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A synthesis of stakeholder perspectives on evidence needs to establish clinical utility for genetic testing

Findings from a Workshop held in Seattle, Washington on October 29-31, 2007, to develop a road map for the integration of genetic testing into the delivery of health care: addressing the gap between advances in genomics and health care

The Workshop was sponsored by the Centers for Disease Control and Prevention's National Office of Public Health Genomics; the National Institutes of Health's Office of Rare Diseases; the Health Industry Forum; the Center for Medical Technology Policy; Premera Blue Cross; and the Resource Center for Health Policy (RCHP), the Center for Genomics and Healthcare Equality (CGHE), the Pharmaceutical Outcomes Research and Policy Program (PORPP), and the Center for Genomics and Public Health (CGPH) at the University of Washington.

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“Where funds are required to generate potential truth in biomedicine, and where the allocation of such funds depends inescapably upon the calculation of financial return, commercial investment shapes the very direction, organization, problem space, and the solution effects of biomedicine and the basic biology that supports it.”

Rose, Nikolas. *The Politics of Life Itself*. Princeton Press, 2007, pp 31-32.

Statement of the Problem:

After a slow start, our focus on basic science and clinical and translational research, triggered by the sequencing of the human genome and advances in genomics and related fields, is now expanding the supply of potentially effective medical products. At the same time, we have yet to bring a symmetric focus to the development of evidence to support their adoption and use.

Why is This a Problem?

Put plainly, insufficient evidence is being produced to support decisions about utilization and coverage for many genetic tests. Further, we lack agreement as to which programs and metrics we should use for assessments of “value.” Among the many challenges, for example, is that product manufacturers are not generally informed about the evidence needs of health care service decision makers. In addition, there are disincentives to generating evidence not required by regulation. Hence, existing approaches to priority setting, research methods, and funding strategies only infrequently produce the evidence they seek. This disconnect is compounded by an uneven and uncertain regulatory framework. Because of these and other issues, health care decision makers, particularly clinicians and payers, frequently have to make difficult decisions about many of these technologies without actionable information about their benefits and risks. As a further consequence, the absence of such information will undoubtedly delay adoption of demonstrably effective products and technologies and/or cause inappropriate use of ineffective ones.

This constellation of policy issues can be distilled into two fundamental questions: (1) *what evidence is necessary and appropriate to support the utilization and coverage of a genetic test that meets the test(s) of clinical utility and incremental value, and (2) how can incentives be structured to produce this evidence?*

Exploring the Problem: A Workshop on the Clinical Utility of Molecular Diagnostics (Genetic Testing)

A Workshop was held in Seattle, Washington on October 29-31, 2007, to begin to address this problem. The Workshop was sponsored by the Centers for Disease Control and Prevention's National Office of Public Health Genomics; the National Institutes of Health's Office of Rare Diseases; the Health Industry Forum; the Center for Medical Technology Policy; Premera Blue Cross; and the Resource Center for Health Policy (RCHP), the Center for Genomics and Healthcare Equality (CGHE), the Pharmaceutical Outcomes Research and Policy Program (PORPP), and the Center for Genomics and Public Health (CGPH) at the University of Washington.

Stakeholder groups met over the course of two and one-half days. The groups included manufacturers, payers, researchers/academics, consumers, public agencies (with either oversight or financing mandates), and providers/clinicians.

The singular goal of the Workshop was the development of a road map to identify the steps to be undertaken to improve the quality, type, and supply of evidence for clinical and health care policy decision makers regarding provision, use, coverage, and payment for genetic testing by incorporating key stakeholder and decision-maker perspectives.

Appendix A contains lists of the participating organizations, sponsors, participants, and the agenda.

Thinking about the Problem

Recognizing that it was time to begin to address the problem more systematically, we held the Workshop to initiate the complex negotiations among stakeholders that take place in order to reach consensus on contended policy questions. We began these negotiations by asking each stakeholder group to articulate its unique perspective, then to work in mixed groups to identify points of agreement and disagreement against a backdrop of policy trends.

