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*Cancer Centers: Permanent Reinvention*

## Called "Unscrupulous" in Abramson Lawsuit Thompson Calls Abramson A Rich Man Scorned

*By Paul Goldberg*

Attorneys for Craig Thompson characterized a legal action against him as the work of a rich man who apparently feels slighted.

"In short, this proceeding is brought by a wealthy donor to the University of Pennsylvania, upset that Dr. Thompson, one of the country's leading cancer scientists, is no longer associated with Penn or the donor," Thompson's lawyers said in a document filed March 16 in the U.S. District Court for the Southern District of New York.

The donor in question is, of course, Leonard Abramson, a Philadelphian who once ran U.S. Healthcare and who founded a research institute at Penn, providing $110 million to the endeavor.

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*Personalized Medicine*

## IOM Omics Committee Offers Blueprint To Prevent Other Duke-Style Disasters

*By Conor Hale*

A panel convened by the Institute of Medicine called on FDA to publish a guidance or regulation on submitting omics-based tests for regulatory review.

The panel that formed in the wake of the Duke University genomics scandal reaffirmed the existing FDA policy that requires that all tests used to guide management of patients obtain an Investigational Device Exemption clearance from FDA.

The panel took a broad view of the issues involved, looking beyond the troubling events in Durham, N.C., and focused on providing recommendations for the development pathway of omics-based tests from discovery to clinical trials.

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*In Brief*

## Charles Sawyers New AACR President-Elect

**CHARLES SAWYERS** was elected president-elect of the **American Association for Cancer Research** for 2012-2013.

He will officially become president-elect on Monday, April 2, at the AACR's annual meeting in Chicago, and will assume the presidency in April 2013.

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# Craig Thompson's Legal Filing Both a Response and a Retort

(Continued from page 1)

The tone of Thompson's filing is consistent with the personal attacks embedded in the complaint the Abramson side filed late last year. The name-calling commenced in the suit filed by the Leonard and Madlyn Abramson Family Cancer Research Institute, which characterized Thompson as "an unscrupulous doctor" who "chose to abscond with the fruits of the Abramson largess."

Thompson left Penn in 2010 to become the president and CEO of Memorial Sloan-Kettering Cancer Center. Last week's retort by Thompson's lawyers represents their first stab at telling his side of the story.

In a nutshell, the Abramson institute, which is a separate non-profit affiliated with Penn, claims that Thompson had deliberately evaded disclosing his inventions to the university, and instead made them available to a company he co-founded, Agios Pharmaceuticals Inc.

Nonsense, Thompson and Agios say.

The defendants named in the Abramson suit are asking the judge to dismiss the case, arguing that the Abramson institute has no standing to file the suit. Moreover, Thompson had made appropriate disclosures, the defendants argue.

Regardless of what the judge does in this case, Thompson and Agios will still be facing a separate suit from Penn (The Cancer Letter; March 9, March 16). Abramson is seeking hundreds of millions in damages. Penn is seeking billions.

Thompson's response in the case states that while he and Agios work in the same area of science—cancer metabolism—that area happens to be enormous. It was established by Otto Heinrich Warburg, who published a hypothesis in 1924 that holds that cancer cells metabolize glucose in a manner that is different from such metabolism in normal tissue.

A motion by Agios, also filed March 16, states that the company isn't using any of Thompson's inventions.

"The [Abramson] complaint nowhere identifies the 'medical research' in which the plaintiff claims an interest, what dispute, if any, exists about it, or whether any intellectual property based on such research even exists," the Agios complaint reads.

"Nor are any facts alleged about when or how Agios interfered with the plaintiff's alleged interest in the undefined medical research at issue, or the extent (if any) of the plaintiff's resources used in developing such interest."

The filings by Thompson and Agios are posted at: http://www.cancerletter.com/categories/documents.

**Thompson, Agios Release Documents**

The Abramson institute's complaint alleges that Thompson hadn't told either the institute or Penn that he was a founder of Agios.

Thompson's response says that his Agios role was anything but a secret. In fact, on three occasions since the company's founding in 2007, information posted on the Abramson Cancer Center website identified him as an Agios founder.

Thompson also released a disclosure form on which he describes his role.

The disclosure to Penn stated that, in 2008, Thompson received $24,204 as a member of an advisory board to Agios. This activity took four days, the disclosure states.

Thompson's role in the company was also disclosed in his publications. His attorneys released a copy of an email in which he forwarded one such article to the Abramson institute president, John Glick.

"The notion that Dr. Thompson's involvement with Agios was somehow 'hidden' from anyone is thus blatantly false," the filing states.

Also, the document asserts that the Abramson institute has no standing to sue. "Dr. Thompson was an employee of Penn, and only Penn," the document states. "He is not alleged to have signed any written employment or other agreement with the institute."

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The institute is well-positioned to collect revenue from intellectual property.

Penn and the institute evenly split the proceeds from intellectual property produced by Penn scientists funded by the institute. However, in cases where the institute is the sole funder of research, it gets to keep all the proceeds.

Agios has raised $261 million in capital, most of it from the pharmaceutical company Celgene Corp. This money represents investment in research, not revenues.

The Abramson institute initiated the action against Thompson without Penn's involvement.

