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An Impromptu Group Proposes Standards For Publication Of Genomics Research

By Paul Goldberg

After the revelation that a Duke genomic researcher had misstated his credentials, a group of biostatisticians wrote a letter to NCI Director Harold Varmus, asking him to step in and investigate.

The letter, signed by 33 prominent biostatisticians, was cited as one of the factors that prompted NCI, Duke and the Institute of Medicine to start an independent investigation of the affair (The Cancer Letter, July 23, July 30). The letter was also quoted in The New York Times.

The investigation, which appears to be unprecedented for IOM, is about to begin, sources said. Allegations of errors in the work of the Duke genomics

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In the Cancer Centers:

UPCI Receives $27 Million Core Grant Renewal; Names Chu Chief of Hematology, Deputy Director

UNIVERSITY OF PITTSBURGH CANCER INSTITUTE received a five-year, $27 million core grant renewal from NCI to support research, clinical, and outreach programs. The UPCI retains its designation as comprehensive. The UPCI was established in 1985 and has received continuous NCI designation since 1989. "We are thrilled to received this renewal and elite designation during our ongoing celebration of our 25th anniversary year," said UPCI Director **Nancy Davidson**.

Also at UPCI, **Edward Chu**, an expert in the biology and treatment of colorectal cancer, has been named chief of the Division of Hematology/Oncology at the University of Pittsburgh School of Medicine and deputy director of the University of Pittsburgh Cancer Institute.

Before coming to UPCI, Chu served as a professor of medicine and pharmacology at Yale University School of Medicine, chief of the Section of Medical Oncology and deputy director of the Yale Cancer Center. Chu is well-recognized for his contributions in understanding the action of antimetabolites in cancer therapy.

In addition, UPCI and University of Pittsburgh School of Medicine researchers have been awarded $13.9 million over five years by the National Institute of Allergy and Infectious Diseases to continue developing small molecule radiation protectors and mitigators that can be easily accessed and administered in the event of a large-scale radiological or nuclear emergency.

Joel Greenberger, chair of the Department of Radiation Oncology at Pitt,

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IOM Investigation Expected To Begin Soon, Sources Say

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group have swirled about for nearly three years, but reached the level of a scandal on July 16, when this publication reported that Duke researcher Anil Potti had lied about his credentials, claiming to have been a Rhodes scholar.

The group of statisticians didn't disband after penning their letter to Varmus. They still had a lot to say on the subject of reproducibility of genomic research. Their thoughts, summarized in a letter to the editor in the Sept. 23 issue of the journal Nature, are likely to influence the agenda for the IOM committee when it convenes.

"Journals have a duty to help the community by maintaining reproducibility as a cornerstone of the scientific process," reads the letter signed by 47 experts in statistics and reproducibility of research. "The independent reanalysis of [Duke data] took so long because the information accompanying the associated publications was incomplete."

The letter was produced by what is now an expanding, diverse group of people interested in the issues raised by the Duke scandal.

"Many of the folks who signed the letter to Varmus started further discussions, saying, are there ways we can do this better, in general?" said Keith Baggerly, a biostatistician at MD Anderson Cancer Center who devoted thousands of hours to tracking down mistakes in the work of the Duke researchers.

The statisticians agreed on the idea of suggesting standards, but the logistics of drafting another letter were getting unruly.

"There were discussions that were left unfinished, so we kept having them after the letter to Varmus, but at some point somebody complained that they were happy to sign the letter, but they didn't want to keep getting emails," said Rafael Irizarry, professor in the Department of Biostatistics in the Johns Hopkins Bloomberg School of Public Health.

To keep discussion moving along, Irizarry set up a Google group. "It takes 20 seconds or less to set up, and then I emailed everybody," he said.

The group's address is http://groups.google.com/group/reproducible-research. Anyone can read the posts. To post messages, one has to be admitted.

After the group was created, both the membership and the scope of discussion started to expand.

New members include Victoria Stodden, assistant professor of statistics at Columbia University, who studies the way in which large-scale computation is changing science.