The Policy Context: Baseline Trends

Over the next ten years we are likely to experience more volatility and turbulence in our health care system than we have in decades. Health care reform as a policy issue is the dominant domestic theme of the 2008 presidential electoral cycle. Every candidate has a reform initiative afloat and nearly all established analysts of our system think the inflationary cost spiral in health care costs is unsustainable. To most, it would not be an overstatement to say that we are approaching a crisis stage.

Among the factors that contribute to the deepening unease about our system are these:

—the aging of our population, which is expected to cause steadily greater demands for health care, among other things, acutely stressing the Medicare Trust Fund;

—our poor performance in achieving improvements in the health status of our population, especially given the enormous resources we commit to health care services;

—the surge of new medical products, including molecular diagnostics, and in particular, expensive biotechnology and specialty drugs, which frequently lack evidence of clinical utility;

—the heavy and growing burden of chronic disease, especially diabetes and obesity;

—and, finally, the continuing burden borne by the nearly 50 million uninsured U.S. citizens, coupled with the steady erosion of the group insurance market, a rising problem of under-insurance, and the looming demise of employer-sponsored benefit plans.

In this changing environment, calls are being made for new and improved approaches to better assess and evaluate the clinical utility of new medical products, including molecular diagnostics. We are recognizing that we cannot continue to rely on physicians as the nearly exclusive arbiters of the utility of new diagnostics and therapeutics, particularly when the evidence upon which to make coherent and sound decisions is so often lacking.

Against this backdrop, there was near unanimity on the critical nature of the challenges, though stakeholder groups differed on the degree of urgency.

Prevailing Stakeholder Perspectives

Before discussing ways to address these challenges, we provide capsule characterizations of how each stakeholder group framed its perspective during the Workshop.

Research: The incentives in academic and institutional research, even with a renewed emphasis on translational initiatives, largely shape its investigations and are often divorced from the needs for thorough analyses of our delivery system. Improvement in the delivery of care is ostensibly one of the voiced objectives of the research undertaken, but our health care system managers have said little about (and provide virtually no funding for) setting priorities for research. Moreover, researchers often pursue projects in which the dispositive factor is the nature of the intellectual and scientific challenge, rather than its potential to address problems in the cost-effective delivery of services. This, of course, mirrors an underlying tension between the relative merits of basic versus applied (i.e., translational) research, in general. Unfortunately, there are few, if any, mechanisms for exchange of information between the research community and decision-makers in our health care delivery system.

Agencies, regulation and resources: Federal and state agencies lack a consistent overall perspective on the subject, primarily because they operate under statutory and regulatory mandates with differing objectives. The FDA and the NIH, for example, have substantially dissimilar mandates. Among federal agencies, both AHRQ and CDC support translational research while NIH's National Human Genome Research Institute (NHGRI), with vastly greater resources, supports basic research that seldom focuses on the evidentiary needs of clinicians and payers. Moreover, all agencies consistently suffer from inadequate resources to meet these mandates. Notwithstanding differing mandates and resource limitations, there are unmistakable signs of increasing agency focus on molecular diagnostics. For example, the FDA recently proposed regulation of multi-gene expression tests and announced its Critical Path initiative. CMS is also increasingly active in the molecular diagnostics field, recognizing that molecular diagnostics holds great potential for more cost-effective therapeutics and disease prevention services. Further, CDC continues to support its ACCE and EGAPP evaluation programs.

In sum, although agency activity is increasing, by default many questions regarding the necessary level and type of evidence are being negotiated by payers and manufacturers in an ever more complex marketplace as the sheer volume of diagnostic (DX) products increases at a rapid rate. Moreover, all of this occurs as we head into the uncertainties of a presidential electoral cycle accompanied by hortatory promises to reform regulatory requirements.

Providers/Clinicians: Generally, most clinicians have either been inadequately trained and/or have had relatively little clinical experience in genetic medicine. As a result, the use of genetic tests in mainstream clinical practice is uneven, uncertain, and, worse yet, largely unknown (and more challenging because of rising consumer demands for genetic information and testing; note recently announced "personal genomics" companies such as 23andMe, Navigenics, and deCODEme). That said, clinicians are accustomed to the need to absorb new information, and are generally comfortable with complex decision-making. However, they need reliable information about new technologies from unbiased sources.