However, Penn ultimately jumped in, filing its own separate lawsuit, which has been referred to the same judge as the Abramson case (The Cancer Letter, March 16).

Penn's suit focuses on two papers, which list Thompson as an author. Thompson is not listed as an inventor on patents stemming from the inventions (The Cancer Letter, March 9).

That case, if it goes forward, will likely turn on the distinction between authorship and inventorship.

The Agios filing in the Abramson suit focused briefly on these issues:

"[For] a patent to be valid, it must properly list all of the invention's inventors," the filing states. "Therefore, if Dr. Thompson had invented subject to the Penn Patent Policy, but diverted it to Agios, Agios would still need to identify Dr. Thompson as an inventor, or otherwise would be unable to obtain a valid patent. But there is no allegation that Agios has named Dr. Thompson as an inventor on any patent or patent application.

"Indeed, there is no allegation that Agios has obtained any patents at all."

Responses to the Penn lawsuit are expected next month.

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*Personalized Medicine*

## Committee Avoided Investigating Misconduct In Duke Scandal

(Continued from page 1)

IOM assembled the committee at NCI's request after The Cancer Letter reported that one of the leaders of the Duke cancer genomics program, Anil Potti, claimed credentials he didn't have, including a Rhodes Scholarship (The Cancer Letter; July 16, 23 and 30, 2010).

Though the work of the Duke team had been thoroughly scrutinized by M.D. Anderson Cancer Center biostatisticians Keith Baggerly and Kevin Coombes, the Rhodes disclosure caused Duke to stop clinical trials. Ultimately, Duke review triggered retractions of multiple papers by the world's premier medical journals.

The IOM Committee on the Review of Omics-Based Tests for Predicting Patient Outcomes in Clinical Trials didn't focus on who did what to whom, but considered the events at Duke along with eight additional biomarker test case studies in oncology and other therapeutic areas. The report, published March 23, aims its recommendations at academic, scientific and industry institutions, the FDA, journal editors and funders of research.

"We were working under a statement of task from the National Academies of Sciences, which was to learn what we could from the cases that we chose to examine—and from our knowledge of the development process, propose the most appropriate ways to develop and validate this kind of omics-based technology for patient care," said committee chair Gilbert Omenn, professor of medicine, genetics and public health at the Center for Computational Medicine and Bioinformatics at the University of Michigan Medical School, in a telephone conference with reporters.

"What we did not do, and what we were not empowered to do, was to do a misconduct investigation or any kind of legal investigation, or to inquire specifically participants one at a time or even groups of participants in the [Duke] trials that had been launched and were later terminated."

Asked about the potential for harming patients in trials that rely on genomics, Omenn said, "It's certainly a hypothetical question, and I think the best answer is to say that we are confident that pursuing the scheme we've laid out here would be in the best interest of patients.

"Credible, scientifically-based tests, scrutinized by others in the field, represent the best approach to developing tests of early diagnosis, prognosis and

treatment choice.

"Obviously, if a test of any kind is used to determine that some patients get a therapy that works in some percentage of patients—and other patients are not given that therapy based on result of that test—it's very important that the test results be reliable. Otherwise the patient benefit would be potentially reversed, or at least lost, if the test were predicting unreliably."

**Validation Process**

The committee proposed using a two-stage validation process before an omics test could be used in a clinical trial: a discovery and test validation phase, and then evaluation for clinical use.

In the discovery phase, the candidate test is developed on a training set—and then its computational procedures should be fully "locked down" and "remain unchanged in all subsequent development steps," according to the report.

The test should then be confirmed on a separate, independent sample set, if one is available, or an unused subset of the training set. The test should be blinded to any outcome until after computational procedures have been locked down, said the report. The test should not be changed during the trial without a protocol amendment and discussion with the FDA, because any substantive change could require the restarting of the trial, cautioned the committee.

The report described this as the "gold standard" for test validation, by avoiding overfitting the model to the data used to develop the computational procedures.

"Overfitting due to use of improper statistical methods leads to a computation model that fits the training samples well, but will perform poorly on independent samples not used in the discovery phase," said the committee's report.

During test validation, the committee recommended that both the data-gathering assay and the computational procedures be tested, and that the test's intended use be discussed with FDA prior to clinical validation studies. This phase includes approval by an independent review board and clinical validation using a blinded sample set.

At this point, the test reaches a "bright line" in its validation pathway. In order to cross it, the test needs to be fully defined, locked down, and validated—analytically and biologically. After crossing the bright line, any changes to the test require a return to the validation phase and an updated approval from the independent review board.

On the other side of the bright line, the test enters the clinical utility evaluation phase, where the committee recommends three potential pathways to FDA approval, and finally clinical use.

Prospective or retrospective studies with archived specimens, or prospective trials where the test does not direct patient management would not need an IDE to proceed.

However, tests that do manage the treatments patients received, or otherwise direct patient care, would legally require an IDE before being considered for use in clinical trials.

The committee recommended consultation with the FDA "because the requirement for an IDE based on trial design is not always clear."

To that end, the report said that FDA should publish new guidance clarifying those requirements, and that the agency should communicate the requirements for omics-based tests to the Office of Human Research Protections, IRBs and other leadership groups.

