THE CANCER LETTER

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Over 48 Hours, Power Shifts at NCI, ACS, Dana-Farber and MD Anderson

By Paul Goldberg

Over the first two days in April, massive leadership changes occurred at top institutions in cancer research:

• On April 1, the top job at NCI switched from Harold Varmus to Douglas Lowy, with the Lowy being formally named acting director.

• On April 1, Edward Benz announced his plans to leave presidency at Dana-Farber Cancer Institute, and the institution's board began the search for his successor.

• On April 2, the American Cancer Society announced that the job of CEO would go to former Johnson & Johnson executive Gary Reedy.

• On April 2, the UT System announced that Lynda Chin will be vacating her jobs as head of genomic medicine and scientific director of a research institute she co-founded. Chin, who is married to MD Anderson President Ronald DePinho, came to Houston from Dana-Farber as a team in 2011.

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Resolving Disputes in Precision Medicine: The Question of CYP2D6 Remains Open

By Paul Goldberg

What does it take to declare that a scientific dispute is resolved?

A long-running argument over the role of a biomarker in the treatment of breast cancer illustrates a challenge that runs through the heart of precision medicine: the absence of mechanisms for resolving disagreements between scientists.

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In Brief

Cantley, Adams-Campbell to Deliver Lectures At AACR Annual Meeting in Philadelphia

LEWIS CANTLEY was honored with the ninth annual Princess Takamatsu Memorial Lectureship, to be delivered at the **American Association for Cancer Research** Annual Meeting in Philadelphia, April 18-22.

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A Biomarker Court? Who Should Decide? . . . Page 9

Question: What's the Optimal Method for Resolving Disputes Over Biomarkers?

Answers from: Carmen Allegra, Lisa McShane, Robert Cook-Deegan, Barnett Kramer, Frances Visco, and FDA . . . Page 9

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Drugs and Targets

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Big Chances at NCI, ACS, Dana-Farber and MD Anderson

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Now Chin will be moving to Austin to assist the UT System's new chancellor. Not only has she been DePinho's key collaborator, but the controversies at MD Anderson went public as a result of an effort by the cancer center to obtain $18 million in state funding for Chin's institute.

In another development, the Houston Chronicle published an editorial that draws parallels between managing cancer and managing a cancer center. "The chancellor and the board of regents should treat this management problem with the same urgency as physicians do when treating their patients," the editorial urged.

Lowy Pledges to be an "Active" Acting Director

Lowy's selection to run NCI as an acting director was announced by his predecessor, Varmus, last month, and was made official April 1 (The Cancer Letter, March 27).

In a letter to NCI staff, Lowy pledged to be an "'active' acting director."

He wrote:

"I have known many of you for years, and look forward to working together in my new role at the Institute. I would like to thank Harold Varmus for his enlightened leadership of NCI since 2010 and wish him well in his new pursuits.

"I fully intend to be an 'active' acting director, because the challenges and opportunities we face demand no less. It is essential that we come together as a community to build understanding and support for investing in cancer research at this time of great scientific opportunity, as recently outlined in the NCI Annual Plan and Budget Proposal for FY2016: Building on Opportunities in Cancer Research.

"I hope to see many of you at the American Association for Cancer Research annual meeting later this month, where I will speak about my initial plans and priorities at NCI. I will also be joining National Institutes of Health Director Dr. Francis Collins at the April 30 Senate appropriations hearing on the NIH budget.

"I deeply appreciate your dedication to and support for NCI's mission of advancing cancer research on behalf of patients everywhere."

Since Lowy's research has led to the development of the human papillomavirus vaccine, observers are waiting to see whether NCI would assume a greater public health role under his leadership.

As chief of the Laboratory of Cellular Oncology in the Center for Cancer Research at NCI, Lowy's research includes the biology of papillomaviruses and the regulation of normal and neoplastic growth. His laboratory, in close collaboration with John Schiller, was involved in the initial development, characterization, and clinical testing of the preventive virus-like particle-based HPV vaccines that are now used in the three FDA-approved HPV vaccines.

Lowy received the National Medal of Technology and Innovation from President Barack Obama last year. He is a member of the National Academy of Sciences, as well as the Institute of Medicine. For their pioneering work, Lowy and Schiller have received numerous honors in addition to the National Medal, including the 2011 Albert B. Sabin Gold Medal Award and the Federal Employee of the Year Award in 2007 from the Partnership for Public Service.

"We are fortunate to have a scientist of such stature stepping into the role of Acting Director of the NCI," NIH Director Francis Collins said in a statement. "Dr. Lowy possesses not only a sharp intellect, deep knowledge of science, and proven leadership experience, but he takes a warm and humane approach to all things. He is superbly positioned to lead the NCI at a time of exceptional progress in cancer research."

Lowy received his medical degree from New York University School of Medicine and trained in internal medicine at Stanford University, and dermatology at Yale University.

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Reedy to Become ACS CEO April 27

The American Cancer Society announced April 2 that its board of directors selected Gary Reedy as the society's next CEO, effective April 27.

Reedy replaces John Seffrin, who has served as CEO of the society since 1992 and previously announced his retirement in January 2014 (The Cancer Letter, Jan. 24, 2014).

Reedy is the former worldwide vice president of government affairs and policy for Johnson & Johnson. He played a role in J&J's handling of controversies stemming from erythropoiesis-stimulating agents, and was a key player in the National Dialogue on Cancer, later renamed C-Change.

Reedy has been a volunteer leader with the ACS for 15 years. His challenge will be to bring back the society's donations, which haven't rebounded since the economic downturn and to lead the organization as it adjusts to its new centralized structure (The Cancer Letter, Nov. 18, 2011).

"After conducting a thorough and deliberate selection process, our Board of Directors is very pleased that Gary will lead the American Cancer Society to its next chapter as we continue working to eliminate cancer as a major health problem," said Robert Youle, chair of the society's board of directors. "He has the breadth and depth of experience we were looking for in our next CEO. We are confident that Gary will continue the organization's commitment and diligent work to save even more lives from cancer."

Reedy has been an ACS volunteer since 2000 and is a past chair of its board of directors.

"I am honored the American Cancer Society board of directors has chosen me to lead the organization at a time in history that such significant progress is being made against cancer," Reedy said in a statement. "I look forward to working with members of the board, the Society's leadership and experts, and our millions of dedicated volunteers and health coalition partners to continue advancing the life-saving work of the Society."

During his 37-year professional career, Reedy held senior leadership positions with SmithKline Beecham, Centocor, and J&J. He retired from J&J on March 27.

Reedy serves on the boards of directors of Emory & Henry College, the Campaign for Tobacco-Free Kids, and the Tobacco-Free Kids Action Fund. He recently served as an officer on the C-Change board of directors and was a charter member of the CEO Roundtable on Cancer. Reedy will be based in Atlanta.

"It is no accident that this very best candidate is someone who knows our organization well, and who also brings a wealth of outside expertise to the position," Seffrin said in an email to the ACS staff. "I have every expectation of witnessing strong and visionary leadership in this new chapter for the American Cancer Society. I will be working closely with Gary over the next several weeks on our leadership transition. I hope you will all tune in to our special webcast on Tuesday, where you will hear more directly from Gary.

"Never before have we been faced with so many opportunities to save more lives from cancer. With this leadership decision and your unconditional support of our next CEO, I am more certain than ever that your American Cancer Society is the right organization to fully seize those opportunities to eliminate cancer as a major health problem."

Benz Stepping Down at Dana-Farber

On April 1, Dana-Farber's Benz sent this email to the faculty and staff:

Dear Friends and Colleagues,

Earlier today, I asked the Executive Committee of the Board of Trustees to initiate a search for my successor as President and CEO of the Dana-Farber Cancer Institute. It is my intention to retire from this role on June 30, 2016. At that same time, I will also vacate my positions as CEO of Dana-Farber/Partners Cancer Care, Director and Principal Investigator of the Dana-Farber/Harvard Cancer Center, and Trustee of Dana-Farber/Children's Hospital Cancer Care. I will remain on the Harvard Medical School faculty as Professor of Medicine, Pediatrics and Genetics, and will return full time to my research, clinical, and teaching activities at Dana-Farber.