In assessing the potential value of a genetic test, and the specific information needs relevant to the test, clinicians focus on the purpose of a given test:

1. to reduce mortality and morbidity;
2. to provide health information (in the absence of definitive treatment); and,
3. to inform reproductive decision-making.

Most medical tests serve the first purpose. For tests of this kind, clinicians need evidence regarding the test's predictive value in the population to be tested and the outcomes that result from test use.

Genetic tests for highly penetrant genotypes are also commonly used by geneticists for the second and third purposes; however, other clinicians have much less experience with these kinds of tests, and may have difficulty identifying appropriate testing candidates or

providing appropriate pre- and post-test counseling. Referral to geneticists for these services may also be difficult because of limited reimbursement for counseling and/or geographic distance. Appropriate boundaries guiding use of genetic tests in reproduction is also debated, particularly in the case of pre-implantation genetic diagnosis (PGD).

Tests for less penetrant genotypes (e.g., tests for susceptibility to type 2 diabetes or cardiac disease) could potentially be used to reduce morbidity/mortality, but, with a few exceptions, evidence of improved health outcomes for tests of this kind is so far lacking. The issue is whether such tests provide sufficient benefit in the absence of evidence that they improve health outcomes, given that such testing can lead to undue anxiety, unacceptable levels of false positives, and potentially inappropriate demand for services.

On the other hand, many of these new tests address common complex diseases and hence offer the promise of more effective treatment of conditions that are both very costly and frequently intractable. Some of these tests also identify conditions for which therapy does not yet exist, such as Alzheimer's Disease, and/or they generate information that may only have value for the person tested and his/her family, such as a test of ApoE for allelic variations that indicate susceptibility to Alzheimer's. In still other cases, tests are being developed for conditions associated with lifestyle choices based on the unproven but probative premise that personalized risk data will motivate healthy behavioral change. These susceptibility tests also face the challenge of limited, if any, reimbursement from payers (from public payers because such tests look like screening, and from private payers because they rarely monetize information).

Manufacturers: For years, diagnostics stirred little contention in health care. Most available tests were basic in design, simple to administer, and priced at commodity rates, so payers rarely pushed back. Contemporary molecular diagnostics, and particularly genetic testing, on the other hand, infused by torrents of data produced by the research community since the sequencing of the human genome, are disrupting this tranquility. Many new tests, such as Genomic Health's Oncotype DX test, are far more complex in design, pose substantial challenges in interpretation, and are more costly. Moreover, as noted, susceptibility tests that only generate information, such as the deCODE test for diabetes, raise additional questions about the need for interpretation, for whom the information is useful, and who should pay for it.

Manufacturers recognize that the demands for more and better evidence to support test use are intensifying and must be addressed, yet they also urge that such evidence be "adequate," not necessarily "optimal." In addition, they argue that inadequate reimbursement, limited as it is by the absence of updated CPT codes, often renders the costs of generating evidence economically prohibitive. In short, they argue that these factors, along with excessively stringent regulations, will further stifle innovation and discount the value of many new diagnostic tools.

Sensing the inevitable in an era of evidence-based medicine, however, manufacturers are beginning to entertain payment schemes based on value-based models, including emerging concepts of "comparative effectiveness," "coverage with evidence

determination,” and “performance pricing.” These concepts are gaining in currency (short of acceptance, however) as a result of the sharply increased number of newer and more expensive tests entering the market.

Payers, public and private: Frequently, the buck stops here. For molecular diagnostics, this is surely true. Until very recently, payers gave relatively little attention to diagnostics because these products historically represented a small fraction of their costs. As a result, many payers failed to develop decision rules or administrative programs and infrastructure to better understand and analyze these emerging markets. In the last few years, however, the scene has been changing. The high cost of many new products and a pipeline swelling with tests yet to come is a growing concern. At the same time, payers are beginning to appreciate that in some cases, particularly with respect to pharmacogenomics (PGx), the prospects for cost-effective care may be increased, thus justifying re-evaluation of the opportunities and risks ahead.

Of course, public and private payers also face different issues:

—Public payers face issues related to the demographics of Medicare enrollees (tests are most likely to benefit and be cost-effective in populations under age 65), and statutory restrictions on reimbursement for screening.