**"A Wakeup Call"**

In a conference call with reporters, committee chair Omenn discussed the testimony of Duke officials presented to the committee Aug. 22, 2011.

"They had done a survey of the 162 co-authors of Nevins and Potti, and the series of papers, and those papers' descendants. Not a single one of those investigators had raised a peep in the transparent flaws in these original papers," Omenn said.

"Hundreds of papers cited each of the 2006 papers in The New England Journal of Medicine and in Nature Medicine, and dozens of others have cited the Journal of Clinical Oncology and the Lancet Oncology 2007 papers. A lot of grants have been awarded based upon this work. Even first year graduate students can see serious problems in these papers. The review process was flawed.

"The process of putting one's name on a manuscript that becomes a publication was flawed. And there are consequences. So far, 27 of the 40 identified publications have been retracted or partially retracted. This is a huge stain on the record of everyone involved.

"It's a wakeup call, not just to people doing this kind of research, but all kinds of translational research."

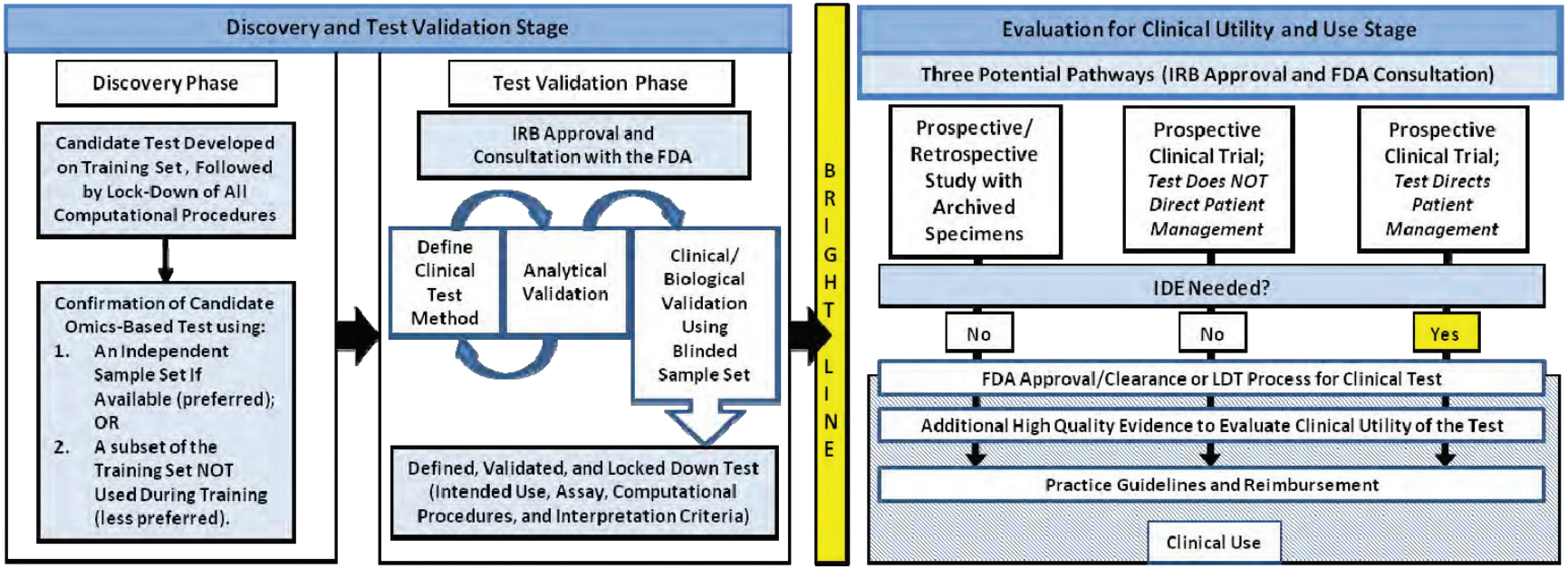


**FIGURE S-1** Omics-based test development process. In the first stage of omics-based test development, there are two phases: discovery and test validation. In the discovery phase, a candidate test is developed and confirmed. The fully specified computational procedures are locked down in the discovery phase and should remain unchanged in all subsequent development steps. Ideally, confirmation should take place on an independent sample set. Under exceptional circumstances it may be necessary to move into the test validation phase without first confirming the candidate test on an independent sample set if using an independent test set in the discovery phase is not possible, but this increases the risk of test failure in the validation phase. In the test validation phase, the omics-based test undergoes analytical and clinical/biological validation. The bright line signifies the point in test development where a fully defined, validated, and locked down clinical test (analytical and clinical/biological validation) is necessary. Changes to the test after the bright line is crossed require a return to the test validation phase, approval by the Institutional Review Board, and possibly consultation with the Food and Drug Administration. In the second stage of test development, the fully defined, validated, and locked down omics-based test undergoes evaluation for its intended clinical use. Evaluation of clinical utility and use is a process that often continues after initial adoption into clinical use. Statistics and bioinformatics validation occurs throughout the discovery and test validation stage as well as the stage of evaluation for clinical utility and use.
NOTE: FDA = Food and Drug Administration, IDE = investigational device exemption, IRB = Institutional Review Board, LDT = laboratory-developed test.

