Integration into the Health Care Ecosystem

Expert moderator – Jared Schwartz, M.D., Ph.D., Chief Medical Officer, Leica Biosystems

- Kelly Burgeson, Executive Director, Access and Reimbursement, Oncology, Boehringer Ingelheim Pharmaceuticals
- Andrea Ferris, President of the LUNGevity Foundation
- Mike Kolodziej, M.D., National Medical Director for Oncology Strategies, Aetna
- Paul Landauer, Senior Director, Global Commercial Support, Abbott Molecular

Break

Panel 4:

Incentivizing personalized medicine diagnostic development

Expert moderator – Vicki Seyfert-Margolis, Ph.D., Chief Scientific and Strategy Officer, Precision for Medicine and Chief Executive Officer and Founder, MyOwnMed

- Marc Boutin, J.D., Executive Vice President & Chief Operations Officer, National Health Council
- Mary Dwight, Vice President of Government Affairs, Cystic Fibrosis Foundation
- Stephen L. Eck, M.D., Ph.D., Vice President, Global Head of Medical Oncology, Astellas Pharma Global Development
- Hawazin Faruki, DrPH, Managing Director, Clinical Diagnostic Strategies, LLC
- Amy M. Miller, Ph.D., Vice President, Public Policy, Personalized Medicine Coalition
- Paul Sheives, J.D., Director, Diagnostics and Personalized Medicine Policy, Biotechnology Industry Organization

Concluding session:

Overview of solutions discussed during today's summit and next steps



Introduction

In a 2010 white paper co-sponsored by BIO, Gary Gustavsen and colleagues wrote, "the success of personalized medicine is dependent on the healthcare industry's ability to overcome several clinical, economic, and logistical challenges to commercialization. Some of the most pressing challenges relate to the reimbursement system, specifically in obtaining affirmative coverage, appropriate coding, and value-based payment for novel diagnostics." Since then, a number of conferences sponsored by the Personalized Medicine Coalition, the Institute of Medicine, and others have emphasized that the promise of personalized medicine may indeed be severely impeded by a lack of coherent federal and commercial policies. We still face a system that is filled with unnecessary barriers and incompatible standards from the perspective of both the market availability, and the clinical adoption of innovations in personalized medicine.

Jointly, BIO and the Personalized Medicine Coalition shared a vision that the time has come to move decisively from the arena of problem description to the arena of practical solutions based on a consensus understanding of the problems and how they may be reduced. On April 17, 2013, the summit was introduced by BIO's President and CEO, James Greenwood. Greenwood shared that, now more than ever, BIO recognizes the growing importance and exciting ability of personalized medicine and targeted therapies to bring about a new level of impact on human disease.



**Meeting Organizers: Amy Miller (PMC)
and Paul Sheives (BIO)**

Keynote Address: Dr. Reed Tuckson

Dr. Reed Tuckson, formerly Executive Vice President and Chief of Medical Affairs at UnitedHealth Group, provided a framework for the conference speakers and attendees. Tuckson noted that there was wide conceptual agreement on the "Triple Aim" voiced by Dr. Donald Berwick (head of CMS, 2004-2008): to improve the experience of care, improve the impact on population health, and reduce per



Reed Tuckson, Tuckson Health Connections.

capita costs. Dr. Tuckson described in powerful terms that the reality of healthcare is falling short of the “Triple Aim.” Instead, our healthcare system is floundering on four profound dysfunctions and challenges: continual cost escalation, poor quality delivered to patients, frank waste, and a public health explosion in preventable chronic illnesses.

In the viewpoint of most payers, according to Tuckson, the promise of molecular diagnostic remains only occasionally realized and concerns about overuse of molecular tests loom large, because spending in this industry niche is already in the billions of dollars and rising at 14% per year in his health plan. The proliferation of diagnostic tests seems exponential, whereas the cognitive capacity of physician decision-makers remains flat.