—Private payers are concerned about the uncertainty in the regulatory environment and the lack of clarity among clinicians about guidelines and standards of practice, among other issues.

For both groups, how should the value of a genetic test be evaluated in the absence of more definitive evidence of clinical utility?

What both types of payers have in common is an expressed need for more and better evidence to support coverage decisions. This evidence could potentially be funded through reimbursement at levels roughly commensurate with the increased vendor costs needed to produce it. This said, and although far from uniform in their responses, payers are increasingly willing to discuss value-based reimbursement models, as thinly conceptualized as they have been to this point. (For an overview of a few of these models, see the website for the Health Industry Forum, one of the Workshop sponsors, at www.healthforum.brandeis.edu.)

Consumers: It is difficult to articulate the consumer position because there is really no singular consumer position. This is emphatically true with genetic information. Genetic literacy among consumers is astonishingly low. Consumer advocates, nonetheless, dispute the perception of many providers and others that consumers without professional advice are prone to make inappropriate and potentially risky decisions about their health care needs. Providers are further troubled by the threat of widespread consumer misinterpretation of the spate of new and unvetted information about genetics to which they are being exposed. On the other hand, consumers of genetic tests and health care are generally likely to put the argument this way: “If there is something that can help my

family and me to be healthier, I want it, and don't give me too many fancy answers along the way..."

This is an argument that is far from resolved.

Not all of the consumers of genetic information and testing are similarly situated; the outlines of five fairly distinct categories of consumers can be characterized:

- women and families seeking guidance for reproductive decision-making;
- individuals, newborns, children, and their families dealing with rare genetic conditions;
- patients who have or are predisposed to developing common complex diseases who are eager for more effective care;
- patients taking or considering drugs for which a genetic test is available, with the intended purpose of guiding treatment decisions;
- consumers seeking a foothold in the mounds of genetic “data” piling up (most not rising to the level of “information,” and virtually none to “knowledge”), typified by the arrival of companies such as Navigenics, 23andMe, and deCODE.

Access by this last group to genetic testing raises some of the same issues about genetic data in general, but also some distinctly different ones. A central question is whether harm exceeds benefit if consumers cannot constructively interpret and weigh the evidence. In fact, consumers and patients face considerable jargon in their navigation of the health care system. As a result, in the stakeholder dialogs hosted at the Workshop, consumer representatives often found that terminology about evidence and its uses was not easily grasped. Glibly put, many consumers presume that sufficient evidence underlies that which is available (or why would they be given access at all?). Further, to many consumers (patients), “clinical utility” is what their doctor says it is. Also, many consumers, when facing a life-threatening condition, or at least their perception of one, often become less risk-averse and more demanding. Beyond these generalizations (which is all they are), each category of consumer poses different public policy questions. For our purposes, the categories of consumers that are most relevant to achieving the goal for the Workshop are those having or predisposed to developing common complex conditions and those with rare diseases.

A negotiated road map to improved evidence

Do all of these perspectives come together to map out a path to securing actionable evidence? One way to chart a constructive path is to identify the drivers and barriers ahead, and then outline ways to optimize select drivers and address the key barriers.

Drivers

A singular and potent driver is the very promise of molecular diagnostics itself: improved health, a greater emphasis on prevention, and a more productive health care system fueled by better outcomes. This promise is reflected in the zeal of the proponents of

“personalized medicine,” the tactical phraseology designed to spur investment in the discovery and use of molecular diagnostics and more targeted therapeutics. To date, however, the yield of more genomics research and more powerful scanning technologies, with some notable exceptions, is unimpressive in both quality and quantity, and still less impressive given the lack of acceptable evidence of clinical utility for most of the new diagnostics reaching the market. Nevertheless, it remains realistic to expect an enhanced yield over time, given the acceleration of commitment and resources for basic, applied, and market research.

Other key drivers include aggressive marketing practices, a comparative advantage for savvy companies when regulatory barriers are low, markedly increased R&D investments, and the expected development of enabling technologies such as point of care tools and health care professional education programs. Though negligible to date, every indicator suggests rapidly rising consumer interest and demand sparked by widespread, sometimes breathless, press coverage of genetics.