**A diagram from the report's executive summary, detailing the two-stage omics test validation process.**

The committee determined that a lack of full access to the data and code at Duke constituted a barrier to the investigation, and hindered attempts to reproduce the trials' results. The committee suggested changing the standard of practice that follows the discovery phase—making all data, metadata and computer code publicly available in an independently managed database.

The committee recognized "that it might not always be possible to make this information publicly available due to the protection of intellectual property. For publicly funded research, the committee recommends that code and fully specified computational procedures should be made available at the time of publication or at the end of funding.

"For commercially developed tests, code and fully specified computational procedures would be submitted for FDA review if seeking approval or clearance, or would be described in a publication in the case of a laboratory developed test. Companies that seek FDA clearance or approval for their tests would have had to submit data to the FDA as part of the 510(k) clearance processes or premarket approval processes, respectively, but only the information reported in the FDA decision summary is made publicly available."

With regard to institutional responsibility, the committee said that "academic institutions, other non-profit research organizations, and for-profit companies that support the development of omics-based tests also bear responsibility for proper oversight of the discovery, translational, and clinical research conducted and reported by their faculty or research staff seeking to generate successful omics-based tests.

"As the Duke case study clearly demonstrates, existing procedures in some institutions may not adequately ensure the scientific integrity of translational omics.

"For example, although most institutions have clear policies and procedures for financial conflicts of interest for individuals, there is often less clarity when handling institutional conflicts, both financial and non-financial. An institution might appear so conflicted in certain situations that an outside body should be asked to take responsibility for an investigation."

Omenn offered an example:

"Institutional conflict of interest is a problem acknowledged by the Duke officials that over a four-to-five year period, they basically stood behind their senior investigator and refused to investigate the science of the protocols for these clinical trials," he said. "They approved human subjects, they approved starting trials, their office of technology transfer approved starting companies, and they promoted the investigators for all kinds of awards, and put in new grants without examining the scientific basis for the work.

"There were a lot of missed signals, any one of which could have prevented this series of events from being exacerbated over such a long period of time."

Duke officials welcomed the report.

"It represents an important contribution to the field of genomics and translational research and the recommendations contained in the report provide a clear path forward that will guide researchers as they bring genomic research through the translational system to benefit patients," university officials said in a statement. "The impressive depth of the report will provide great value to the spectrum of participants in the research and development system, including regulatory agencies, basic and clinical research communities, and, ultimately, patients.

"We welcome the opportunity to incorporate the recommendations from this report with our ongoing efforts to strengthen the rigor of our research enterprise. We have learned from our situation, and with the dedicated efforts of our faculty and administration we have begun to implement solutions under our Translational Medicine Quality Framework. This report will provide additional valuable approaches.

"'Omics' research is a critically important area of scientific investigation that holds great promise for improving patient care, and today's report is perhaps the most important contribution to date in providing analysis and guidance to ensure its rigor and reproducibility."

The statement was signed by Victor Dzau, chancellor for health affairs and CEO of the Duke University Health System; Nancy Andrews, dean of the school of medicine; and Rob Califf, vice chancellor for clinical and translational research.

To ensure that the two-stage validation process is adopted, the committee made several recommendations aimed at institutions, such as designating a specific IRB member to be responsible for considering IDE and investigational new drug requirements, and an making a single institutional official responsible for contacting journals when concerns are raised over a manuscript.

"Institutional culture starts with the dean, more senior leaders, and members of their team stating how research is to be conducted, with integrity and transparency, and with clarity that shortcuts will not be tolerated and that dishonesty is the basis for dismissal," the report said.

"If an institution does not have the infrastructure or capability to follow the recommended Test Development

and Evaluation Process defined in this report, then the committee believes that institution should consider not engaging in the translation of omics-based discoveries into validated tests intended for clinical use."

The IOM report is posted at http://iom.edu/Reports/2012/Evolution-of-Translational-Omics.aspx.

*A portion of the report's executive summary follows:*

"Omics" is a term 'encompassing multiple molecular disciplines, which involve the characterization of global sets of biological molecules such as DNAs, RNAs, proteins, and metabolites. For example, genomics investigates thousands of DNA sequences, transcriptomics investigates all or many gene transcripts, proteomics investigates large numbers of proteins, and metabolomics investigates large sets of metabolites.

Omics research generates complex high-dimensional data; these data are often generated through measurement of many more variables per sample than the total number of biological samples used to generate the dataset. These data can be used to produce a computational model that potentially distinguishes a health-related characteristic of clinical significance and is intended for eventual analysis of individual patient specimens in a clinical setting.

High-dimensional data are particularly prone to overfitting; as a result, a computational model emerging from the research and discovery phase may function well on the samples used for the discovery research, but is inaccurate on any other sample. A carefully designed and executed series of studies is necessary to develop a clinically useful omics-based test for patient management and care, with the goal of improving patient outcomes.

Several characteristics distinguish omics-based tests from other medical technologies, including a different regulatory oversight process, the difficulty in defining the biological rationale behind a test based on multiple individual biomarkers, the complexity of data sharing with other scientists, and the high degree of hope placed in the promise of omics-enabled technologies and medical care.