Peggy and I have made this difficult decision together and only after much thought. It will be hard to leave the Presidency. We have loved being the "First Family" of DFCI. Of all the fabulous jobs that I have been lucky to have, this one has definitely been the best. I remain energized about the great work that we do, and am as optimistic as ever about our future. DFCI is in excellent condition. The Board continues to be wonderfully supportive of our work and my leadership. Continuing to serve as long as I am allowed would be a very tempting proposition.

However, I believe strongly that we should launch an orderly process of succession, and do so while things are this good. I will have been at the helm for almost 16 years when I step down, longer than any previous DFCI President.

With longevity in the lead role comes the risk of becoming stale, especially in this dynamic and disruptive

period in our history. Before that happens, DFCI should identify someone new to take the tiller, someone who will bring the fresh experiences, perspectives and skills that we will need for a challenging future. The core grant that supports our NCI designated comprehensive cancer center will also be renewed in 2016, allowing my successor to begin with 5 more years of support secured. This was a gift that I was given by my predecessor. My 70th birthday will occur in May of 2016. That strikes me as a good age to return to the more flexible and contemplative life of an academic that I cherish. Peggy and I also would like to have a bit more time for each other and for our 4 children and 8 grandchildren while our health is still good.

There will be ample opportunities during the next 15 months to reflect on our years together. For now, I will simply say, for the first of many times, how grateful I am to have been given the blessing of leading this, the greatest cancer center in the world. It is a profound honor to have been given the trust and support that you bestowed on me by accepting my leadership.

We have experienced both tough times together and the exhilaration of seeing our work bring far better outcomes to our patients. We have thrived even as we soldiered through one of the worst financial and funding epochs in history. We have grown, expanded, and become more comprehensive in our scope while maintaining our strong sense of connectedness and humanity, never losing our focus on providing the ideal experience of care that we offer to our patients. I will relish every moment of the remaining months we have to work together. We have much to do. I will strive as hard and as eagerly as ever to tackle that work with you.

With gratitude for your support,

—Ed

Changes in Houston

Lynda Chin will be vacating her key jobs at MD Anderson to join the UT System as an associate vice chancellor for health transformation and chief innovation officer for health affairs.

Chin will step down as founding chair of Genomic Medicine and scientific director of the Institute for Applied Cancer Science at the Houston-based cancer center to assume her new job in Austin effective April 6, officials said.

MD Anderson's IACS, which was envisioned as a hybrid of an academic institution and a pharmaceutical company, has been viewed as a centerpiece of the vision Chin and her husband DePinho brought to the institution in 2011. The two had been collaborating during the previous phase of their careers, at Dana-Farber Cancer Institute and as founders of startup companies focused on cancer.

From the outset, officials at MD Anderson and the UT System worked to devise bureaucratic mechanisms to manage potential conflicts of interest inherent in having DePinho and Chin work together. Though management of conflicts wasn't among stated reasons for Chin's transfer, the change eliminates even appearances of conflict, potentially strengthening DePinho's position as MD Anderson's president.

No information was provided on who would succeed Chin as scientific director of IACS. MD Anderson scientist Andrew Futreal will serve as chair *ad interim* for Genomic Medicine effective April 6.

In her new UT System role, Chin will create and lead the new Institute for Health Transformation that will seek to "leverage, develop and deploy innovative, technology-enabled solutions to improve access to and affordability of quality health care," officials said.

"If we want to transform the way health care is delivered, then we need bold and innovative solutions," UT System Chancellor McRaven said in a statement. "Dr. Chin is a very talented physician scientist who has the vision and the ability to get it done."

McRaven is a key figure in fixing the morale problems at MD Anderson. On a visit to MD Anderson last month he declared that the binds of trust at the cancer center have been broken and called for shared governance at the institution (The Cancer Letter, March 20).

Chin landed in the center of controversy when her center attempted to get $18 million a year in funding from the Cancer Prevention and Research Institute of Texas. The effort bypassed standard review procedure, CPRIT Chief Scientific Officer Alfred Gilman said at the time (The Cancer Letter May 25, 2012). A subsequent audit by the UT System identified no conflicts of interest on the part of M.D. Anderson.

Chin's center at MD Anderson was outfitted with modern classic furniture and translucent walls (The Cancer Letter, May 24, 2013).

Chin and DePinho were among co-founders of AVEO Pharmaceuticals, a biotechnology company that failed to get its drug approved despite being praised on national television by DePinho as a good investment (The Cancer Letter, June 1, 2012). Records obtained by The Cancer Letter show that on May 7, 2012—exactly 11 days before DePinho offered this ill-advised stock tip—Chin traveled to the Boston area to take part in a meeting of the AVEO Scientific Advisory Board as it prepared to present clinical data to FDA.

The results of a trial—which showed a survival deficit on the experimental arm—were presented to that advisory board. Chin said to The Cancer Letter that she didn't discuss the trial results with DePinho (The Cancer Letter, Sept. 13, 2013).

The UT System said its new Institute for Health Transformation initially will focus on Project DOC, abbreviation for Diabetes Obesity Control, which was funded by the Board of Regents in 2014 to improve diabetes care and management in South Texas through the use of big data and technology.

"The current health care model is based on providing acute care to sick patients; that is very ineffective in management of chronic diseases like diabetes," Chin said in a statement. "A system re-design is needed. Today's social, mobile and cloud technology along with big data and cognitive analytics can be the keys to a much-needed transformation."

UT System officials said to the Houston Chronicle that Chin had been working on the diabetes issues since last year. In June, she was named a health fellow on the project, which received the first-phase funding of $5 in November 2014.

Chin's departure was announced to MD Anderson faculty and staff in an email from Provost Ethan Dmitrovsky. The email, dated April 2, reads:

Dear Colleagues,

We write to announce that our Genomic Medicine Chair Lynda Chin, M.D., is leaving MD Anderson to assume a critically important role with UT System Administration: Associate Vice Chancellor for Health Transformation and Chief Innovation Officer for Health Affairs. Last year, Dr. Chin was appointed a UT System Chancellor's Health Fellow to pursue the promise of cognitive computing beyond cancer, in particular using these technologies to impact diabetes in South Texas, which is a substantial public health problem. This expanding scope made a permanent role with UT System a natural evolution.

Dr. Chin assumes her new position on April 6. In her new role, Dr. Chin will create and lead a new Institute for Health Transformation at UT System. We are pleased that Genomic Medicine Professor Andrew Futreal, Ph.D., has agreed to serve as Chair *ad interim* for Genomic Medicine effective April 6. To aid in the transition, Dr. Chin will serve as a visiting professor at MD Anderson from April 6 through July 6.

We thank Dr. Chin for her service and the innovation she championed during her time at MD Anderson, and we wish her the very best in her important new leadership role.

Dr. Chin joined MD Anderson in 2011 as the founding Chair of Genomic Medicine and Scientific Director of the Institute for Applied Cancer Science. During her career, she has made seminal scientific discoveries spanning the fields of transcription, telomere biology, and mouse models of human cancer and cancer genomics. For her scientific accomplishments, Dr. Chin has received distinguished honors and recognitions, including election to the Institute of Medicine of the National Academies in 2012. During her tenure at MD Anderson, Dr. Chin has been the trailblazing driver in the development of the MD Anderson Oncology Expert Advisor (OEA) system, which promises, with its associated applications, to enable dissemination and sharing of cancer treatment expertise so that any cancer patient – no matter the geographic location or socioeconomic status – can access quality cancer care. In addition, she and Dr. Futreal have spearheaded the APOLLO-Big Data platform as part of our Moon Shots Program.

Dr. Futreal joined our faculty in 2012 as Professor of Genomic Medicine. In May 2014, he and Dr. Giulio Draetta assumed joint leadership of our Moon Shots Program. Dr. Futreal's scholarship includes the identification of BRCA1 and BRCA2, BRAF mutations in melanoma and chromatin modifier gene mutations in human cancer. He co-directed the Sanger Cancer Genome Project that pioneered application of systematic genome-wide approaches to the study of human cancer. Today, his focus centers on integrating clinical and comprehensive genomic data to improve treatment outcomes for cancer patients. In recognition of his excellence, Dr. Futreal became holder of the Robert A. Welch Distinguished University Chair in 2013. That same year, he received MD Anderson's Ernst W. Bertner Memorial Award, and this past February became the inaugural recipient of the prestigious Jack and Beverly Randall Prize for Excellence in Cancer Research.