The channels for the introduction of new diagnostics to the marketplace, however, may soon narrow if more and more products head to market unsupported by at least some reliable evidence of clinical utility. In fact, the Workshop would have been difficult to organize even a year ago due to a lack of threshold interest among many stakeholder groups. These stakeholders are now standing on that threshold because:

- payers see a brimming pipeline of new products for which coverage will be sought, representing added costs without threshold evidence of commensurate value;
- clinicians are increasingly uncomfortable with the degree of uncertainty about the utility of many of these new products;
- public agencies perceive a need for more oversight and more translational research;
- manufacturers are experiencing heightened demands by both payers and clinicians for improved evidence that they are finding difficult to resist;
- the research community favors the prospect of greater funding; and,
- consumers sense the promise and availability of improved therapeutics and preventative care programs and are intrigued by the allure of personalized genomics information.

In short, the key stakeholders are becoming engaged, but the barriers to securing better evidence remain largely unshaken.

Barriers

The chief barriers identified by Workshop participants are these:

—growing realization that genomics is a far more complex and challenging science than has been assumed;

—lack of genetic literacy by clinicians and consumers (patients), compounded by inadequate educational and training programs;

—primacy of marketing and promotion programs by diagnostic developers resulting in skepticism by many researchers, providers, and payers;

—historical and still prevalent commoditization of much of the diagnostics product line, slowing recognition of the arguably enhanced value of some new diagnostics;

—lack of current CPT and other coding programs, resulting in low reimbursement rates for new diagnostics in the absence of consensus about new payment and reimbursement models, such as coverage with evidence development;

—accumulation of diagnostic data from the proliferation of new genetic tests, potentially leading to an unacceptable level of false positives, e.g., the “incidentalome” problem;

—lack of resources (both claimed and real) to produce evidence;

—lack of payer infrastructure to reach consistent coverage decisions, compounded by lack of clarity about what types of evidence are needed and what assessment tools should be used;

—the absence of work flow and information technologies to guide the appropriate use of genetic services and information;

—uncertainties in how genetic services and information policy will be formulated in both legislative and regulatory arenas.

In pursuit of evidence to establish clinical utility: the road ahead

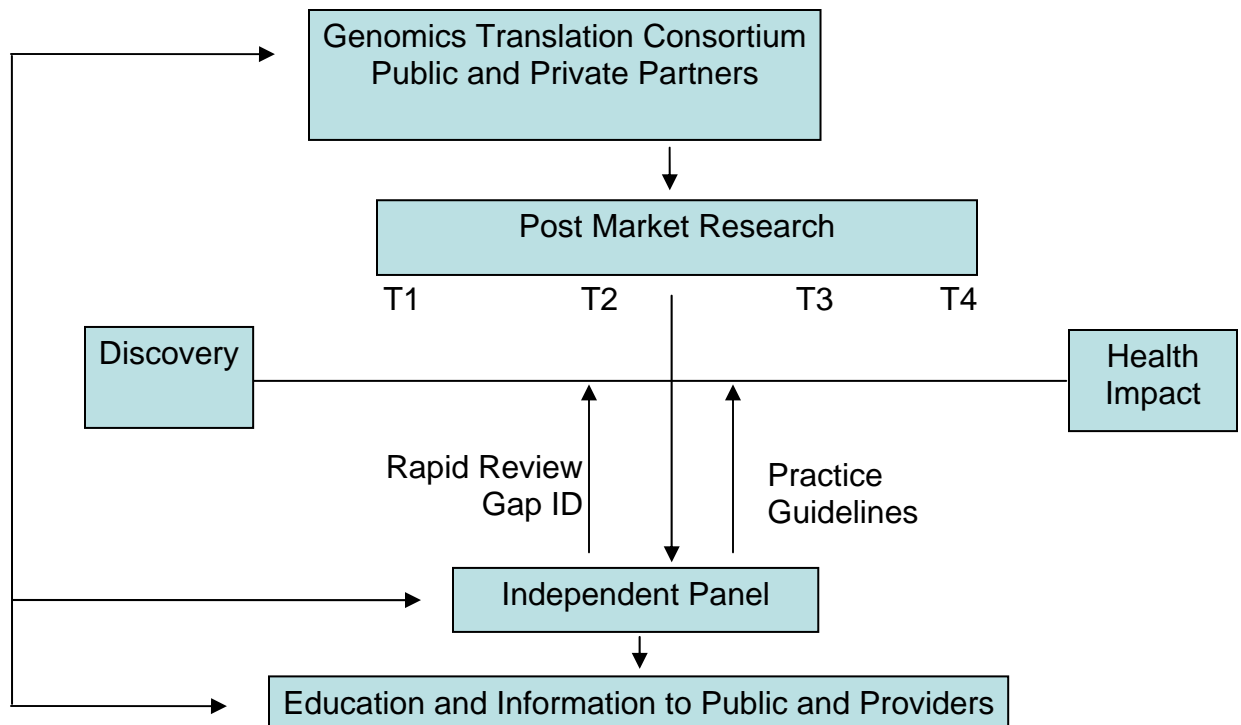
Understandably, Workshop participants did not produce a finite articulation of the various measures and programs that might be needed to address the problem of insufficient evidence; such was not a realistic outcome for a two-day Workshop. Nonetheless, participants discussed a number of tools, resources, and measures that provide some signposts along the evolving road map.