Omics-based tests, and indeed all clinical laboratory tests, are subject to a different regulatory framework than drugs. Specifically, there are more pathways for regulation of in vitro diagnostic test devices—the category under which omics-based tests fall—than there are for drugs. Tests can be developed, validated, and placed into clinical use either through review by the Food and Drug Administration (FDA) or through validation and performance in a specific laboratory, also called laboratory developed tests (LDTs).

Any clinical laboratory that reports tests for clinical management of patients falls under the purview of the Clinical Laboratory Improvement Act (a CLIA-certified clinical laboratory) that provides a baseline level of oversight with respect to test development and the quality of laboratory operations. While the Food and Drug FDA has the authority for regulatory oversight of all tests used in patient care, the FDA has not defined a regulatory framework that includes oversight of LDTs and has only reviewed LDT tests determined to be of high complexity and therefore high risk to patients.

This alternate LDT pathway is not possible for drug development, and all drugs must be approved by the FDA. It is precisely this LDT pathway that allows academic medical centers to move omics-based tests from discovery to clinical use without external regulatory review of the new test, and places a new and mostly unrecognized demand on academic institutions to provide proper oversight for omics-based test development, validation, and clinical implementation.

While pharmaceutical and medical device companies follow well-established medical product development pathways and have many process controls in place for strong oversight of development, clinical validation, and manufacturing, academic institutions are not as accustomed to overseeing the development of medical products.

The frequent lack of a clear biological rationale further distinguishes omics-based tests from most other clinical laboratory tests based on a single analyte. The biological rationale behind a single-analyte test is frequently quite evident: The test is useful because the gene, RNA, protein, or metabolite plays an understood role in the disease pathology or other biological process under investigation.

Examples of single-analyte tests include human epidermal growth factor receptor 2 (HER2) testing of breast cancers or measuring low-density lipoprotein (LDL) cholesterol level for cardiac risk assessment. In contrast, the biological rationale for the set of biomarkers in an omics-based test frequently is not well defined scientifically. This difference puts an additional burden on the statisticians and bioinformatics experts involved in test validation to ensure that the biological data and computational model are scientifically sound. Due to the increased risk of overfitting large data sets in the development of the computational model, the need for rigor, validation, and accountability is even higher

than for other single biomarker-based tests.

The complexity of omics research also makes data provenance more challenging and makes sharing of the complex data sets and computational models difficult, which limits the ability of other scientists to replicate and verify the findings and conclusions of omics research studies. Database repositories for genomic data sets are available, but data sharing is not routine, and without access to the data sets or a precisely defined computational model, replication and verification are more difficult than for single biomarker tests.

While independent confirmation studies are expensive, the need for replication is beneficial in the omics field given the data complexities that can lead to errors, from simple data management errors to incorrectly designed computational models. This level of complexity does not exist for single-biomarker test research, development, and validation.

Despite the nearly complete identification of the human genome sequence in 2001, development of omics-based products that influence or improve patient health has been slower than expected. One possible reason for this limited progress is that there has not been a widely agreed-upon process for translation of omics discoveries into clinical omics-based tests intended to improve patient outcomes and care. Many hope that the promise that omics science holds for medicine and public health will be realized. With the creation of high-throughput measurement technologies, it is now feasible to take a snapshot of a patient's molecular profile at specific stages in the progression of disease pathology or at a given location in the body.

However, the complexity of these technologies and of the resulting high-dimensional data introduces major challenges for the scientific community, as rigorous statistical, bioinformatics, laboratory, and clinical procedures are required to develop and validate these tests and evaluate their clinical usefulness.

The failure of scientific collaboration, review processes by journals, regulatory oversight, institutional systems for protection of patient-participants, and institutional systems for management of conflicts of interest in a recent case involving the premature use of gene expression-based tests in clinical trials at Duke University led the National Cancer Institute (NCI) to request establishment of this Institute of Medicine (IOM) committee. The committee's charge was to develop recommendations to clarify and improve the pathway from discovery to first use of omics-based tests in a clinical trial, to assess the potential for new omics-based tests to benefit patients.

**Study Scope**

Recent events have highlighted the lack of clarity about best practices for omics-based test validations and the failure of current oversight systems. In July 2010, NCI Director Harold Varmus received a letter from more than 30 statisticians and bioinformatics scientists expressing concerns over several genomics-based predictive tests already in use in clinical trials at Duke University to predict the type of chemotherapy that individual cancer patients were most likely to benefit from.

As a result, an IOM committee was convened to help clarify questions about how to effectively develop omics-based tests to enable progress toward improving patient outcomes. The IOM study was focused on making recommendations useful to investigators in the broader field of omics-based test development, rather than simply examining what went wrong in the test development process at Duke University.

With support from NCI, FDA, the Centers for Disease Control and Prevention, the U.S. Department of Veterans Affairs, the American Society for Clinical Pathology, and the College of American Pathologists, the IOM committee's charge was to recommend sound principles for appropriate development and evaluation for translating omics-based tests from the research laboratory into clinical trials, with the ultimate goal of guiding therapeutic decisions to improve patient outcomes. The complete charge to the committee can be found in Chapter 1.