Please join us in wishing Dr. Chin well in her new leadership role at UT System and thanking Dr. Futreal for assuming these new leadership duties.

Sincerely,

Ethan Dmitrovsky, Provost and Executive VP
Thomas Buchholz, Executive VP and Physician-in-Chief
Thomas Burke, Executive VP, MD Anderson Cancer Network
Helen Piwnica-Worms, Vice Provost of Science
Patrick Hwu, Head, Cancer Medicine

Code Blue?

In an editorial April 1, the Houston Chronicle likened the problem at the city's storied cancer center to—well—disease.

"Early detection of a problem can often prevent the spread of cancer, at least according to the physicians at the crown jewel of the Texas Medical Center, the University of Texas M.D. Anderson Cancer Center," the editorial read. "Today, M.D. Anderson itself needs a checkup.

"The center's obvious symptoms aren't the most worrisome. Take the cancer center's drop last year in the U.S. News & World Report rankings from the No. 1 hospital for cancer care to No. 2. The survey is often criticized as a popularity contest, and after all, the hospital's showing was still strong. We can overlook M.D. Anderson's ongoing squabble with the American Association of University Professors although this could result in a censure by the nation's union of professors. With policies set by a capable board, even the allegations of conflict of interest and nepotism—and heartburn over expensive office furniture—can be counted as distractions.

"The one dangerous symptom that shouldn't be ignored is faculty dissatisfaction. The faculty has spoken in four negative surveys as well as in a recent faculty senate resolution sent to UT System leaders, where members cited a 'climate of fear' and 'pervasive dissatisfaction' at M.D. Anderson...

"Lives are at stake in the important work done at M.D. Anderson. The chancellor and the board of regents should treat this management problem with the same urgency as physicians do when treating their patients."

MD Anderson officials did not comment on the editorial.

Debate Over CYP2D6 Biomarker Continues With No End in Sight

(Continued from page 1)

The story of CYP2D6, a mutation that may (or may not) predict the manner in which the patient metabolizes the cheap, widely used drug tamoxifen, is of the sort that makes insiders shake their heads.

The question is relevant to an estimated 150,000 newly diagnosed estrogen receptor-positive breast cancer patients a year in the U.S. alone.

The controversy is more important than CYP2D6, tamoxifen and breast cancer. The same questions have to be answered as Food and Drug Administration and the Centers for Medicare and Medicaid Services establish validity and decide on coverage of biomarker tests.

Is anyone—the academic journals, government agencies or private payers—capable of resolving controversies over the role particular biomarkers play in disease? The Cancer Letter asked a group of experts to answer this question. Their answers appear on page 9.

Here is how the controversy has played out in the context of CYP2D6:

In December 2010, at the San Antonio Breast Cancer Symposium, two groups of researchers presented separate analyses of tissues obtained in two large randomized clinical trials, the Breast International Group 1–98 (BIG 1–98) and the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial.

Both groups reached the same conclusion: metabolism of tamoxifen has no bearing on the outcome of disease in post-menopausal women. The controversy was over—or so it seemed.

By the time the data from the two trials were published in the peer-reviewed journal, very few clinicians tested women with estrogen receptor-positive tumors for CYP2D6. The papers were published in the March 21, 2012 issue of JNCI.

But publication didn't resolve the controversy.

Top-level experts in pharmacogenomics wrote a letter to JNCI to point out that the researchers made a fundamental mistake in the way they collected tumors.

If your goal is to measure CYP2D6, you shouldn't get the sample by punching through the tumors, but should instead get the sample from blood.

The fact that the data from the two studies were wrong should have been seen by testing whether the results were consistent with the Hardy-Weinberg equilibrium, which is expressed by two simple formulas. The group of pharmacogenomics experts asked that the papers be retracted (The Cancer Letter, May 18, 2012).

Nearly three years went by.

The journal didn't retract the paper, but instead published several letters from both camps—and, last month, an additional paper from the pro-CYP2D6 camp and asked an expert in pharmacogenomics to write an editorial commenting on all the data in hand.

"The CYP2D6-tamoxifen story is not closed," the editorial, by Julie Johnson et al., declared. "In fact, there should be a reboot, with a focus on doing the genotyping and analyses correctly. Women with breast cancer deserve for the scientific community to continue to work on this question and to get it right. It is unacceptable that a woman might be placed on 10 years of therapy with a drug for which her genotype predisposes her to

reduced efficacy and poor outcomes. She deserves an evidence base that can truly guide the most appropriate treatment for her."

Johnson is the dean and distinguished professor of the University of Florida College of Pharmacy and a member of the Institute of Medicine.

Johnson and colleagues were commenting in part on a JNCI paper in which researchers asked whether use of tumor tissue to obtain DNA could result in CYP2D6 genotyping errors.

The researchers first looked for loss of heterozygosity at the CYP2D6 locus in genomic tumor data from two large breast cancer datasets, the Cancer Genome Atlas and Foundation Medicine. They found loss of heterozygosity in over 40 percent of the breast tumors analyzed. These findings suggested that genotyping techniques using DNA extracted from tumor samples could misclassify a patient's CYP2D6 genotype, they argued.

Next, the researchers sought to directly compare CYP2D6 genotypes derived from patients who provided normal and tumor tissue. Using samples from patients enrolled in the NCCTG 89-30-52 tamoxifen trial, they showed that there was perfect agreement between CYP2D6 genotypes derived from non-malignant tissue and those derived from cheek swabs. In contrast, 20 percent of the CYP2D6 genotypes were misclassified when tumor tissue was used.

Johnson et al. concurred with the pro-CYP2D6ers that the Hardy-Weinberg Equilibrium should apply, which would suggest that the anti-CYP2D6ers got their genotyping wrong.

"These data provide clear evidence that CYP2D6 genotyping should not be done on breast tumor samples, but rather on adjacent normal tissue, or preferably a traditional germline DNA source for genotyping such as white blood cells from blood or saliva or buccal cells," the editorialists write.

"While the positive association studies did not exclusively use nontumor tissue for their genotyping, one cannot help but notice that the positive studies were much more likely to use non-tumor tissue for genotyping and their genotyping results did not deviate from HWE or deviated with much less statistical significance. A basic tenet of genetics research is that the quality of the genotype data are confirmed before genetic association analyses with the genotype data are considered. Unfortunately, this basic tenet was violated in a substantial percentage of the CYP2D6-tamoxifen studies that comprise the current literature."

Getting Past Jousting Luminaries

So, is the issue resolved as per the JNCI editorial?

Anything but.

"I have the utmost respect for Dr. Johnson who is a leader in the field of pharmacogenomics," said James Rae, the Thomas H. Simpson Collegiate Professor in Cancer Research and associate professor of Internal Medicine and Pharmacology at the University of Michigan Medical School, and the lead author of one of the papers that led to the demise of CYP2D6 as a biomarker. "However, her editorial does not cite the five previous studies which have shown clear analytical validity of CYP2D6 genotyping from frozen or FFPE breast cancer specimens."

Responding to questions from The Cancer Letter, Rae concurred with the idea that the question needs to be addressed.

"The pathway forward is to objectively analyze all the data, both for and against the CYP2D6 tamoxifen hypothesis," he said in an email. "And my colleagues and I continue to test this hypothesis in additional clinical datasets. However, the current data do not support changing clinical practice to include CYP2D6 genotype to guide tamoxifen therapy in breast cancer patients."

Rae said the methodology—obtaining samples from the tumor rather than somatic tissue—remains valid.

"Yes, tumors samples can be used to determine a patient's germline CYP2D6 genotype," he said. "In 2013, we demonstrated that CYP2D6 genotypes from formalin-fixed, paraffin-embedded (FFPE) breast cancers are highly concordant with those from obtained from whole blood germline DNA in 122 patient matched samples (Rae, et al., JNCI, 2013).