Stodden, who also has a law degree, became aware of the Duke controversy while preparing a workshop on reproducibility of research for Yale Law School last year. The issues involved are bigger than Duke, genomics and oncology, she said. They affect geosciences, computational chemistry, fluid dynamics, scientific computing, microarray research, signal processing—any field that uses computation.

"If the journals verified code and if code and data publication were standard practice with publication of the paper itself, we could have avoided the Duke scandal," Stodden said. "I don't think we would have avoided the Rhodes scholar scandal. We certainly could have avoided all the hours that were wasted trying to figure out what in the world they had done."

A set of recommendations stemming from Stodden's workshop is posted at http://reproducible-research.googlegroups.com/web/CISE-12-5-News.pdf.

The letter to Nature is consistent with these recommendations.

The text of the letter follows:

After thousands of hours of investigation, three clinical trials at Duke University in Durham, North Carolina, were suspended in late 2009 because of the irreproducibility of the genomic 'signatures' used to

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select cancer therapies for patients.

Journals have a duty to help the community by maintaining reproducibility as a cornerstone of the scientific process. The independent reanalysis of these signatures took so long because the information accompanying the associated publications was incomplete.

Unfortunately, this is common: for example, a survey of 18 published microarray gene expression analyses found that the results of only two were exactly reproducible (J. P. Ioannidis et al. Nature Genet. 41, 149–155; 2009). Inadequate information meant that 10 could not be reproduced. To counter this problem, journals should demand that authors submit sufficient detail for the independent assessment of their paper's conclusions.

We recommend that all primary data are backed up with adequate documentation and sample annotation; all primary data sources, such as database accessions or URL links, are presented; and all scripts and software source codes are supplied, with instructions. Analytical (non-scriptable) protocols should be described step by step, and the research protocol, including any plans for research and analysis, should be provided (see go.nature.com/UaF2Kv).

Files containing such information could be stored as supplements by the journal. There may be some situations that preclude authors from supplying complete data or code—in protecting patient confidentiality, for example.

In such cases, authors should justify the omission and assure independent reproducibility by alternative means. The quality of scientific output will benefit from setting these standards. As a community, we owe it to patients and to the public to do what we can to ensure the validity of the research we publish.

IOM Investigation About to Begin

Knowledgeable sources said the launch of the IOM investigation is imminent.

The probe would be conducted by a "consensus committee" that would be operating under the National Cancer Policy Forum, a component of the IOM Board on Health Care Services. Potential members of the committee have been identified, sources said. After the committee is appointed, it would decide how to proceed.

Though Duke has pledged to cooperate with the investigation, it will not be among its funders. The money will come from the policy board's budget, sources said.

Sources said that the IOM group would likely focus on science, as opposed to potential misconduct. However, separating the two would likely be a challenge. If misconduct is involved, it has substantially contaminated medical literature.

Duke officials said in August that their internal investigation has found "issues of substantial concern" in Potti's credentials. This has resulted in "sanctions," which Duke officials didn't disclose.

"A final decision about Dr. Potti's future status as a Duke employee and faculty member will also be informed by the results of the research misconduct inquiry and the independent external evaluation of the science," Mike Schoenfeld, Duke vice president, public affairs, said at the time. "Until such time, he will remain on administrative leave from his research, teaching and clinical responsibilities."

Some internal critics said the administration's decision seems to suggest that misrepresentation of credentials is insufficient to cause one to get fired from Duke.

"As has been stated previously, significant sanctions have already been applied to Dr. Potti, and we believe it is appropriate to reserve a final decision regarding his future at Duke until all the facts are in and questions have been answered," said Doug Stokke, a Duke spokesman.

The university is conducting a scientific misconduct investigation as well.

Duke officials stopped short of referring to the IOM investigation by name, but described it generically.

"Efforts to facilitate the initiation of an independent, external investigation of the science in question by one of the country's leading research bodies, to which Duke would supply any and all data and information, but would otherwise have no involvement," Schoenfeld said in August.

In a related development, The Duke Chronicle, a student newspaper, reported that Eli Lilly and Co. and CancerGuide Diagnostics ended their relationships with Potti.

