IOM Workshop: Solid Clinical Evidence, Reimbursement Are Keys to Adoption of Genomic Advances in Clinical Practice

By Peggy Eastman

WASHINGTON, DC—In an era of exploding knowledge on the function of genes and their proteins, compelling clinical data and reimbursement are most often the driving forces behind which advances make it into practice and which do not. So said speakers here at an Institute of Medicine (IOM) workshop sponsored by the Institute’s Roundtable on Translating Genomic-Based Research for Health.

The Roundtable’s Chair, Wylie Burke, MD, PhD, Professor and Chair of the Department of Medical History and Ethics at the University of Washington School of Medicine, noted that the plan is to release a report on the findings about genomics and health later this year.

In October, the National Research Council (which, like the IOM, is part of the National Academy of Sciences) released a report recommending that government agencies step up their efforts to incorporate genomic data into risk assessments of chemicals and medicines to protect the public from toxicities caused by altered gene expression.

Scientifically, translating genomic innovations such as a new diagnostic test into practice is complicated because penetrance of a genotype may differ from low to high and because an individual patient’s risk depends on environmental as well as genetic factors, Dr. Burke explained.

As an example, she cited testing for an increased risk of colorectal cancer: The inherited risk of familial adenomatous polyposis (FAP) is about 1 in 8,000 with a 100% lifetime risk of colorectal cancer for those affected, whereas for those not affected, the risk of hereditary nonpolyposis colorectal cancer (HNPCC) is about 1 in 500 with an 80% lifetime risk of colorectal cancer.

If the patient is obese, exercises only a little, and eats a diet high in red meat and low in fruits and vegetables, these environmental variables can also raise the risk. But, Dr. Burke asked, “what happens when we start combining variants? We will identify a very small part of the population at very high risk...A lot of our conversation is about managing genetic information right now. Clinicians want information about billable services that improve outcome.”

Others agreed that real-time clinical utility and reimbursement can make or break a new genomic discovery.

“Genomic innovations are increasingly leading to new clinical interventions,” said Annette Gelijns, PhD, Co-Director of the International Center for Health Outcomes and Innovation Research; and Associate Professor of Health Policy, Management and Surgical Sciences at the College of Physicians and Surgeons and the Division of Health Policy and Management of Columbia University’s Mailman School of Public Health.

But, she noted, diffusion is slow, and “stakeholders seek evidence to guide their adoption decisions...evidence is a critical factor in the diffusion of technology.” The diffusion of new genomic technologies such as diagnostic tests hinges not only on their clinical benefits but also on “the institutional environment in which they are to be embedded.”

FDA’s Role

Dr. Gelijns noted that the US Food and Drug Administration has taken a proactive role in the evidence needed for diffusion when new genomic advance has specific clinical utility. As an example, she cited FDA fast-track approval of trastuzumab to treat breast cancer patients and FDA fast-track approval of HER2 testing for breast cancer patients and FDA fast-track approval of trastuzumab to treat patients whose tumors overexpress the HER2 protein. “Both were fast-tracked and approved jointly with coordinated labeling,” she said.

Messy, Bumpy, Unpredictable

But other speakers noted that the road from genomic discovery to clinical practice is rarely that smooth or coordinated. As an example, he cited FDA fast-track approval of HER2 testing for breast cancer patients and FDA fast-track approval of trastuzumab to treat patients whose tumors overexpress the HER2 protein. “Both were fast-tracked and approved jointly with coordinated labeling,” she said.

“On the translation highway, many innovations are lost in translation. We don’t want to be the wild west; what I don’t think we should do is release these tests on the public with no evidence at all.”

IOM Roundtable member Kevin A. Schulman, MD, Professor of Medicine and Business Administration and Director of the Center for Clinical and Genomic Economics at Duke University, agreed that uncertainty dogs the pace of turning genomics into useful advances for clinical practice. “Intelligently this is an exciting area; how it’s going to fit into the marketplace is still uncertain,” he said.

Said former Centers for Medicare & Medicaid Services Chief Medical Officer Sean Tunis, MD, founder and Director of the nonprofit Center for Medical Technology Policy and a principal at Rubix Health, “The evidentiary bar isn’t well defined at all; there is tension between innovation and evidence. Payors, physicians, and patients are demanding more evidence on technology...Evidence requirements are often poorly defined, inconsistent, and not feasible.”