"This study confirmed what my group, and others, have published previously. In 2003, we reported 100 percent concordance in CYP2D6 genotypes between breast cancer specimens and whole blood in a small sample set (n=10) (Rae, et al., Pharmacogenetics, 2003). Subsequently, in collaboration with Dr. Goetz, and as part of our original 2005 JCO paper, my laboratory was sent 15 matched normal samples from patients who participated in NCCTG 89-30-52. We performed CYP2D6 genotyping without knowledge of the individual patient or matched samples and returned the genotyping results to Dr. Goetz, who then confirmed (in an email) that concordance was 100 percent, as was stated in our publication (Goetz, et al., JCO, 2005).

"In 2010, a separate group of investigators examined 105 matched FFPE tumor and FFPE normal tissue samples for CYP2D6*4 and found 100 percent

concordance (Adhern, et al., Clinical Epidemiology, 2010). Finally, and to my knowledge the most convincing and comprehensive study to date, was published by Thompson et al. who compared CYP2D6 genotypes from whole blood germline DNA with frozen breast cancer tissue collected from 133 patients (Thompson et al., BCRT, 2011).

"Comprehensive CYP2D6 genotyping was achieved using the AmpliChip CYP450 Test which queries 29 CYP2D6 polymorphisms and the found 100 percent concordance. Thus, prior to Goetz's recent report, five separate studies, conducted by three separate groups, using different genotyping methods, comparing tumor to normal tissue in nearly 400 matched patient samples have shown either very high or complete concordance between CYP2D6 genotypes obtained from breast cancer compared to normal germline DNA.

"Therefore, I firmly stand by our previous studies, which have been confirmed by others, and my conclusion that CYP2D6 genotypes derived from tumors accurately measuring patient germline genotypes. The 19.4 percent discordance rate recently reported by Goetz et al. would suggest problems with their genotyping methodology, and not, as they concluded, that loss of heterozygosity of CYP2D6 locus in breast cancer confounds germline CYP2D6 testing."

Deviations from the Harvey-Weinberg Equilibrium can be explained, Rae said.

"Bottom line is that deviations in CYP2D6 HWE can be due to a number of factors besides genotyping error (discussion by Dr. Donald Berry in his 2014 JNCI editorial) and they are not confined to breast cancer studies as significant deviations have been found in control and otherwise normal populations (discussed in my 2014 letter to JNCI).

"To complicate matters more, the way people calculate HWE differs from study to study. For example, if one looks at the recent International Tamoxifen Pharmacogenomics Consortium meta-analysis study and calculates HWE in a manner similar to what was done for BIG 1-98 study (i.e. combining samples from multiple sites), one finds statistically significant departures including CYP2D6 genotypes obtained from blood DNA."

Correspondence from Rae, et al. is published in the most recent issue of JNCI.

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A Big-Claims Court?

With the Goetz data and Johnson editorial on their side, the pro-CYP2D6 camp is renewing its call for reconsideration of the issue.

"As previously hypothesized, our current report in JNCI confirms that the use of tumor tissue to directly genotype CYP2D6 is inappropriate, and studies that have solely used this approach should be considered invalid, until proven otherwise," said Mark Ratain, the Leon O. Jacobson Professor of Medicine, director of the Center for Personalized Therapeutics, and associate director for clinical sciences at the University of Chicago Comprehensive Cancer Center.

"Given that tamoxifen requires activation by CYP2D6 to exert its antiestrogen effect, women with minimal or no CYP2D6 activity cannot benefit from the drug. Given that the latter represents approximately 7 percent of the population, CYP2D6 genotyping should be strongly considered in the context of tamoxifen prescribing. Furthermore, patients known to be CYP2D6 poor metabolizers should not receive tamoxifen."

Ratain is a co-author on the Goetz et al. paper.

Goetz, who is a co-principal investigator at the Mayo Clinic Breast Cancer Specialized Program of Research Excellence, co-leader of the Women's Cancer Program and chair of the Breast Cancer Disease-Oriented Group, wants the issue resolved.

According to Goetz, the problems are fundamental:

"The BIG 1-98 study needs to be re-genotyped," he says. "Whatever group that does the genotyping for BIG 1-98 needs to have sufficient quality control measures in place, given that only FFPE tumor blocks are available. Once these data are available, it will be clear to the journal and BIG 1-98 what to do with the original data.

"I would note that we and others noted that there was deviation from HWE in the CYP2D6 genotype analysis of the NCCTG 89-30-52 clinical trial published in JCO in 2005. Because of this, the samples were re-genotyped (this time at Mayo) and the results recently included in the meta-anlaysis published in Clinical Pharmacology and Therapeutics (Province, et al.). Of note, the same genotyping methodology and same quality control was used to genotype FFPE samples from another independent study, ABCSG 8. This study randomized over 3,700 patients to either tamoxifen or tamoxifen followed by anastrozole. A secondary analysis of this study demonstrated a significant association between CYP2D6 genotype and the risk of a disease event in patients treated with tamoxifen but not those treated with anastrozole.

"Rae's argument that he can take a limited data set and genotype tumor and get the same result as genotype from lymphocytes is a non-sequitur to the argument that was laid out regarding the genotyping error in BIG 1-98. We and others have shown that one can genotype tumor admixed with lymphocytes and if the quality control is pristine, likely get a reasonable approximation of the germline genotype. We did this in ABCSG 8. However, when you do, and if you apply HWE, you should get results that are within HWE or very close. So HWE still remains the determinant of quality control

"BIG 1-98 is egregiously out of HWE, and therefore, we can confidently state that there are errors. Our paper in JNCI regarding LOH explains a likely reason why there were errors and uses the NCCTG 89-30-52 as a 'case example.'"

What would it take to get past the point or restatement of deeply held views?

"Based on the work of Simon, Paik, and Hayes, the breast cancer community has adopted standards by which biomarkers are analyzed," Goetz said to The Cancer Letter.

"These guidelines stipulate that '1) adequate amounts of archived tissue must be available from enough patients from a prospective trial (which for predictive factors should generally be a randomized design) for analyses to have adequate statistical power and for the patients included in the evaluation to be clearly representative of the patients in the trial; 2) the test should be analytically and pre-analytically validated for use with archived tissue; 3) the plan for biomarker evaluation should be completely specified in writing before the performance of biomarker assays on archived tissue and should be focused on evaluation of a single completely defined classifier; and 4) the results from archived specimens should be validated using specimens from one or more similar, but separate, studies.'"

Goetz proposes formation of a judicial body that would be equipped to resolve such claims.

"What is needed (pending data from prospective clinical trials) is a critical assessment by a 'court' of experts to examine the CYP2D6 literature based upon the stipulations laid out by Simon et al.," he said. "First, this 'court' must call as witnesses, card carrying geneticists, who can examine the evidence with regard to quality of the genotyping data in the published literature.

"Second, the 'court' should examine whether secondary analyses of prospective clinical trials met the first stipulation laid out by Simon et al. (i.e. did the authors include enough specimens to be representative of the study population). The 'court' then needs to make recommendations that resolve the current impasse, and that these recommendations be followed by groups that establish guidelines for patient care."

A Biomarker Court? Who Should Decide?

No pharma company is clamoring to get a response to the question of significance of CYP2D6.

Since an estimated 7 percent of newly diagnosed breast cancer patients are poor metabolizers of tamoxifen, perhaps as many as 93 percent are good candidates for receiving this cheap generic drug.

If the pro-CYP2D6 wing is right, the market for an entire class of drugs—aromatase inhibitors—would shrink dramatically. AIs are also available in generic form, but are typically more expensive than tamoxifen.

"A fundamental responsibility of FDA is looking at safety and efficacy of treatments," said Gregory Curt, executive director for external scientific and medical relations at AstraZeneca. "Would the agency want to weigh in on this discussion? They do have national reach, after all."

To act, FDA needs data. Alas, it cannot force anyone to produce data, especially in a situation where there is no eager sponsor who would be willing to launch clinical trials.

The Cancer Letter asked a group of experts whether existing mechanisms for resolving scientific disputes have the capacity to handle the tidal wave of questions over validity of biomarkers.

Their answers follow:

Carmen Allegra, *chief of the Division of Hematology & Oncology and associate director for clinical & translational research at the University of Florida Cancer Center and editor-in-chief of JNCI:*

What role should the scientific journals play in resolving scientific controversies?