The Chronicle identified CancerGuide as a private company that develops genomics-based cancer tests, has licensed technology based on Potti's research

Eli Lilly employed Potti as a consultant and as a speaker on the company's thoracic speaker faculty. Duke is divesting its interest in CancerGuide, and Lilly is a co-sponsor on a Duke trial testing a Potti technology.

The story is posted at http://www.dukechronicle.com/article/health-care-companies-cut-ties-potti.

NCI Programs:

STRAP Grants Aim To Move Interventions To Trials Faster

By Kirsten Boyd Goldberg

An NCI advisory group on translational research debated whether to throw open the doors to all ideas or take a more targeted "pathway" approach to prioritize ideas under a proposed grant funding mechanism designed to help early cancer research move more quickly into human clinical trials.

Careful research prioritization is time-consuming for NCI staff and advisors, making the open-door, or "umbrella" approach expedient, according to a report by an NCI working group. However, NCI Director Harold Varmus pointed out that this method could bring in too many grant applications and result in low success rates.

The Clinical Trials and Translational Research Advisory Committee voted Sept. 21 to accept the working group's recommendation to begin the new grant program, but encouraged NCI to use a prioritization process with the proposed funding mechanism, called Special Translational Research Acceleration Projects (STRAPs).

The report by the Process to Accelerate Translational Science Working Group recommended that NCI "initiate an umbrella STRAP solicitation immediately to fulfill the urgent need to accelerate translation for patient and public benefit. The more complicated prioritization process should be initiated with the goal of incorporating it into the umbrella STRAP solicitation whenever possible."

The program would fund two to three projects a year for $2 million to $3 million per project over three to five years.

Since 2005, NCI has enlisted extramural advisors to help define translational research and develop ways to move it forward more quickly. In 2007, the Translational Research Working Group issued a 150-page report, and in 2008, published a series of articles in Clinical Cancer Research describing six developmental pathways for reaching clinical goals.

The more recent PATS working group was formed to help implement the TRWG recommendations, including the idea for a new funding program.

The STRAP program would fund translational research opportunities that are ready for acceleration based on scientific quality, technical feasibility and expected patient benefit or public health impact. The STRAP solicitation should cover potential translational opportunities in all six of the pathways, according to the PATS working group report.

These projects would be managed by NCI and would have to meet milestones in moving toward early stage clinical trials. STRAPs would link multiple existing NCI programs and funding mechanisms.

NCI piloted the idea in the area of immune response modifiers. One application is about to be funded for $2 million, and by all accounts the pilot grant program was deemed a success—but the prioritization process was time-consuming, said Lynn Matrisian, co-chairman of the PATS working group and a special assistant in the NCI director's office.

STRAPs are likely to include multiple investigators, institutions, and disciplines. Applicants would submit a preliminary concept of one to three pages in length. The concepts judged by extramural reviewers to be most promising would result in a request to the investigator to submit a full application.

STRAP prioritization committees would have the flexibility to modify or replace STRAP components proposed by the investigators.

STRAPs would not be renewed. A STRAP would be deemed successful if the intervention reached an advanced phase II or phase III trial.

CTAC's approval of the working group report is advisory. For the proposed STRAP program to move forward, NCI staff would develop a concept statement that would be presented to the NCI Board of Scientific Advisors for approval. If approved, NCI would then write a Request for Applications.

A videocast of the CTAC meeting is available at http://videocast.nih.gov/summary.asp?Live=9461.

Medicare:

CMS, FDA To Develop Process For Concurrent Approvals

By Paul Goldberg

The Centers for Medicare and Medicaid Services and the Food and Drug Administration are establishing a process for concurrent approvals.

In cases where sponsors agree to go through the parallel review process, drugs and devices would go through the FDA marketing approval and the CMS national coverage determination.

The agencies said the concurrent procedures would streamline the CMS review process. The program, which allows regulatory agencies to consider costs of therapies at the time they are introduced, was announced in the Federal Register Sept. 17.

"The agencies envision that the decision to undertake the parallel review process with respect to a specific product will be at the request of the manufacturer and with the agreement of both agencies, thus making the process voluntary for all parties involved," the document states.