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Dr. Tunis said this tension between innovation and evidence occurs because of the desire for new technology but also because of the potential for trouble with medical innovation in general and genomics in particular. He stressed that all genomic innovations that make it into clinical practice should be used in a “rigorous post-learning environment” designed to uncover any adverse effects. He added that a relatively undefined evidentiary bar for genomics makes it difficult for companies trying to bring a particular genomic advance to market—“Companies not only have a moving target, they have a fuzzy target.”

Guidance Document on Health Insurance Coverage of Genomic Innovations in Breast Cancer

Dr. Tunis told OT that his nonprofit company plans by the end of this year to produce a free guidance document...
Radical Nephrectomy Shown to Have Long-Term Negative Impact on Survival

By Rabiya S. Tuma, PhD

SAN FRANCISCO—Kidney cancer surgeons continue to favor radical nephrectomy over partial nephrectomy, according to data presented here at the Genitourinary Cancers Symposium, cosponsored by the American Society of Clinical Oncology, the American Society for Therapeutic Radiology and Oncology, and the Society of Urologic Oncology.

Women, older patients, and those with a history of stroke were less likely to undergo a partial nephrectomy than men, younger patients, or those without a history of cerebrovascular disease, the study found. And the long-term health and survival of patients who underwent a radical nephrectomy was significantly worse than those who had a partial nephrectomy.

“The study showed that fewer than 20 percent of the eligible patients are having a partial nephrectomy. Our attitude about that, as a community, needs to change and the standard of care should really be partial nephrectomy whenever it is technically feasible,” commented Eric Klein, MD, Section Head of Urologic Oncology at the Cleveland Clinic Foundation, who was not involved in the relevant studies. “We now have good, solid evidence that preserving as much kidney function as possible is a beneficial thing.”

Although partial nephrectomy and radical nephrectomy are equally effective in terms of cancer control in patients whose tumors are 4 cm or smaller, several retrospective studies have shown that surgeons use radical nephrectomy much more frequently. To find out which patients are more or less likely to undergo radical nephrectomy and determine whether it has an impact on long-term patient health, William C. Huang, MD, Assistant Professor of Urologic Oncology at the New York University School of Medicine and colleagues used the Surveillance, Epidemiology, and End Results (SEER) database, linked to Medicare data for patients over age 65.

Dr. Huang and his colleagues identified 2,991 patients diagnosed between 1995 and 2002 who were surgically treated for a kidney tumor that was 4 cm or smaller and thus appropriate for partial nephrectomy. Of those, 2,547 (85%) had a radical nephrectomy and 556 (19%) had a partial nephrectomy.

However, not all patients were equally likely to be treated with the procedure. Women at low risk for breast cancer, older patients, and those with a history of stroke were less likely to undergo a partial nephrectomy than men, younger patients, or those without a stroke history. Women at low risk for breast cancer, older patients, and those with a history of stroke were less likely to undergo a partial nephrectomy than men, younger patients, or those without a stroke history.

Dr. Shak said that excluding the cost of the study from which the tissue blocks were obtained, developing Oncotype DX probably took a company investment of about $50 million to $100 million over seven years.

Test for UGT1A1 Polymorphisms as a Marker of Irinotecan Toxicity in Colorectal Cancer Patients

Brad Gray, Vice President for Business and Strategic Development at Genzyme Genetics, said that even when a clinically useful, approved new genomics test is available to clinicians, it still may face a challenge to win them over. He cited a population segment of colorectal patients with UGT1A1 polymorphisms who have marked adverse toxicity reactions to irinotecan; Genzyme developed a test to detect that segment of patients.

However, said Mr. Gray, some physicians said they didn’t need such a test, because when toxic side effects occurred, the doctor’s response would be to just reduce the dose, stop the cycle, or stop treatment with the drug altogether. “US physicians have largely ignored this test,” Mr. Gray said.

He noted that the test has largely been neglected by clinicians despite the fact that Genzyme has data showing that the UGT1A1 polymorphism test delivers savings that are three times the cost—because it can prevent these adverse toxic events in the susceptible segment of colorectal patients.

Mr. Gray and other speakers said that incorporation of genomics into clinical practice guidelines by such authoritative groups as the American Society of Clinical Oncology and the National Comprehensive Cancer Network will be critical in the adoption of and reimbursement for genomic advances in clinical practice.