As editor-in-chief of the JNCI where most of the controversy surrounding the utility of CYP2D6 has played out, I had an opportunity to consider our role.

From my perspective, the journal should serve as an impartial forum for scientific discussion and debate but not as an arbiter of the controversy. To this end, I do not believe it is appropriate to retract reports or otherwise censor the scientific discussion in the absence of fraud or scientific misconduct, and provided that the discussion remains focused on the scientific

issue(s) at hand, is not repetitive and does not constitute an unprofessional *ad hominem* attack.

At some point in the discourse, all the evidence is presented and it ultimately falls to the readership to decide how the information should be applied and/or what additional information is necessary to enable a definitive set of conclusions to be drawn. To facilitate this process, the Journal has often turned to commentaries and editorials from experts in the debated field but not directly connected with the publications under discussion to provide a perhaps less biased assessment of the data and the state of the field.

This was the tack taken on two occasions during the controversy surrounding CYP2D6 (Berry and Johnson editorials). Despite the discussion and the sage interpretation of experts, as is often the case in science, the field is left with an unsatisfying set of possibilities to explain the various observations.

Convening a panel or "court" is unlikely to satisfactorily resolve the arguments based on information at hand as they would only have access to the same inconclusive datasets. But such a body may be in an optimal position to enumerate the issues and suggest exactly what additional information would be necessary to bring some level of resolution adequate to allow the field to move forward to new discoveries and new advances that are so dearly needed in our collective endeavor to mitigate the overwhelming burden of cancer.

Lisa McShane, *statistician at the Biometric Research Branch, NCI Division of Cancer Treatment and Diagnosis:*

The NCI requested that the Institute of Medicine establish a committee to recommend ways to strengthen omics-based test development and evaluation. The resulting IOM report, "Evolution of Translational Omics: Lessons Learned and the Path Forward," maps out a process for validation of omics-based tests for use in guiding therapy[1].

Both the IOM Omics report and a related NCI omics checklist[2-3] stress the importance of establishing a locked-down omics test and a pre-specified study plan before embarking on a definitive validation study. Even seemingly minor changes in the conduct of an omics test can affect its performance. Consequently, when validation studies use different designs, specimen types or preparation methods, assay platforms or reagents, or quality metrics for acceptability of specimens or data, inconsistent results across different studies are often observed. This prompts debate about which study's answer is correct.

A number of technical differences, particularly source of DNA for testing and data quality criteria may possibly explain the discrepant findings across the multiple CYP2D6 studies, but small numbers of poor-metabolizers and recurrence events and choice of study design may be confusing the picture as well. It seems unlikely that further debates attempting to draw conclusions from indirect evidence will completely resolve the matter. We need to move forward.

The prospective-retrospective study framework described by Simon, Paik, and Hayes[4] provides a path forward. If a sufficient number of appropriate specimens can be identified, then a new study should be conducted. To address questions about candidate therapy-guiding (predictive) omics tests, stored specimens from randomized clinical trials are needed. Informed by existing data, the clinical question and a study plan must be specified in detail: patient characteristics and therapies received, specimen types and processing, assay methods, quality metrics for specimen and data acceptance.

Ideally non-tumor tissue, possibly in addition to tumor, would be used for the new study. Perhaps blood samples, uninvolved lymph nodes or other non-tumor tissue from primary surgery are available. If tumor specimens will be used, we need a way to increase confidence that measured genotypes are not confounded by somatic alterations, such as loss of heterozygosity. Recent reports suggest that newer, more sensitive assays may be able to reliably detect small subpopulations of germline DNA variants admixed with tumor DNA.

To directly answer the question of whether there is any therapeutic benefit of tamoxifen for patients classified by the omics test as poor metabolizers, specimens from a trial in which patients were randomized between tamoxifen and no adjuvant systemic therapy are needed. The existing studies examined only patients who received some form of endocrine therapy.

Trials that randomize between different types of endocrine therapies are well-suited for examination of candidate omics tests intended to guide selection among different types of endocrine therapy, but that represents a different question, which may or may not have the same answer as the question of whether there is any therapeutic benefit of tamoxifen in poor metabolizers. The existing studies analyzed the association between metabolizer status and outcome within each treatment group separately. In the absence

of a no-adjuvant-therapy control group, prognostic effects, unrecognized off-target effects of tamoxifen, and differential effects of other endocrine therapies can confuse interpretation of the association of the omics test result with outcome. The most informative analysis is to examine treatment effect in each of the test-defined subgroups separately[5].

To establish predictive ability for tamoxifen benefit there should be evidence for a benefit of tamoxifen in the metabolizer subgroup and a lack of benefit in the poor metabolizer subgroup. Limited statistical power due to small number of events in poor metabolizer subgroups of the existing studies results in very imprecise estimates of treatment benefit, making it difficult to draw conclusions.

The CYP2D6 story has many of the typical elements that make validation of omics-based tests so challenging. A concerted effort is needed to find sufficient numbers, and appropriate types, of specimens from randomized clinical trials to answer a carefully framed CYP2D6 question once and for all.

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Robert Cook-Deegan, *research professor, Duke University:*

The debate seems to be a bunch of controversy about methodology, and whether tumor-specific or genotype should be used.

And the resort to a "court" is a natural reflex. But it's the wrong reflex. This is a question about biology, not who wins. Courts are used when you can't get at the facts any better; but biology is about designing methods to find out what's right. That's what has not been done.

If these patient studies had done both tumor and genotype characterization, you could compare which one is right, rather than making indirect, statistical arguments about whether it's safe to rely on genotype or measures of tumor tissue. There is an empirical way to find out which one is preferred, and that's the science that needs to be done.

A procedural solution (a 'court' to sift extant evidence) is not the ultimate solution, although it might (but might not, given the apparent enmity and vitriol) be helpful in the interim. That is, the right answer cannot be different camps saying "our method is right, and I'm not going to use theirs," but rather some empirical approaches that do both methods and resolve which is superior.

We don't need more endless arguments about mammography in women 40-50 or PSA. Those are arguments about clinical tests that are widely used and fairly standardized as measurements, and there is lots of slop in the epidemiology and outcomes data, hence the endless controversy.

But here, the methods are not stable, they're evolving, so it's a different category of controversy. These camps should not be circling the wagons and shooting at one another, but stepping back and designing studies specifically to resolve the measurement controversy.

Barnett Kramer, *director of the NCI Division of Cancer Prevention and former editor-in-chief of JNCI:*

Scientific disagreements that are so obviously marinated with emotion are usually not easily resolved.

They are almost never resolved by calls for retractions of peer-reviewed papers (absent fraud or scientific misconduct).

But convening a "Supreme Court" to retrospectively look at accumulated evidence also has its limitations in sorting out to-and-fro "whipsaw" literature in order to achieve a legitimized, widely accepted resolution.

In particular, the conclusions rest heavily on the choice of "justices", since they have flexibility in accepting or rejecting published evidence with knowledge of the study results in hand.

The National Cancer Institute's Early Detection Research Network (EDRN; http://edrn.nci.nih.gov) was set up to avert such problems, albeit for early detection/screening biomarkers rather than for the issue under discussion here--companion markers for therapeutics.

The strategy at the outset was to achieve independent validation of biomarkers using a prospective set of criteria and methods developed by a range of scientists with a variety of expertise and perspectives. A goal was to avoid emotional debates sometimes caused by post hoc evaluation of biomarkers that often have their champions.

At its inception, EDRN investigators spent a year or more developing and then refining the criteria (Pepe MS et al.: Phases of biomarker development for early detection of cancer. *J Natl Cancer Inst* 2001; 93(14):1054-1061; Pepe MS *et al.*: Pivotal evaluation of the accuracy of a biomarker used for classification or prediction: standards for study design. *J Natl Cancer Inst* 2008;100(20):1432-1438). Perhaps that approach is the way forward?

Frances Visco, *president, National Breast Cancer Coalition:*

This story has so many of the elements of the current research world that frustrate advocates. Clearly, we do not know how to do "precision" medicine.

The research community cannot agree on what the precise treatment is, even though they have the most up to date tools and knowledge. Science is supposed to be about fact, not belief or winning a debate. About collaboration, not competition. This is absolutely not a situation for a court of experts to opine.

