THE CANCER LETTER

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Learning from Duke

NCI Sets Rules For Omics Studies

By Paul Goldberg

Genomics researchers at Duke University revolutionized the conduct of genomics studies—though not in the way they intended to.

In the latest bit of aftermath of the controversy which resulted from Duke's enrollment of patients in studies based on faulty predictor models, NCI published the final version of a checklist of best practices that should be followed for development and evaluation of predictors based on "omics" technologies.

By publishing two papers that set forth a 30-item checklist in the journals Nature and BMC Medicine Oct. 17, NCI is hoping to set a standard for its own trials, as well as the trials sponsored by other government entities, funding agencies, and the industry.

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Exit Joseph Nevins

Duke's Genomics Luminary Quietly Leaves

By Matthew Bin Han Ong

Joseph Nevins, a genomics scientist at Duke University and the one-time mentor of disgraced cancer researcher Anil Potti, has retired—quietly, without fanfare.

There was no formal announcement from Duke; only a short sentence at the end of his faculty bio signaled his departure: "Dr. Nevins retired from Duke University in 2013."

The Institute for Genome Science & Policy page lists Nevins's personal Gmail—as opposed to a duke.edu—email address. (He did not respond to emails from The Cancer Letter.)

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In Brief

Barakat Named Deputy Physician-in-Chief Of Sloan-Kettering's Regional Care Network

RICHARD BARAKAT was appointed deputy physician-in-chief for the **Memorial Sloan-Kettering Regional Care Network and Alliance**.

Barakat will step down from his role as chief of the Gynecology Service, but will remain an active member of the surgical team. Barakat came to Memorial Sloan-Kettering in 1989 as a fellow in gynecologic oncology and was named chief of the service in 2001.

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Two Papers List What It Takes To Run Omics-Based Studies

(Continued from page 1)

In addition to providing guidance on best practices, the checklist will serve as a prospective guide for evaluating proposals for clinical trials.

"The bigger the potential impact, the greater the opportunity for harm, if things are done poorly," said William Bigbee, a past leader of the Cancer Biomarkers Facility at the University of Pittsburgh Cancer Institute, the outgoing chair of the NIH Cancer Biomarkers Study Section, and co-author of the two papers. "That was certainly on everybody's minds: what can we do to be as careful and rigorous as we can? This was at least our collective wisdom on a great place to start."

While the Duke controversy created the urgency to act, the checklist is also based on a wealth of accumulated experience in developing such technologies and using them in clinical trials or on specimens collected from clinical trials.

"Duke brought it to everyone's attention how badly things can go wrong, but we've seen plenty of other situations that didn't have all the other issues that the Duke story had," said Lisa McShane, a biostatistician at the Biometric Research Branch of the NCI Division of Cancer Treatment and Diagnosis and the lead author on the two papers.

Other examples involved "honest investigators who were trying to develop a test and simply overlooked some important factors," McShane said to The Cancer Letter. "We have learned just like all the investigators have learned over the years—that the questions in the checklist are the right questions to ask."

Throughout the Duke controversy, NCI officials have been adamant about focusing exclusively on the high-level scientific and policy questions that the case illustrated.

A related inquiry by the Institute of Medicine, which was requested by NCI Director Harold Varmus, similarly steered away from forensics, focusing instead on proper pathways for conducting clinical trials utilizing genomics predictor models.

The two papers rely on the IOM committee's definition of omics as "the study of related sets of biological molecules in a comprehensive fashion."

An omics-based test is defined as "an assay composed of or derived from multiple molecular measurements and interpreted by a fully specified computational model to produce a clinically actionable result."

McShane said the checklist complements the IOM report by applying its principles prospectively.

"We were aiming to establish a handy reference that people could use as they are going through the process of developing one of these tests," McShane said. "I think the IOM report was terrific. There is a wealth of information there, and they did a beautiful job laying out the principles.

"What we wanted to have was almost a pocket guide to operationalize those principles," McShane said. "If somebody is doing a study, they would be able to refer to this checklist as a reminder of the things they should be thinking about."

There are many places to go wrong.

"Almost every single one of these items in the checklist is there, because we learned a lesson at some point in a study," McShane said. "For example, it's fundamental to have researchers write down the form of the omics test. Yet, on more than one occasion we received proposals where no one can even write down what the test is."

"These are simple things, like making sure that there are no batch effects in the omics data, making sure that you have actually done a little pilot to see that the types of specimens that you are going to be able to get in clinical settings will be appropriate for a successful use of your omics assay.

"We've had cases, not necessarily tests that were ready to be used to guide patient therapy, but earlier in the development process, where someone ran their test in the archived specimens from a previously conducted

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clinical trial and only 20 to 30 percent of the specimens produced usable results.

"The checklist says this is something to think about before you go launching in to analyzing 300 specimens. Another example would be the reproducibility: we will ask the simple question, 'Have you run the test on the duplicate portions of 10 specimens and do you get reasonably concordant results?'"

Now, NCI expects to use the checklist to evaluate proposed studies.

"We really want this to be helpful," McShane said. "We don't want it to be a set of draconian rules from NCI. We believe that if people start asking these questions earlier in the process, the whole system of developing omics tests will be much more efficient, and we will get better products out in the end.