The Translational Framework (TF): To identify issues and challenges toward better evidence, we utilized a Translational Framework model throughout the Workshop. This model was originally developed at the CDC, and modified by Wylie Burke and her co-investigators at the University of Washington’s Center for Genomics and Healthcare Equality (CGHE). This four-step model (T 1 through T 4) highlights the key steps and questions to be addressed from conception of a diagnostic product all the way to

mainstream clinical practice, and hence provides a tactical picture of what determinative issues are to be addressed, and in what order. The TF is attached as Appendix B.

Consortium Models: In retrospect, the Workshop might now be understood as a first step in developing consortia to engage combinations of stakeholders to formulate recommendations about the levels and types of evidence to support the introduction of genetic tests into clinical practice. Figure 1, below, is a conceptualization of the model, originated by Muin Khoury of CDC, which incorporates the TF framework:

Figure 1: A Genomics Translation Roadmap



If implemented, the processes represented in the Figure would entail reviews of novel genetic tests by an independent panel very soon after such tests reached the market and/or relevant information became available. This information could be used by consumers, clinicians, and payers to make initial decisions about these tests. The panel would also identify key areas of future research that might be pursued by the Consortium. Evidence developed by the Consortium could then be used to inform practice guidelines and refine reimbursement policies.

Engaging all stakeholders in a single consortium faces daunting logistics and would be even more difficult to achieve because of the lack of resources to support such an effort. On the other hand, it is conceivable that stakeholders with the most at stake might contribute financial support even as that remains an elusive target. It is more realistic to expect certain combinations of groups, such as researchers and providers and/or manufacturers and payers, to convene, and that should be encouraged. If, for example,

payers and diagnostic developers could agree on the levels and types of evidence needed in today's environment and on a plan to develop more rigorous standards in the future, progress toward the articulated goal for the Workshop could be accelerated.

The Guidance: A process to engage developers and payers, referred to as the "Guidance" (*Evidence and Transparency Recommendations to Support Coverage and Reimbursement Decisions for Medical Testing*), was presented at the workshop. Developed by the Pharmaceutical Outcomes Research and Policy Program (PORPP) at the University of Washington as a utility, the Guidance is based on the widely used dossier process, also developed by PORPP, and administered by the Academy of Managed Care Pharmacy (AMCP) for submission of evidence to support coverage decisions for pharmaceutical products. The Guidance, among other things, was distributed at the Workshop as an infrastructure tool for use by both developers and payers to make coverage decisions a more efficient process. The Guidance, accompanied by an article providing a rationale for its use, was published in the American Journal of Managed Care, and is attached as Appendix C.

Regulatory and Oversight Reform: A number of calls are being made for increased regulatory oversight by key Federal agencies, particularly the FDA. CMS has also considered seeking the authority to upgrade CLIA regulations. In fact, the challenge posed by the lack of evidence of clinical utility was central in the Secretary's Advisory Committee on Genetics, Health and Society's (SACGHS) draft report on the oversight of genetic tests, issued on November 5, 2007, just after our Workshop adjourned. In particular, see pp 20-22 in the Executive Summary (<http://www4.od.nih.gov/oba/sacghs.htm>).