**Findings, Conclusions, and Recommendations**

The committee considered its task in the context of the scientific processes of discovery, confirmation, validation, and evaluation for clinical use of candidate omics-based tests and in relation to the many parties responsible for the discovery and development of omics-based tests. The primary investigators, who often work in interdisciplinary teams, bear the greatest responsibility and accountability for the scientific rigor of the discovery research and test development.

Academic institutions, other non-profit research organizations, and for-profit companies that support the development of omics-based tests also bear responsibility for proper oversight of the discovery, translational, and clinical research conducted and reported by their faculty or research staff seeking to generate successful omics-based tests. Although these

institutions depend on the rigor and integrity with which individual investigators perform and defend their work, they also have a significant role to play in providing necessary infrastructure, supporting scientific integrity, and organizing and conducting investigations of allegations of improper or incorrect research and reporting practices.

The evaluation process recommended in this report defines the best practices for translation of an omics-based discovery into a validated omics-based test for use in a clinical trial, and focuses on the responsibilities of the investigators (Recommendations 1-3; Box S-1), with additional recommendations for other responsible parties, particularly institutions, but also funding agencies, journals, and the FDA (Recommendations 4-7; Box S-2). Throughout its recommendations, the committee emphasized the importance of transparency in reporting—making data, metadata (information about a data set and how it was generated), prespecified analysis plans, computer code, and fully specified computational models available for external evaluation or confirmation. This reinforces recommendations made in several National Research Council reports (NRC, 2003, 2005, 2006).

**Development and Evaluation Process**

The committee's recommended development and evaluation process for omics-based tests is summarized in Figure S-1. The two major stages of test development and evaluation entail (1) discovery and test validation phases, and (2) evaluation of clinical utility and use. The discovery phase includes complete definition of the computational model to be used for data analysis in a clinical test and independent confirmation of that model. At this point, the fully specified computational procedures should be locked down—recorded and no longer changed.

The candidate omics-based test from the research laboratory is then transferred to a CLIA-certified clinical laboratory for development of the clinical testing methods followed by analytical validation and clinical/biological validation. The final stage is assessment of the clinical utility and use of the validated omics-based test within a clinical trial, with multiple design options depending on the intended clinical use of the test and availability of specimens from previous clinical trials. Statistics and bioinformatics validation occurs throughout both development stages. Overfitting of statistical models derived from omics data is common and many published gene expression results have been difficult to replicate.

**Case Studies**

The committee examined several case studies of tests whose development histories provide lessons learned and illustrate the committee's recommendations. These include the series of genomics-based predictive tests used in clinical trials at Duke University; the commercial tests OncotypeDx, MammaPrint, Ova1, AlloMap Testing, CorusCAD, and the Tissue of Origin Test; and the first OvaCheck test, which did not reach clinical use due to errors discovered in the methods used to develop the test. HER2 testing also is included as a case study to illustrate the challenges associated with a single-biomarker test, which could be magnified in omics-based tests. The committee was charged with presenting findings related to the genomics tests used in the three Duke University clinical trials named in the statement of task. Published papers describing the development of those tests have been retracted, and, thus, it is now widely accepted that the clinical trials should not have used the omics-based tests for patient management decisions.

The events at Duke University captured the attention of biological and quantitative scientists around the world. The committee gathered information about the series of events leading to the inappropriate use of the genomics-based predictive tests for patient management decisions in clinical trials at Duke University. Unfortunately, multiple systems put in place by Duke University to ensure the integrity and rigor of the scientific process failed. However, Duke University is not unique. Many of these failures stemmed from problems that may exist at other

institutions: unclear lines of accountability, lack of consistently strong data management, lack of confirmation of the omics discovery using an independent sample set, lack of definition or locking down of the specific assay and computational analysis methods, lack of analytical and clinical/biological validation of the omics-based test prior to commencing clinical trials, and individual and institutional conflicts of interest, both financial and non-financial. As a result, public trust in the scientific and medical systems and patient-participant safety have been put at risk.

During the 10 years since the research leading to the erroneous predictive tests was initiated, omics science and the regulation of omics-based tests have evolved. Institutions are better equipped now to answer investigator questions about appropriate development processes. Nonetheless, the committee identified needs for improvement. The committee believes the problems at Duke University could have been prevented had

its recommendations been available and followed. Furthermore, the committee believes that scientific progress in omics test development will improve if these recommendations are broadly adopted because they ensure wide availability of data and computational models for the scientific community to explore, clarify the regulatory steps that must be followed along the process, and clarify responsibilities for the parties involved in this process.

The committee hopes this report will provide a guide to the entire pathway for the development of omics-based tests, from discovery to clinical trials, to assist the many parties contributing to this translational research in understanding the complete pathway and not just their focused contributions. This broader perspective may help the whole investigative team to understand the entire pathway and the pitfalls of each stage, with the hope of avoiding future problems in translating omics-based discoveries into clinical tests for the benefit of improved patient care.

Envisioning the improvement of omics-based test development through the implementation of its recommendations, the committee joins patients, clinicians, and scientists in seeking revolutionary new omics-based tools for improving patient care.