Someone outside this controversy should just do the experiment and answer the question. Not doing the work that will definitively answer a debated question is a great way to continue to get funding and published. But it is not a great way to make a difference in people's lives.

The Food and Drug Administration:

There are two pathways through which biomarkers can be accepted by the FDA for use in therapeutic product development.

A pharmaceutical sponsor may develop a biomarker as part of a drug-specific program under an Investigational New Drug Application, working with the FDA's Center for Drug Evaluation and Research to develop the data to support the biomarker's use within the context of that program.

Alternatively, a pharmaceutical sponsor, a patient- or disease-specific foundation, another health research organization, or a consortium may request qualification of a biomarker for a particular context of use through the FDA's biomarker qualification program. When there is a lack of clarity regarding the potential role of a biomarker, the FDA has the ability to engage advisory committees, scientific workshops, or other public forums to discuss issues of concern.

The FDA routinely considers the quality and totality of available evidence when making recommendations about the clinical use of biomarkers. While acknowledging the challenges associated with biomarker testing and validation, the FDA must interpret the available data while working within its regulatory framework. As scientific understanding improves, the original labeling for a drug can be revised post-marketing to incorporate genetic testing recommendations when a sufficient amount of quality evidence has accumulated.

The FDA considers the totality of available evidence in making such recommendations, as well as the treatment context to which the test would be applied (e.g., availability of alternative treatments).

Cold Spring Harbor Laboratory And North Shore-LIJ to Form $120 Million Collaboration

Two New York institutions—Cold Spring Harbor Laboratory and the North Shore-LIJ Health System—announced a $120 million cancer research collaboration on April 2.

The collaboration aims to develop a clinical cancer research unit at the North Shore-LIJ Cancer Institute's headquarters in Lake Success, N.Y., support early-phase clinical studies, and recruit and train clinician-scientists.

North Shore-LIJ and CSHL will continue as independent organizations governed by their respective boards of trustees. The sources of funds for the collaboration were not disclosed.

"This is a transformative affiliation for both institutions, bringing the cutting-edge basic discovery science and translational cancer research at CSHL to one of the largest cancer treatment centers in the United States. The unique integration of research scientists, clinical translational researchers and cancer

clinicians promises to speed the advance of novel cancer diagnostics and therapeutics to patients in the region," CSHL President & CEO Bruce Stillman said in a statement.

The institutions appointed a six-member committee to oversee the collaboration. They are, on CSHL's side: Stillman; David Spector, director of research; and David Tuveson, cancer center deputy director. The three representatives of North Shore-LIJ are: Physician-in-Chief Lawrence Smith; Kevin Tracey, president and CEO of the Feinstein Institute for Medical Research; and Thomas McGinn, chair of medicine.

Under the collaboration, clinician-scientists will be trained to perform preclinical cancer research and conduct early-stage human clinical trials.

Advanced-phase clinical trials would be conducted both at North Shore-LIJ facilities and collaborating medical centers.

"Bringing the scientists of Cold Spring Harbor Laboratory together with the more than 200 academic oncologists and clinicians of the North Shore-LIJ Cancer Institute will transform our approach to cancer research and treatment throughout the New York area," said North Shore-LIJ President and CEO Michael Dowling. "North Shore-LIJ oncologists will make CSHL's promising pre-clinical research available as innovative trials to select cancer patients at a much earlier stage, building on the clinical and translational research programs the health system has been offering its patients for more than 30 years and establishing our Cancer Institute as a destination for pioneering cancer therapies."

Over the past two years, North Shore-LIJ has invested more than $175 million to open and expand cancer treatment centers throughout Long Island and New York City. A recently completed $84 million expansion of the cancer institute's headquarters consolidated all cancer services offered by North Shore University Hospital and LIJ Medical Center in a 130,000-square-foot facility, including ambulatory hematology/oncology, chemotherapy and radiation medicine, as well as surgical oncology and brain tumor services.

North Shore-LIJ is also building a $34 million, 45,500-square-foot outpatient cancer center in Bay Shore, N.Y., and is pursuing other major expansions in Long Island, Manhattan, Queens, Staten Island and Westchester County.

CSHL has made discoveries that have helped diagnose and treat cancer patients, including the discovery of the first human cancer gene in 1982. The CSHL Cancer Center has been an NCI-designated cancer center since 1987.

A not-for-profit independent research and education institution, CSHL has an annual operating budget of $145 million and more than 35 independent laboratories focused on basic and applied cancer research. Current research at CSHL focuses on cancers of the breast, lung, prostate, pancreas, cervix, ovary and skin, as well as research on gliomas and medulloblastoma, leukemia and lymphoma, myelodysplastic syndrome, carcinoid tumors and sarcomas.

The North Shore-LIJ Cancer Institute is part of an integrated health system that treats millions of patients annually at 19 hospitals, as well as more than 400 outpatient physician practices throughout the metropolitan area.

North Shore-LIJ receives more than 16,000 new cancer cases annually. The system employs more than 200 physicians in over 25 sub-specialties.

In Brief

Cantley, Adams-Campbell To Deliver Lectures at AACR Annual Meeting in Philadelphia

(Continued from page 1)

Cantley, the Meyer Director of the Sandra and Edward Meyer Cancer Center, the Margaret and Herman Sokol professor in oncology research, and a professor of cancer biology in medicine at Weill Cornell Medical College, is being recognized for his contributions to the field of growth factor and oncogene signaling.

This lectureship honors his discovery of the phosphoinositide 3-kinase enzyme and his subsequent work delineating the PI3K signaling pathway. His research has shown that this pathway is commonly activated in cancer and has paved the way for the development of therapeutics aimed at inhibiting PI3K signaling.

He will present his lecture, "Targeting PI3K for Cancer Therapy," Monday, April 20. Cantley is also chair of this year's AACR Annual Meeting Scientific Program Committee.

The AACR Princess Takamatsu Memorial Lectureship is presented to a scientist whose novel and significant work had or may have a far-reaching impact on the detection, diagnosis, treatment, or prevention of cancer, and who embodies the dedication of the princess to multinational collaborations. Her Imperial Highness Princess Kikuko Takamatsu was instrumental in promoting cancer research and encouraging cancer scientists. She became a champion for these causes following her mother's death from bowel cancer in 1933 at the young age of 43.

Cantley is credited with a key role in elucidating the molecular components of several signaling networks that are fundamental to cell growth. His most significant contribution to cancer research has been his 1988 discovery of the PI3K enzyme. This laid the foundation for his subsequent work, which revealed how biochemical signaling pathways control normal cell growth and trigger the development of cancer when they are defective.

His demonstration of how PI3K is activated by growth factors and oncogenes, coupled with the delineation of the components of the PI3K signaling pathway, including Akt/PKB, have been important for the development of personalized cancer therapies. Cantley's work has also indicated that PI3K is a significant factor in both insulin signaling and immune cell signaling, which has major implications for the treatment of diabetes and other immune-related diseases.

Cantley is a founding co-editor-in-chief of Cancer Discovery, a member of the AACR board of directors, an elected fellow of the AACR Academy, and a leader of the Stand Up to Cancer Dream Team, "Targeting PI3K in Women's Cancers."

Cantley's scientific accomplishments have been recognized with numerous additional honors throughout his career, including the Canada Gairdner International Award, the inaugural Breakthrough Prize in Life Sciences, the H.C. Jacobaeus Prize, the Pasarow Award for Cancer Research, the Rolf Luft Award from the Karolinska Institute, the Pezcoller Foundation-AACR International Award for Cancer Research, and the Caledonian Prize Lectureship in Biomedical Science from the Royal Society of Edinburgh. Additionally, he is an elected member of the National Academy of Sciences and the American Academy of Arts and Sciences.

LUCILE ADAMS-CAMPBELL was awarded the 10th annual **American Association for Cancer Research** Minorities in Cancer Research Jane Cooke Wright Lectureship, to be delivered at the AACR annual meeting in Philadelphia.

Adams-Campbell is professor of oncology, associate director of minority health and disparities research, and associate dean of community health and outreach at the Georgetown Lombardi Comprehensive Cancer Center at Georgetown University Medical Center.

She is being recognized for her scientific contributions in the area of cancer epidemiology and health disparities and for her dedication to fostering the development of minorities in cancer research, according to AACR.