While payers do not want to kill innovation, they do face a world in which there is “not one dollar more.” Tuckson repeated this point, and emphasized to the diverse range of stakeholders gathered for the Summit that when there is not one dollar more, the kind of innovation that will be welcomed is *disruptive innovation*: innovation that simultaneously reduces costs while raising quality. Personalized medicine may have the potential to do that, and if you can show it, then the payer and business community will welcome the innovations that you are bringing to the table. As an example, Tuckson pointed to how UnitedHealth is contributing to this effort by investing in data, citing a recently announced large scale collaboration between its subsidiary, OptumHealth, and the Mayo Clinic.

Panel One: Evidentiary Standards and Data Requirements for Payer Coverage

The first panel was designed to dive directly into the confusing topic of how payers make coverage decision and what evidence and standards must be brought to them to support their decision-making process. The panel was moderated by Kristin Poithier, Health Advances, and featured Jeff Allen, PhD, Friends of Cancer Research; Jerry Conway, Vice President, Foundation Medicine; Mathew Zubiller, Vice President, McKesson Health Solutions; and Tamara Syrek Jensen, Deputy Director of the Coverage and Analysis Group at CMS. Dr. Allen noted that in fields like leukemia, greater diagnostic precision over several decades was accompanied all along the way by steady advancements in survival and even cures. The costs of, or the value of, more accurate diagnosis of leukemia doesn’t seem to have been

questioned. Today, the costs, methods, data, and regulatory standards for improved diagnostics get far more scrutiny, including both the FDA and payer levels. Conway noted that the horizon of molecular tests goes beyond the traditional categories of “diagnosis” and “subtype,” by providing genomic landscapes of each patient’s tumors, studying up to several hundred genes at once. This can have a dramatic impact on cancer care, but an entire system of evidence, payment, and reimbursement needs to be updated and shaped to this kind of transformational testing.

Jensen and Zubiller both described different aspects of Medicare’s innovative regional coverage and reimbursement program, called MOLDX. This program has been supported by the coverage group at CMS but is developed and iterated at the Medicare local contractor level. Under the MOLDX program, which was piloted over the past two years in California and is currently being contemplated for the Northwest, Mountain, and several Mid-Atlantic states, molecular tests receive individual and granular identification codes developed by McKesson, called Z codes. These codes are not only more specific than the vague “stack” codes that existed up through 2012, but are even much more granular than the new set of molecular or “mopath” AMA CPT codes, which describe less than 150 genomic tests specifically. The McKesson Z-code system is open-ended and could potentially describe thousands of genomic tests, and even locally specialized implementations of tests, reflecting the fact that a relatively common genetic test (such as testing the EGFR gene in lung cancer) may be carried out differently in the protocols of two different laboratories, each with distinct advantages and disadvantages. Zubiller noted that this granularity will actually raise the incentive to invest in test data (the test code isn’t lost in the crowd of generic codes), and creates a real-world mechanism through which payers can incent different types of tests and innovations differently.

When the discussion turned to exactly what “standards” payers should use for evidence, Jensen of CMS pushed back and questioned whether the simplistic idea of “yes” and “no” coverage decisions – with no gray area in between – was realistic or not. CMS has tried to be considerably more flexible than that, and introduced at the federal level the concept of “Coverage with Evidence Development.” Under this program, Medicare pays its full current fee schedule price for the test or service at issue, but does require some level of data collection and reporting from the test providers. Use of this reimbursement framework has allowed significant expansions in the coverage of PET scans in oncology in the last



**Jeff Allen, Friends of
Cancer Research**

several years, because along with other academic clinical studies, PET scans conducted under Coverage with Evidence Development resulted in numerous peer-reviewed publications and supported the end of data gathering and the transition to regular coverage for a number of cancer indications.