CMS conducts coverage determinations for a small portion of drugs and devices that end up on the market. Requests for NCDs can come from outside the agency or from its staff.

Review would still have to be staggered. "To avoid CMS reaching a coverage determination deadline before FDA has completed its review process and to minimize the possibility that CMS will begin its coverage process for a product that is subsequently not approved or cleared by FDA, the CMS process and FDA process should be carefully staged," the document states. "FDA and CMS also seek comment on whether they should establish a voluntary process to allow companies to meet with both agencies to develop clinical trial protocols that would meet each agency's respective statutory standard rather than potentially conducting separate clinical studies."

FDA is prohibited by law from considering the cost of therapy as a component of an approval decision.

"From time to time CMS finds that developers of new technology fail to recognize the differences between the regulatory requirements of FDA and CMS. They may undertake clinical studies that are designed to address FDA questions but do not adequately address CMS questions concerning the impact of the technology on Medicare beneficiary health outcomes," the document states. "This omission can slow the developer's quest for Medicare coverage. We believe that a parallel review process can furnish an opportunity to educate developers regarding clinical study designs that are more likely to simultaneously address both FDA and CMS questions."

FDA is seeking public comment on the plan. The deadline is Dec. 16.

Tobacco Cessation: Medicare has increased coverage of evidence-based tobacco cessation counseling, removing a barrier to treatment for all tobacco users covered by Medicare.

Previously, Medicare covered tobacco counseling only for individuals diagnosed with a recognized tobacco-related disease or showed signs or symptoms of such a disease. Under the new coverage, any smoker covered by Medicare will be able to receive tobacco cessation counseling from a qualified physician or other Medicare-recognized practitioner who can work with them to help them stop using tobacco. All Medicare beneficiaries will continue to have access to smoking-cessation prescription medication through the Medicare Prescription Drug Program (Part D).

Despite the expansive list of adverse effects caused by tobacco use, and smoking in particular, about 46 million Americans continue to smoke. Of these, an estimated 4.5 million are Medicare beneficiaries 65 or older and less than 1 million are younger than 65 and are covered by Medicare due to a disability.

The new benefit will cover two individual tobacco cessation counseling attempts per year. Each attempt may include up to four sessions, with a total annual benefit thus covering up to eight sessions per Medicare patient who uses tobacco.

The final coverage decision will apply to services under Parts A and B of Medicare and does not change the existing policies for Part D, or any state-level policies for Medicaid or the Children's Health Insurance Program. HHS will issue guidance in the coming months about a new benefit for pregnant women to receive Medicaid-covered tobacco cessation counseling. This new benefit, a provision of the Affordable Care Act, requires states to make coverage available to pregnant Medicaid beneficiaries by Oct. 1.

Under the Affordable Care Act, effective Jan. 1, Medicare will cover preventive care services, including the tobacco cessation counseling services, and other services such as certain colorectal cancer screening and mammograms at no cost to beneficiaries. The Affordable Care Act also gives beneficiaries access to a no-cost annual physical exam so they can partner with their doctors to develop and update personal prevention plans, which will be based on their current health needs and risk factors.

Professional Societies:

AACI To Honor Scientist King, Ohio Sen. Sherrod Brown

ASSOCIATION OF AMERICAN CANCER INSTITUTES will present the AACI Distinguished Scientist Award to **Mary-Claire King** on Oct. 4, during the 2010 AACI/CCAF annual meeting in Chicago.

The award recognizes King's scientific accomplishments and contributions to the cancer center and cancer research communities. She is known for three major career accomplishments: identification of the gene BRCA 1, proving that breast cancer is inherited in families and where the gene is located; demonstrating in her 1973 PhD dissertation that humans

and chimpanzees are 99 percent the same, at the level of genes; and, showing that human remains can be identified by sequencing DNA.

Also at the annual meeting, **Sen. Sherrod Brown** (D-Ohio) will receive AACI's Distinguished Public Service Award. Brown will be recognized for exceptional leadership in promoting cancer research and passionate commitment to the needs of patients with cancer. He led the effort to pass federal legislation requiring health insurance plans to provide coverage for routine costs associated with participation in clinical trials. The measure was signed into law as part of the Patient Protection and Affordable Care Act.