She will present her lecture, "A Prospective Approach to Breast Cancer Risk in Black Women: A View from Two Cohorts – WHI and BWHS," Sunday, April 19.

Adams-Campbell's research focus has been diseases that disproportionately affect African Americans, including breast, prostate, and colon cancers, and identifying ways to overcome health disparities through disease prevention. She leads the National Institute of Minority Health and Disparities Center of Excellence for Health Disparities. She also is the co-principal investigator of the Black Women's Health Study, which led to the identification of obesity, diet, and physical inactivity as factors influencing risk for diseases disproportionately affecting African-American women such as cancer, lupus, high blood pressure, and diabetes, as well as served as co-principal investigator of the Women's Health Initiative.

Additionally, Adams-Campbell served as principal investigator for the NCI's Minority Based Community Oncology Program, which was implemented to improve the number of black participants in clinical trials.

In 1983, Adams-Campbell became the first African-American woman in the country to receive a doctorate in epidemiology, when she received hers from the Graduate School of Public Health at the University of Pittsburgh.

A member of the AACR since 1995, Adams-Campbell has been involved in numerous committees, including the Women in Cancer Research Council, of which she is currently a member, and the Cancer Prevention Research editorial board. She has also served as chair of the MICR Council and Minority Issues Committee. Her work was also recognized in 2010 with the AACR Minority-Serving Institution Faculty Scholar in Cancer Research Award.

Adams-Campbell is an elected member of the Institute of Medicine and has received gold medallions from both of her alma maters, Drexel University in Philadelphia, where she received her bachelor's and master's degrees, and the University of Pittsburgh.

Before joining the Lombardi Comprehensive Cancer Center in 2008, Adams-Campbell was director of Howard University Cancer Center. She is also a visiting professor of oncology at Johns Hopkins University School of Medicine, adjunct professor of epidemiology at the University of Pittsburgh, and adjunct professor of medical and clinical psychology at the Uniformed Services University of the Health Sciences, F. Edward Hébert School of Medicine.

ROBERT GENTLEMAN was appointed vice president of computational biology at **23andMe Inc**.

Gentleman will focus on the use of genetic and trait data in the 23andMe database to identify new therapies for disease. Gentleman previously served as senior director of bioinformatics and computational biology at Genentech.

He will also specifically focus on collaborating with Richard Scheller, chief science officer and head of therapeutics. Gentleman will work to utilize data analytics and theoretical models to identify trends and advance the drug research and discovery process, according to the company.

Prior to joining Genentech, Gentleman was head of the computational biology department at Fred Hutchinson Cancer Research Center. Gentleman served as a professor at Harvard University, the University of Auckland, and the University of Waterloo. During his tenure at Harvard, Gentleman founded the Bioconductor Project, an open-source software project to provide tools for the analysis and comprehension of high-throughput genomic data.

Gentleman recently served as member of the board of directors of Revolution Analytics where he helped the company through an acquisition by Microsoft. He has been awarded the Benjamin Franklin Award, an award for Open Access in the Life Sciences presented by the Bioinformatics Organization, and is a fellow of the International Society for Computational Biology.

Gentleman, along with Ross Ihaka at the University of Auckland, is also recognized as one of the originators of the R programming language, a widely-used programming language software environment for statistical computing and graphics.

ALEKSANDAR ZAFIROVSKI was named executive administrative director and associate director for administration for the Robert H. Lurie Comprehensive Cancer Center of **Northwestern University**. He has served as interim associate director since 2014.

Zafirovski is responsible for administrative operations including finance and accounting, purchasing, human resources, information systems, research safety and security, and public affairs and communications, as well as oversight of development programs and affiliated organization relations. He is a full member of the center's senior leadership, and is a member of the Executive Committee and Leadership Group.

Zafirovski previously helped the efforts to launch and expand the Northwestern Medicine Developmental Therapeutics Institute in the Lurie Cancer Center.

Since joining Northwestern in 2001, Zafirovski has also served as administrative director of the School of Radiation Therapy and director of Oncology at Northwestern Memorial Hospital.

SCRIPPS CLINIC MEDICAL GROUP expanded its radiation oncology services to include CyberKnife of Southern California at Vista, Oncology Therapies of Vista and Pacific Radiation Oncology in Encinitas.

The agreement expands Scripps' services in North County and adds CyberKnife stereotactic radiosurgery to Scripps Health's cancer treatment offerings. The physicians and staff at the centers will continue to practice at their current locations.

The three centers will be renamed:

• **Scripps Clinic Radiation Therapy Center Encinitas**, formerly Pacific Radiation Oncology.

• **Scripps Clinic Radiation Therapy Center Vista**, formerly Oncology Therapies of Vista Medical Group.

• And **Scripps Clinic Radiation Therapy Center Vista CyberKnife**, formerly CyberKnife of Southern California at Vista.

Five radiation oncology physicians joined Scripps Clinic as well: Patrick Linson, Eva Lean, Norbert Kased, Anuradha Koka, and Kenneth Shimizu. All five have privileges at various Scripps hospitals and have provided radiation oncology services for years at Scripps Memorial Hospital La Jolla. Koka and Shimizu also have worked closely with Scripps Clinic physicians at the Scripps Radiation Therapy Center in La Jolla since it opened in 2012.

The centers offer radiation treatments including: intensity-modulated radiation therapy; Xoft electronic radiotherapy, which uses a miniaturized X-ray tube directly inserted onto the tumor to treat skin cancer; Accuboost, a breast radiotherapy treatment that also targets the lumpectomy cavity margin; and prone breast board radiation therapy, which allows women to receive radiation face down rather than on their backs, using a specially made table and a technique that limits the amount of radiation doses to normal tissues like the heart and lungs.

AETERNA ZENTARIS Inc. has agreed to transfer its discovery library of roughly 100,000 unique compounds to the South Carolina Center for Therapeutic Discovery & Development, part of the **Medical University of South Carolina**.

The library will be used for the discovery of

drug development candidates for Aeterna Zentaris in the areas of oncology, neurology, endocrinology and women's health. The center may make the library available to all investigators in the University of South Carolina system without restriction on its use and will own any therapeutic compounds discovered outside Aeterna Zentaris' areas of therapeutic interest.

The center has agreed to conduct screening and pre-clinical activities with the goal of submitting at least one development candidate per year for 10 years, beginning in 2018.

GLAXOSMITHKLINE plans to establish its third center for vaccine research and development in Rockville, Md. The site follows existing R&D centers in Rixensart, Belgium and Siena, Italy, which GSK acquired from Novartis in March.

The U.S. center will consolidate vaccine research currently being conducted at other GSK sites, such as Philadelphia and Cambridge, Mass. Late-stage development programs, as well as discovery and platform technology development will be led from Rockville, according to the company.

GSK anticipates site operations for vaccines to begin in Rockville as early as September 2015.

Drugs and Targets

FDA Approves Chelator Jadenu, An Oral Formulation of Exjade

FDA approved Jadenu (deferasirox) tablets, a new oral formulation of Exjade (deferasirox) tablets for oral suspension, for the treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older, and chronic iron overload in non-transfusion-dependent thalassemia syndromes in patients 10 years of age and older.

Jadenu contains the same active ingredient in Exjade. Exjade currently is the most-prescribed chelator in the U.S.

Novartis, Jadenu's sponsor, has submitted additional regulatory applications for Jadenu in other countries worldwide.

Jadenu is an iron chelator indicated for the treatment of chronically elevated levels of iron in the blood caused by repeated blood transfusions (transfusional hemosiderosis) in patients ages 2 years and older. Jadenu is also indicated to treat patients ages 10 years and older who have chronic iron overload resulting from non-transfusion-dependent thalassemia.

These indications were approved under accelerated approval based on a reduction of iron levels in the liver (measured by liver iron concentration) and blood (measured by serum ferritin levels). Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials. There are ongoing studies to find out how Jadenu works over a longer period of time.

FDA granted Priority Review to Kyprolis (carfilzomib) for Injection for the treatment of patients with relapsed multiple myeloma who have received at least one prior therapy. The agency also accepted the drug's supplemental new drug application designed to support the conversion of accelerated approval to full approval and expand the current Kyprolis indication. FDA set a target action date of July 26.