Panel Two: Becoming the Standard of Care: Inclusion of New Molecular Diagnostics into Clinical Guidelines

The Summit's second panel emphasized the growing recognition that coverage decisions are not just an issue that arises between a laboratory and a payer. Nor are they just the result of a single physician ordering a test for a particular patient. Rather, there is a critical role for objective but authoritative policy positions and reviews that come from organized medical associations or entities that act through transparent processes to produce guidelines. These guidelines or best practices are a mix of pure "technology assessment" with the judgment of clinical experts who can apply the data to real-world clinical situations that are necessarily both different and more complex than the artificial scenarios of a clinical trial.



**Gail Daubert (Reed Smith), Paul Billings (Life Technologies),
Tadd Lazarus (Qiagen), Joan McClure (NCCN), and
Steve Shak (Genomic Health) (from left to right)**

The panel was moderated by Gail Daubert, JD, of Reed Smith LLP. Panelists included Paul Billings MD, Chief Medical Officer, Life Technologies; Tadd Lazarus MD, Chief Medical Officer, Qiagen; Joan McClure, the Senior Vice President of the National Comprehensive Cancer Network (NCCN); and Steve Shak MD, Chief

Medical Office of Genomic Health. Billings opened the discussion by emphasizing that the evolution of genomic technology is moving past us at lightning speed. Sequencing itself is not controversial at all: clinical tests based on Sanger sequencing have been available for decades, and there are FDA approved diagnostics for some of them. What is new is the rapid advent of clinical applications of next-generation sequencing. (Billings had brought along and demonstrated a small sequencing chip that can yield gigabytes of genomic information in minutes.) Dr. Lazarus added that medical revolutions happen at intervals, but when they happen, the results are unmistakable. He noted that in the 1940s, his mother and countless others were at tuberculosis sanatoria – large long-term care hospitals that “closed overnight” with the rapid advent of effective antibiotics for TB. While some applications of genomics will be whole genome sequencing, there will be a vast layer where faster, reliable, inexpensive targeted sequencing will answer clinical questions very quickly, in the area of infectious disease as well as other clinical areas.

Turning to the role of “standard of care” decisions, McClure noted that NCCN as an institution is strongly in favor of using the right diagnostics and ensuring patient access to them. However, NCCN has not found any royal road to data evaluation and decision-making – the crucial test remains whether a biomarker is actionable and falls at a critical decision-making point in the patient’s care pathway. Otherwise, the diagnostic report may be “nice to know” and it won’t get a premier position in guidelines. Shak noted that for many clinical topics in oncology, there won’t necessarily be just “one guideline.” There are conditions that fall under the jurisdiction – that is to say, under the natural interest – of different groups. NCCN might be one relevant group, and a coalition of breast cancer experts might be another. It’s alright if the different guidelines evolve at different rates, and might not always be in sync, if the evidence and discussion standards presented by each advisory body are transparent to the readers. Billings noted that the impact of guidelines is already variable and it is uncertain what direction it is going in – different guidelines might have different impacts on the various government and commercial payers already today.



Tadd Lazarus (Qiagen) and Steve Shak (Genomic Health)(from left to right)

Lazarus noted that many clinical guidelines or payer decisions don't fully grasp the enormous amount of work that goes into any well-conceived molecular test. A great deal of the precision and engineering remains below the surface to the typical clinical reviewers. There was a discussion that guidelines, such as at NCCN, tend to prefer to work at the level of the generically described test – e.g., “a genetic test for BRAF” – and not go too far into the nuances of the technology or the particular performance characteristics that may have been pivotal points of innovation or uniqueness for an individual manufacturer. McClure noted that the “biological activity” – not the specific test, or even whether a test is FDA cleared or not – was the touchpoint for clinical guidelines at NCCN.

Panel Three: Market Access Issues for Companion Diagnostics

Even with the areas of disagreement highlighted in the first two panels, this panel addressed the fact that just dividing the world into “guidelines” and “coverage decisions” may be too simplistic. The adoption of medical technologies and best practices of all sorts is variable, with a consensus that too frequently medical practice is inconsistent, slow, and difficult to change.