Any substantive changes would undoubtedly bear on the questions raised at the Workshop, but with presidential elections in 2008, it is doubtful that the Congress will take on significant regulatory reviews and modifications before then. It is, however, a reasonable bet that the environment will be more supportive of reform agendas by 2009-10.

Emerging Programs in Health Technology Assessment (HTA): In the U.S., unlike the situation in some European countries with programs such as NICE in the U.K., technology assessment programs are uneven, under-funded and rarely timely. The rapid pace of introduction of new medical products, buttressed by effective marketing campaigns, often outflanks efforts by programs such as the Technology Evaluation Center (TEC), sponsored by the Blue Cross Blue Shield Association (BCBSA), public initiatives such as EGAPP, and even entrepreneurial programs such as those promoted by the Hayes Group. While this may be the state of HTA today, most Workshop participants agree that more initiatives will soon arise; an oft-cited example is the pending legislation in the Congress to establish a Center for Comparative Effectiveness.

Experiments in Pricing and Reimbursement: A recent *New York Times* article featured examples of pharmaceutical and diagnostics manufacturers' value-based reimbursement models. As a variation on the theme of coverage with evidence development advocated

by one of the Workshop sponsors, the Center for Medical Technology Policy (CMTP), these models discussed at the Workshop represent innovations in reimbursement that could advance the use of appropriate diagnostics while accommodating the ongoing development of evidence to establish clinical utility. The value proposition underlying use of these models is that payers might reimburse manufacturers with value-based, rather than administered, pricing models for drugs or tests. These models would be based on an acceptable threshold level of evidence of clinical utility in exchange for additional information and post-market tracking and analysis to determine whether the drug, or test, performed as expected.

According to the *Times*, as an example, UnitedHealthcare has entered into a novel coverage and reimbursement arrangement with Genomic Health, developer of the Oncotype Dx test. The test is designed to assess the risk of recurrence among women who have had surgery for breast cancer, and is one of the tests assessed at the Workshop as a case study. The premise for use of the test is that appropriate adjuvant chemotherapy will be covered and made available to patients for whom the test result indicates a high likelihood of successful outcomes, and will not be covered or made available for those whose test result indicates a low likelihood of success. A significant concern amongst payers is that patients and clinicians will continue to use chemotherapy, irrespective of the Oncotype Dx test score, thus compromising the value of the test. UnitedHealthcare and Genomic Health have addressed this issue by agreeing to post-test monitoring, and further, to adjust the price paid for the test if the expected adjuvant chemotherapy use in breast cancer patients is not as projected.

Although this may seem to be a one-off example, there are broader developments that hint at the potential shift in the payment environment toward incentive-based or reward-based payments:

- 1) Intensifying emphasis on evidence-based practice and the desire to link coverage and reimbursement decisions to evidence of benefit;
- 2) Continuing interest by CMS in its administration of Medicare in coverage with evidence development models;
- 3) Recent papers and legislation calling for independent comparative effectiveness research;
- 4) Continuing calls for national HTA programs; and,
- 5) The high visibility report of the UK Office of Fair Trade calling for value-based pricing to replace the Pharmaceutical Price Regulation Scheme (PPRS).

A final consensus across all stakeholder groups was that the problem of insufficient evidence to establish clinical utility for genetic testing, particularly tests developed over the past few years and those now under development, had matured as a policy question; hence, measures such as those discussed, and others, would frame the ongoing negotiations amongst them.

Summing Up and Next Steps

The evolution of the U.S. health care system tells us that change, if at all, arrives slowly and fitfully. But *all* systemic change is precipitated by recognition of a problem—a practice, program, or process that can be better done. Two years ago, maybe as little as one year ago, the problem we addressed at the Workshop might not have been conceived as a problem. Now it is. The Workshop was obviously only a first step toward finding answers; in fact, its purpose was more to get the questions right. We hope this synthesis helps to accomplish that task. Much more work lies ahead. Plans are now being formulated for another Workshop with an agenda designed to start where this first Workshop ended. Stay tuned for details.