THE ENDOCRINE SOCIETY hired **Paul Hedrick** as senior director, finance. Hedrick, who has more than 20 years of financial experience, will lead the finance and IT operations at the society. He is a certified public accountant and a certified internal auditor. He served for eight years as controller of the Service Employees International Union.

In the Cancer Centers:

Dartmouth Wins NCI Grant In Nanotechnology Research

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leads a team of researchers with the university's Center for Medical Countermeasures Against Radiation.

Co-principal investigators include **Valerian Kagan, John Lazo, Hulya Bayir, Peter Wipf, Detcho Stoyanovsky, Song Li, Xiang Gao, Paul Floreancing, Alexander Star, Oleskandr Kapralov, Hong Wang**, and **Michael Epperly**, all with the University of Pittsburgh School of Medicine.

DARTMOUTH has been designated as a Center of Cancer Nanotechnology Excellence with a five-year, $12.8 million grant from NCI. The CCNE brings together Dartmouth's Thayer School of Engineering, Norris Cotton Cancer Center, and Dartmouth Medical School to focus on using magnetic nanoparticles to destroy malignant tumors. The Dartmouth CCNE will focus on breast and ovarian cancer.

Ian Baker, Dartmouth's Sherman Fairchild Professor of Engineering, is the CCNE program director. The CCNE deputy director is **Keith Paulsen**, the Robert A. Pritzker Professor of Biomedical Engineering.

With the grant, Dartmouth also becomes a member of the NCI Alliance for Nanotechnology in Cancer.

HOLLINGS CANCER CENTER at the Medical University of South Carolina has recruited two researchers through the state's Centers of Economic Excellence Program (CoEE). **Zihai Li**, previously of University of Connecticut, will lead the CoEE in Cancer Stem Cell Biology. Li also directs the cancer immunology program at Hollings and serve as co-director of the Cell Therapy Facility. Li is an associate professor of Immunobilogy and Cancer Immunology in the College of Medicine. **George Simon**, formerly of Fox Chase Cancer Center, will lead the CoEE in Tobacco-Related Malignancy Research with in the Department of Medicine, Division of Hematology/Oncology. Simon is an expert in thoracic malignancies, with an emphasis on lung cancer and meothelioma. He is an associate professor in the College of Medicine.

ARIZONA STATE UNIVERSITY and Quintiles have signed an agreement on clinical research. ASU's Center for Healthcare Innovation & Clinical Trials will become a global prime site partner for Quintiles, giving the center access to more clinical research initiatives. In return, the center will deploy its unique community-based model to recruit more physicians and nurse practitioners who can identify patients who are willing and eligible to participate in the research.

The ASU center is the only one of Quintiles' five global prime sites that is a community-based, non-academic medical center. ASU's model, the Community Oriented Network to Enhance Clinical Trials and Research (CONECTR), will serve as the hub for placing, subcontracting, consulting and supporting multi-phased research studies within Arizona.

Quintiles' other prime site partners are Kaiser Permanente in Southern California, the University of Pretoria in South Africa, Queen Mary's College in London, Washington Hospital Center in Washington, D.C., and the University of Malaya in Malaysia.

DAVID ALBERTS, director of the Arizona Cancer Center, received the Association of Community Cancer Centers' 2010 Clinical Research Award at ACCC's 27th National Oncology Economics Conference.

He received the award for his extensive research, leadership, and commitment to individuals with cancer. Alberts is Regents Professor of Medicine, Pharmacology, Nutritional Science, and Public Health at the University of Arizona College of Medicine.

DANA-FARBER CANCER INSTITUTE's Belfer Institute of Applied Cancer Science and sanofi-

aventis have entered into a collaboration and license option agreement to identify and validate novel oncology targets for further discovery and development by sanofi-aventis of therapeutics agents directed to such targets and related biomarkers.

Research at the Belfer Institute is focused on understanding the fundamental mechanisms of cancers, discovering and validating therapeutic targets and their clinical context in sophisticated model systems, enabling development of drug response biomarkers and supporting the discovery and development of innovative cancer treatments. Belfer Institute and sanofi-aventis' scientists will work jointly with the goal of discovering new anticancer drugs targeted at specific patient populations.