*Paul Goldberg contributed to this report.*

*In Brief*

## Sawyers To Take Position As AACR President-Elect

(Continued from page 1)

Sawyers is chair of the Human Oncology and Pathogenesis Program at Memorial Sloan-Kettering Cancer Center and a Howard Hughes Medical Institute investigator. He is also a professor in the Cell and Developmental Biology Program and the Department of Medicine at the Joan & Sanford Weill Graduate School of Medical Sciences at Cornell University.

He has been a member of AACR since 1998. He is a scientific editor of *Cancer Discovery* and was associate editor for *Cancer Research*, both AACR journals. He is past president of the American Society of Clinical Investigation; served on NCI's Board of Scientific Councilors; and is a member of the National Academy of Sciences and the Institute of Medicine.

"We are in the midst of a transformative decade in cancer research, with many new therapies emerging from our work that are improving the lives of cancer patients around the world," said Sawyers. "Yet we are at risk of failing to realize this full vision due to the economic challenges faced by our nation. Now is not the time to cut our investment in cancer research. I will work with the outstanding staff of the AACR to get this important message to the leadership in Washington."

His research efforts focus on the signaling pathways that drive the growth of cancer cells. In collaboration with Brian Druker, of Oregon Health Sciences University, he developed the ABL kinase inhibitor imatinib as a primary therapy for patients with chronic myeloid leukemia. Shortly thereafter, his group discovered that resistance to imatinib is caused by BCR-ABL kinase domain mutations.

He worked closely with John Kuriyan and colleagues at the University of California, Berkeley, to examine the structural consequences of these mutations on the ABL kinase domain and postulated that second-generation ABL kinase inhibitors that bind to ABL differently from imatinib might retain activity against imatinib-resistant mutants.

In collaboration with scientists at Bristol-Myers Squibb, his research showed that the dual Src/Abl inhibitor dasatinib has such properties in preclinical models, then co-led the clinical development of dasatinib as a treatment for imatinib-resistant CML.

**ASCO** announced the winners of its **Special Awards Program**, to be recognized at the society's 2012 annual meeting. These are ASCO's highest, most prestigious awards.

*The 2012 ASCO Special Awards Honorees are:*

• **Kanti Rai**, the recipient of the David A. Karnofsky Memorial Award and Lecture, is chief of the Chronic Lymphocytic Leukemia Research and Treatment Program at North Shore-Long Island Jewish Health System and the Joel Finkelstein Cancer Foundation Professor of Medicine at Hofstra North Shore-LIJ School of Medicine, where he also holds the title of professor of molecular medicine. As an investigator with The Feinstein Institute for Medical Research, he is known for establishing the Rai clinical staging system for chronic lymphocytic leukemia.

• **Rakesh Jain**, the recipient of the Science of Oncology Award and Lecture, is the Cook Professor of Radiation Oncology (Tumor Biology) at Harvard Medical School and director of E.L. Steele Laboratory of Tumor Biology at the Massachusetts General Hospital Cancer Center. Jain created an approach to imaging technologies in cancer research that has provided molecular, cellular, anatomical and functional insights into tumor barriers and how to overcome them.

• **Rowan Chlebowski**, the recipient of the

ASCO-American Cancer Society Award and Lecture, is chief of medical oncology and hematology at the Harbor-UCLA Medical Center and researcher at the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center. As a Women's Health Initiative investigator, he led reports on estrogen alone and estrogen plus progestin influence on cancer endpoints where findings have substantially changed clinical use of menopausal hormone therapy worldwide with associated reduction in breast cancer incidence.

• **Monica Morrow**, the recipient of the Gianni Bonadonna Breast Cancer Award and Lecture, is the chief of the Breast Surgery Service, co-chief of the Breast Program, and Anne Burnett Windfohr Chair of Clinical Oncology at Memorial Sloan-Kettering Cancer Center. Morrow's clinical interests include the application of advances from clinical trials to daily surgical practice, the evaluation of new technology related to local therapy of breast cancer, and understanding how patients make breast cancer treatment decisions.

• **Matti Aapro**, the recipient of the B.J. Kennedy Award and Lecture for Scientific Excellence in Geriatric Oncology, is dean of the Multidisciplinary Oncology Institute in Genolier, Switzerland, and executive director of the International Society of Geriatric Oncology. He was chair of the scientific and organizing committees of the International Union Against Cancer's World Cancer Congress in 2008 in Geneva, Switzerland, and continued to serve UICC in 2010, in Shenzhen, China.

• **Ching-Hon Pui**, the recipient of the Pediatric Oncology Award and Lecture, is the chair of the department of oncology at St. Jude Children's Research Hospital; co-leader of the hospital's Hematological Malignancies Program; medical director of the St. Jude International Outreach China Program; and holder of the Fahad Nassar Al-Rashid Chair of Leukemia Research. His current research emphasis is on genome-wide studies to understand leukemogenesis, and to identify driver molecular lesions and new drugs for target therapy.

• **Marlo Thomas**, recipient of the Partners in Progress Award, is an award-winning actress, author, and activist. Thomas is the national outreach director for St. Jude Children's Research Hospital, and is being honored for her efforts to increase public awareness of childhood cancer and for her support of cancer research.