The sNDA is based on data from the phase III ASPIRE trial and other relevant data.

Kyprolis is currently approved by the FDA for the treatment of patients with multiple myeloma who have received at least two prior therapies, including bortezomib and an immunomodulatory agent, and have demonstrated disease progression on or within 60 days of completion of the last therapy.

The ASPIRE trial evaluated Kyprolis in combination with lenalidomide and low-dose dexamethasone, versus lenalidomide and low-dose dexamethasone alone, in patients with relapsed multiple myeloma following treatment with one to three prior regimens. The primary endpoint of the trial was progression-free survival, and secondary endpoints included overall survival, overall response rate, duration of response, disease control rate, health-related quality of life and safety.

Patients were randomized to receive Kyprolis (20 mg/m(2) on days 1 and 2 of cycle 1 only, escalating to 27 mg/m(2) on days 8, 9, 15 and 16 of cycle 1 and continuing on days 1, 2, 8, 9, 15 and 16 of subsequent cycles), in addition to a standard dosing schedule of lenalidomide (25 mg per day for 21 days on, 7 days off) and low-dose dexamethasone (40 mg per week in 4 week cycles), versus lenalidomide and low-dose dexamethasone alone. The study randomized 792 patients at sites in North America, Europe and Israel.

The ASPIRE data were presented at the annual meeting of the American Society of Hematology in December 2014 and published in the New England Journal of Medicine.

FDA approved a label update for Zytiga (abiraterone acetate) plus prednisone to include overall survival results in chemotherapy-naive men with metastatic castration-resistant prostate cancer.

The update was based on the final analysis of the phase III, randomized, double-blind, placebo-controlled COU-AA-302 study, which showed that Zytiga plus prednisone significantly prolonged median overall survival, compared to placebo plus prednisone.

After a median follow-up of more than four years (49.2 months), the Janssen Research & Development-sponsored registration study demonstrated a median OS of 34.7 months in the patients randomized to Zytiga plus prednisone compared to 30.3 months in the placebo plus prednisone arm (HR= 0.81 [95% CI, 0.70-0.93]; p = 0.0033).

Overall survival is particularly meaningful in this final analysis because 65 percent of men in the ZYTIGA plus prednisone arm and 78 percent in the placebo plus prednisone arm received subsequent therapy that may prolong OS in mCRPC. This includes 44 percent of men in the control arm who subsequently received Zytiga plus prednisone. Additionally, with a median of 49 months of follow-up, there were no notable changes in the safety profile of Zytiga since the previously reported interim analyses.

The final analysis data was recently published in the February 2015 issue of The Lancet Oncology with an independent commentary. Additionally, Janssen first presented these data at the European Society for Medical Oncology Congress in Madrid in September 2014. Based on the results from the final analysis, Janssen is working with relevant global health authorities to revise the label for Zytiga to include the final analysis results.

Zytiga is indicated in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer. Zytiga blocks CYP17-mediated androgen production that fuels prostate cancer growth at three sources: in the testes, adrenals and the prostate tumor tissue.

MD Anderson Cancer Center and Astellas Pharma Inc. signed an option agreement to research and develop a new treatment for patients with acute myeloid leukemia.

The collaboration grants Astellas an option to firstly negotiate an exclusive, worldwide license at the end of phase Ib, with both phase Ia and phase Ib studies to be conducted by MD Anderson. The agreement also includes up to $26 million as an option premium and research and development funding.

The collaboration will focus on h8F4 technology, a humanized monoclonal antibody invented by Jeffrey Molldrem, professor of stem cell transplantation and cellular therapy at MD Anderson. The antibody h8F4 targets an HLA-restricted peptide called PR1/HLA-A2, which is expressed in cancer cells and cancer stem cells. Molldrem will lead these research efforts with Carlo Toniatti, executive director of MD Anderson's Oncology Research for Biologics and Immunotherapy Translation platform, part of the institution's Moon Shots Program.

Eli Lilly and Co. and OncoMed Pharmaceuticals Inc. entered into an agreement to evaluate the combination of demcizumab and Alimta (pemetrexed for injection) in lung cancer.

Demcizumab, OncoMed's anti-DLL4 antibody, will be tested in combination with Lilly's Alimta and carboplatin for the treatment of first-line advanced non-small cell lung cancer. Lilly will provide clinical supply of Alimta for OncoMed's ongoing phase II DENALI trial.

OncoMed initiated enrollment in the randomized DENALI trial in January 2015 to test the efficacy and safety of demcizumab in combination with Alimta and carboplatin. Alimta is approved as an initial treatment in combination with cisplatin for locally advanced or metastatic NSCLC for patients with non-squamous histology. The DENALI trial is expected to enroll approximately 200 patients with first-line metastatic Stage IV non-squamous NSCLC whose tumors do not have an epidermal growth factor receptor or anaplastic lymphoma kinase mutation.

Demcizumab is a humanized monoclonal antibody that inhibits Delta-Like Ligand 4 in the Notch signaling pathway. Based on preclinical studies, demcizumab appears to have a multi-pronged mechanism of action: halting cancer stem cell growth and reducing CSC frequency, disrupting angiogenesis in the tumor and potentially augmenting anti-tumor immune response.

Demcizumab is part of OncoMed's collaboration with Celgene Corporation.

In 2009, Alimta was approved as a maintenance therapy for locally advanced or metastatic NSCLC, specifically for patients with a nonsquamous histology whose disease has not progressed after four cycles of platinum-based first-line chemotherapy. In 2012, Alimta was approved by the FDA as a continuation maintenance therapy for locally-advanced or metastatic

NSCLC, following first-line therapy with Alimta plus cisplatin in patients with a nonsquamous histology.

Merck and Syndax Pharmaceuticals Inc. entered into a clinical trial collaboration to evaluate the safety and efficacy of combining Syndax's entinostat, an investigational epigenetic therapy, with Merck's Keytruda (pembrolizumab).

The phase Ib/II study will evaluate this novel combination regimen in patients with either advanced non-small cell lung cancer or melanoma. The study is expected to begin enrolling patients in the second half of 2015.

Entinostat is an oral, highly selective histone deacetylase inhibitor granted Breakthrough Therapy Designation in combination with hormone therapy in advanced hormone receptor positive (HR+) breast cancer and currently in phase III testing in this indication. Entinostat has been shown in preclinical models to reduce the number and function of host immune suppressor cells thereby enhancing the anti-tumor activity of immune checkpoint blockade.

Keytruda is ahumanized monoclonal antibody that blocks the interaction between PD-1 (programmed death receptor-1) and its ligands, PD-L1 and PD-L2.

The financial terms and additional details of the agreement between Syndax and Merck, through a subsidiary, were not disclosed. The agreement includes a provision where the parties may extend the collaboration to include a potential phase III clinical trial.

Intrexon Corporation and Merck Serono, the biopharmaceutical arm of Merck KGaA, announced an exclusive collaboration and license agreement to develop and commercialize Chimeric Antigen Receptor T-cell cancer therapies.

CAR-T cells are genetically engineered T-cells with synthetic receptors that recognize a specific antigen expressed on tumor cells. When CAR-T cells bind to a target, an immunological attack against the cancer cells is triggered.

Using Intrexon's cell engineering techniques and RheoSwitch platform, the collaboration aims to develop products that use the immune system in a regulated manner to overcome the current challenges of CAR-T therapy.

The agreement provides Merck Serono exclusive access to Intrexon's proprietary and complementary suite of technologies to engineer T-cells with optimized and inducible gene expression.

Intrexon will be responsible for all platform and product developments until IND filing. Merck will nominate targets of interest for which CAR-T products will be developed. Merck will also lead the IND filing and pre-IND interactions, clinical development and commercialization. In addition, Intrexon has the opportunity to explore targets independently, granting Merck opt-in rights during clinical development.

Under the terms of the agreement, Intrexon will receive an upfront payment of $115 million. For the first two targets of interest selected by Merck Serono, Intrexon will receive research funding and is eligible to receive up to $826 million development, regulatory and commercial milestones, as well as tiered royalties on product sales. In addition, Intrexon is also eligible to receive further payments upon achievement of certain technology development milestones.