Under the terms of the agreement, Dana-Farber will receive $33 million in upfront and research funding for a minimum of three years. Dana-Farber will also be entitled to preclinical, clinical and commercial milestone payments and royalties on sales of commercial products. In return, sanofi-aventis obtains exclusive access to certain components of a transformative cancer target identification and validation platform originally developed in the laboratory of **Lynda Chin**, the Belfer Institute's scientific director.

DAVID CHERESH, professor of pathology at the University of California, San Diego School of Medicine and associate director for translational research at the Moores UCSD Cancer Center, has been named the 2010 recipient of the Paget-Ewing Award, the highest prize bestowed by the Metastasis Research Society.

Cheresh was honored at a recent joint meeting of the MRS and the American Association for Cancer Research in Philadelphia. In recent research, Cheresh and colleagues identified a key microRNA molecule that controls a molecular switch governing blood vessel growth.

JAMES THOMAS has been appointed professor of medicine in the division of hematology/oncology at The Medical College of Wisconsin and to the medical staff of Froedtert Hospital, a major teaching affiliate of the college. Thomas was an associate professor of medicine at Ohio State University, in the comprehensive cancer center. He directed clinical trial activity of 85 research staff. His clinical research interests are in early phase drug development.

Thomas also is chairman and chief executive officer of Perscitus Biosciences, LLC, a company he formed in 2006.

HHS News:

AHRQ Funds $473M Research In Comparative Effectiveness

The Agency for Healthcare Research and Quality said it has awarded $473 million in grants and contracts for patient-centered outcomes research, also known as comparative effectiveness research.

The funding covers all of AHRQ's allocation and $173 million administered for the HHS Secretary by AHRQ. The awards are part of the investments made under the American Recovery and Reinvestment Act of 2009, which included $1.1 billion to support patient-centered outcomes research. Of that total, $300 million was designated to AHRQ and $400 million was designated to be allocated at the discretion of the HHS Secretary for a variety of patient-centered outcomes research and related activities. An additional $400 million was directed to the NIH.

A list of awards by category is available at http://www.ahrq.gov/fund/recoveryawards/.

NIH News:

NIH Clinical Center Offers Sabbatical In Clinical Research

The NIH Clinical Center is accepting applications for a sabbatical program in clinical research management.

The program is open to clinical investigators, health care managers and administrators, and others who oversee clinical trials, including international research studies. Participants can expect flexible and specialized education in this field and the opportunity to work and learn with the full complement of clinical research experts at NIH, HHS, and FDA.

Sabbatical participants select electives from six core modules that offer exposure to all aspects of the clinical research environment: critical infrastructure, support services, legal and regulatory infrastructure, communications and outreach, strategic management, and funding opportunities.

There is no fee for participating in the program, and applications are accepted year-round. The Clinical Center expects to have approximately 10 participants per year. Stipends are not provided by the NIH for travel or living expenses, so it is expected that most individuals will be self-supported or supported by their home institution.

For further information, visit http://clinicalcenter.nih.gov/training/sabbatical/index.html

NEW NIH INSTITUTE: The National Center on Minority Health and Health Disparities (NCMHD) at NIH has become an institute: The National Institute on Minority Health and Health Disparities (NIMHD).

The transition, as a result of the Affordable Care Act, gives the institute a more defined role in the NIH's research agenda against health disparities, which it defines as differences in the incidence, prevalence, mortality, and burden of diseases and other adverse health conditions among specific population groups.

The move authorizes the NIMHD to plan, coordinate, review and evaluate all minority health and health disparities research activities conducted and supported by NIH, and it reaffirms the authority of the NIMHD director as the primary federal official with responsibility for coordinating such activities.

"We have made some progress towards eliminating health disparities. Yet there is much unfinished business," said John Ruffin, NIMHD director. "We have to reexamine our strategy and accelerate the pace through innovative, sustainable and results-oriented approaches. Our goal is to establish an integrated research enterprise, building upon lessons learned and working with our many partners to address the complexity of health disparities."