This session was moderated by Jared Schwartz, MD PhD, Chief Medical Officer of Leica Biosystems. Panelists included Kelly Burgeson, Executive Director, Oncology, Boehringer Ingelheim; Andrew Ferris, President of the LUNGevity Foundation; Michael Kolodziej MD, National Medical Director for Oncology Strategies at Aetna; and Paul Landauer, Senior Director for Global Commercial Support at Abbott Molecular. This panel again brought together multiple stakeholders with one panelist representing the payer position. Dr. Kolodziej of Aetna noted, however, that the clinical world is still very fresh to him, as it is only a few months since he left his clinical oncology position to take a management position at Aetna. Kolodziej emphasized that most cancer care is delivered in the community, 85% of it.

Within that large swath of cancer care, the proportion delivered through hospitals rather than physician practices is over 40% and rising. He noted that third party entities are likely to develop to assist local hospitals and oncology groups in carrying out best practices in evidence-based medicine and coordinated care.



Michael Kolodziej, Aetna.

Schwartz and other panelists turned to the need for better and more efficient clinician education in the rapidly growing armamentarium of molecular diagnostics. Electronic health records and other channels can feed information when it is needed not only to physicians, but to allied professionals such as nurse practitioners and physician assistants. It will be impossible to teach the needed information in medical schools and residencies, although this needs to be improved. Continuing

and accessible education and decision aids will be crucial. However, the panelists agreed this will not be light work. It was noted that producing evidence based standards for molecular strep throat testing was surprisingly difficult, and Schwartz noted the duration and level of work that went into consensus standards for the quality and accuracy of her2neu testing. Another feature of the healthcare system today, both at commercial payers and in the Medicare system, is the siloed payment policies for injected drugs, oral drugs, and diagnostics. Landauer, with an international perspective from Abbott Molecular, noted that different countries from Asia to Europe each have their own problems with fragmentation and adoption, even in companies with a nominally nationalized health service program.



Paul Landauer (Abbott) and Bruce Quinn (Foley Hoag)

Panel Four: Incentivizing Personalized Medicine Diagnostics Development

The fourth and final panel faced “head-on” the issues of conflicting or missing incentives. This topic has reached a flashpoint in 2013, when both commercial payers and the Medicare program have announced substantial reductions in the payments for companion diagnostics. While these reductions are intended to avoid overpayments, and reduce the profit incentive for providers to order additional tests, they create the collateral damage of raising great uncertainty among test innovators and developers. These stakeholders are confronted with not knowing whether current investments will ever yield products and sales which, over time, give each product line a viable return on investment.

The panel was chaired by Vicki L. Seyfert-Margolis, PhD, of the Precision Medicine consultancy. Panelists included Marc Boutin, Executive Vice President of the National Health Council, Mary Dwight, Vice President of the Cystic Fibrosis Foundation, Stephen Eck MD, Vice President at Astellas, and Hawazin Faruki DrPh, a consultant for Clinical Diagnostic Strategies. Boutin noted that the National Health Council is a broad-based coalition of both large and small patient groups. The National Health Council has taken a strategic approach, by the classic tools of first defining the problem, then laying out one potential solution, and finally working to trigger a critical mass of policymakers and stakeholders to take action. The National Health Council has supported legislative initiatives to reduce the misalignment between diagnostic test developments, biopharma, and the federal policy system. It has promoted the MODDERN CURES act, which has been co-signed by 50 legislative sponsors. Different aspects of this legislation propose ways to speed the coding process, extent the duration of proprietary rights for combination diagnostics with drugs, and provide more rational reimbursement for the diagnostic itself.