• **Robert Ozols**, recipient of the Distinguished Achievement Award, was the first Audrey Weg Schaus and Geoffrey Alan Weg Chair in Medical Science at Fox Chase Cancer Center, and also served as senior vice president and chief clinical officer at Fox Chase until his retirement in 2008, following two decades at the institution. His research has focused on how cancer cells develop drug resistance and strategies for overcoming resistance.

• **David Satcher**, recipient of the Special Recognition Award, is director of the Satcher Health Leadership Institute at Morehouse School of Medicine, and has served as the 16th Surgeon General of the United States, Assistant Secretary for Health, and director of the Centers for Disease Control and Prevention.

• **Nancy Brinker**, recipient of the Public Service Award, is founder and CEO of Susan G. Komen for the Cure. From 2001 to 2003, she served as U.S. ambassador to Hungary, and from 2007 to 2009 she served as U.S. Chief of Protocol, responsible for all protocol matters for visiting heads of state and presidential travel abroad. In 2009, she was named Goodwill Ambassador for Cancer Control by the World Health Organization.

• **Edith Peterson Mitchell**, recipient of the Humanitarian Award, is a clinical professor in the departments of medicine and medical oncology and program leader of gastrointestinal oncology at Jefferson Medical College at Thomas Jefferson University. She is honored for demonstration of the importance of community service and outreach, especially to those individuals who may not have the means to seek out more conventional medical advice.

ASCO will also honor the **2012 Fellows of The American Society of Clinical Oncology**, an award formerly called the ASCO Statesman Award, given to the most active ASCO volunteer members. The full list of FASCO recipients can be found here: http://bit.ly/GEVhX0.

All of the above awards will be presented at the society's annual meeting in Chicago, June 1-5 at, with the exception of the Gianni Bonadonna Breast Cancer Award and Lecture, which will be presented at the 2012 Breast Cancer Symposium, September 13-15 in San Francisco.

**ELI LILLY & CO.** launched its global **Innovation Starts Here** initiative. It includes the Lilly Research Awards Program and the Lilly Innovation Fellowship Awards.

The Innovation Fellowship Awards will foster post-doctoral career development through the selection

of highly innovative research proposals. The awards establish a pre-competitive academic-industry training partnership where a post-doctoral fellow and academic mentor are paired with a Lilly scientist to provide the industry resources that can enable the advancement of the post-doctoral scientists' research proposal.

In 2012, the Lilly Fellowship Award Program will be by invitation only to applicants at academic research centers in the United States and United Kingdom.

The Research Awards Program was established in late 2011 to identify and support research and technology collaborations between Lilly scientists and external academic experts worldwide.

The collaborations established under the program provide a pre-competitive environment in which scientists in academia gain invaluable access to tools to conduct basic research, and in turn, Lilly scientists receive critical information to help inform the future of drug discovery and development.

By 2014, Lilly expects to support approximately 30 active projects a year, according to a statement from the company. Examples of projects would include development of new assays, validation of disease targets or biomarkers and improvement of preclinical models.

Three collaborative research projects selected for funding in 2011 under the Research Awards Program are:

• A two-year program exploring the potential expression and function of novel receptor variants in the brain to generate more robust findings regarding their roles in cognition, particularly as they relate to schizophrenia and Alzheimer's disease, which could lead to the advancement of new molecules into clinical development, at the University Hospital Copenhagen in Denmark.

• A two-year program to advance the understanding of the neurobiology of schizophrenia in order to help manage cognitive impairment and treat negative symptoms of the disease, at the Institute of Neuroscience, in Alicante, Spain.

• And a two-year program to study the roles played by distinct types of signals associated with chronic pain disorders with the long-term goal of discovering new treatments for neurological disorders and pain, at the Indiana University School of Medicine.

**THE CHINESE ACADEMY OF MEDICAL SCIENCES Cancer Institute and Hospital** signed a statement of intent to collaborate biomedical research with **NCI**.

Both NCI Director **Harold Varmus** and **Jie He**, president of the Chinese Academy cancer institute, signed the statement at NCI's Setting Priorities for Global Cancer Research meeting. The institute was recently designated as China's National Cancer Center, and will have an expanded role in China's cancer prevention and control efforts.

The institutes intend to collaborate on basic and translational research; pre-clinical and clinical trials; and cancer prevention, early detection trials and epidemiologic studies

**UNIVERSITY HOSPITALS CASE MEDICAL CENTER** announced a $250 million initiative, **The Harrington Project for Discovery and Development**, to provide a comprehensive model to advanced discoveries into development and create novel drugs and therapies.

The project is powered by a $50 million gift from the Harrington family in Cleveland.

It includes a new clinical research initiative, the University Hospitals Harrington Discovery Institute, and a new development company. The institute will be based at Case Medical Center in Cleveland.

"The current system nationally has been flawed, and we believe this new initiative is the solution. One of the challenges that we have today is that many biomedical discoveries end up staying on the shelf; they never get commercialized," said Achilles Demetriou, University Hospitals chief operating officer.

The institute will provide funding, mentoring and infrastructure to advance clinical research projects. It is assembling an advisory panel to select the first 10 Harrington Scholars this year, who will receive funding in two-year intervals.

The development company, with a CEO and management team in place, has raised its initial capital and is in the process of attracting additional investors and evaluating programs with an initial capital plan of more than $100 million. The company will be formally announced later this year.