Seyfert-Margolis and Eck described the remarkable collaboration between the Cystic Fibrosis Association and Vertex in bringing an effective and highly targeted new drug (Kalydeco) to cystic fibrosis patients, directly addresses the underlying disease process with a novel mechanism of action. Because this drug will work only in those cystic fibrosis patients with a certain spectrum of mutations, the collaboration of national patient groups in the education and enrollment process was critical. The association also contributed through what is now called “venture philanthropy” – advancing the healthcare goals of its members through investment in technology. As a new targeted drug, Kalydeco actually did not require its own designated diagnostic test, because cystic fibrosis patients have usually already been sequenced and the medical record information is accurate enough to support prescription decisions. Eck noted that for a good diagnostic, as in this example, the regulatory framework at the FDA is not the bottleneck.

Farucki acknowledged that the development of Kalydeco is an important milestone, but the landscape for small businesses and venture funded companies that want to develop innovative combination diagnostics is still difficult, due to uncertain payer coverage decisions and excessively frugal reimbursement for the diagnostic test. Much value will be left unrealized, and important advances will



Mary Dwight, Cystic Fibrosis Foundation

never be brought about, if only pharma-funded clinical development is feasible. Ideally, we would have far more information and more tests validated and available, for example, to tell us whether diabetics with different genetic profiles are likely to respond to certain treatment approaches rather than others. In summary, the panel noted that the Kalydeco collaboration was visionary on all sides, from the perspective of patients, of the disease association, and the drug manufacturer. The important feature is not that this particular constellation of stakeholders worked, but that new and creative collaborations are just waiting to be discovered and carried out.

Program Summary: A Playbook for the Future

Amy Miller, PhD, Vice President for Public Policy for the Personalized Medicine Coalition, and Paul Sheives JD, Director, Diagnostics and Personalized Medicine Policy, BIO, summarized the meeting. The three most important features of the Summit were first, that a clear playbook needs to be developed – important signposts in this direction were cited through the day. Second, change is occurring so rapidly that major improvements in patient and physician education are required, probably through new communication channels like electronic-records-based point-of-care decision aids. Finally, while a major focus of next steps will be those that do not require legislative change, major policy initiatives like MODERN CURES are a critical part of the national dialog, because the possibility of new legislation is a powerful magnet for all stakeholders.

Since the Summit, BIO and PMC have brought a solution to the forefront where multiple stakeholders can develop a common playbook for evidence and coverage that can be a lever for system change. This is the most impactful route to change that can spread through the diagnostics and payer system in the near term.

First, when the wide range of diagnostic tests are considered – those that rule in and rule out drug choices, those that are developed during Phase III trials and those that are developed later, and those tests that are classificatory, diagnostic, or prognostic – it is unlikely that any one definition of “clinical utility” or “required evidence” will be satisfactory. Therefore, a reasonable spectrum of prototypical test categories needs to be established as the basis for evidence guidelines.

Next, it should be possible to lay out what clinical evidence is appropriate for quantifying clinical utility. Clinical utility is always comparative – something happens in a scenario where the test is used, versus what happens in the same scenario absent the test. The clinical utility of the test is the difference between the



At the reception following the summit, meeting attendees discuss the information presented at the meeting, and the prospect of a path forward to providing an approach to evidentiary requirements for coverage of molecular diagnostic tests.

two scenarios, implying that there are necessarily some units (possibly quite different types of units, depending on the context) in which the difference can be expressed. And there will be some concept of the error, or key assumptions, under which the amount of clinical utility is established.

Third, there must be a more clear process for the coverage decisions made by different payers. Today, it may be difficult for test developers to access staff and protocols among the numerous payers of our fragmented health system. While drugs may be presented by standardized dossiers to pharmacy benefit and formulary committees, no similar pathway exists for pure diagnostics. Using the models existing for drug reviews and approvals, it should be possible to develop consensus processes that can be used for decision-making at different payers for the same diagnostics.

The opportunity exists for multiple stakeholders to realize the vision of a “playbook” through which efficient and innovative diagnostics can earn their place in the healthcare system, and positively impact patient care.



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