"We will be looking for evidence that these best practices have been followed and that the relevant information has been acquired when we review protocol submissions. Investigators will need to document for us that they have addressed each of these items if they are proposing to use an omics test in the trial."

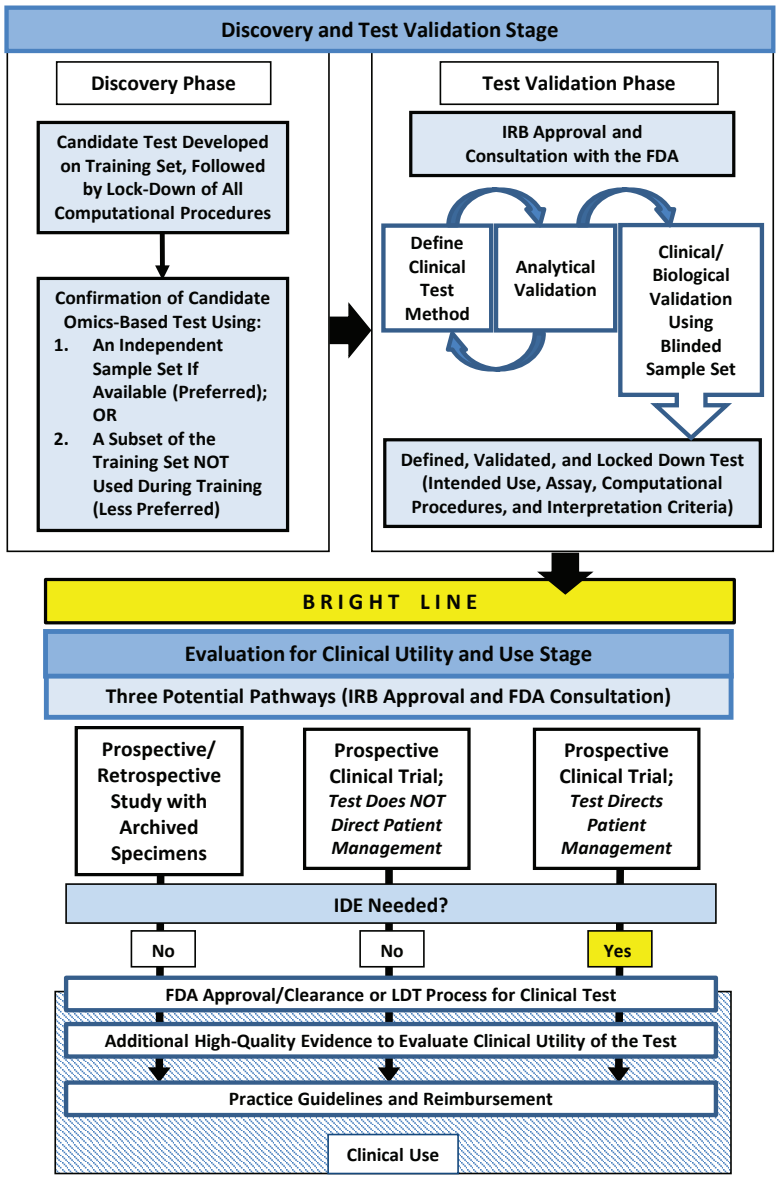
Will the industry pay attention to the NCI checklist?

"If they are going to be requesting specimens from NCI-sponsored trials, they would be well advised to listen to us."

Bigbee said good practices are the same regardless of who is sponsoring the studies.

"This is regarded as a very important issue by the leadership at the NCI, and trying to get something of a formalism in place that investigators can think about, but also that the NCI can use as a metric to hold up to their internal evaluations of NCI-sponsored clinical trials to be sure that these potentially very powerful omic-based predictors are valid and are used appropriately in the context of NCI-sponsored clinical trials," he said.

"Of course, the fact that these things can be used in clinical trials rather than just as a research exercise really raises the ante for the need for rigor across the board in the development, annotation and validation of these complex omics predictors."



NOTE: The computational procedures are locked down in the discovery phase, meaning they are recorded and no longer changed in the subsequent development steps. A clinical test should be fully defined, validated, and locked down before crossing the bright line to enter the stage in which the test undergoes evaluation for its intended clinical use.

From the brief of the IOM report "Evolution of Translational Omics: Lessons Learned and the Path Forward"

How a Workshop Became a Paper in Nature

"The checklists introduced by McShane, et al., (Nature, BMC Medicine) are not rocket science," said Keith Baggerly, a biostatistician at MD Anderson Cancer Center whose investigation brought the Duke controversy into public view.

"They are neither conceptually difficult nor surprising," Baggerly said to The Cancer Letter. "They are, however, necessary, because all too often the questions allowing these points to be addressed have been overlooked.

"This has slowed progress and could potentially put patients at undue risk. The main import is that these checklists will now be used by NCI in evaluating trials they fund. This is a change in policy.

"While the checklists target clinical trials, they are also useful in terms of thinking about papers (which come before), and eventual marketing of any assays (which comes after).

"Papers where these points have been addressed are more likely to yield reproducible results. FDA approval will be contingent on much of the same information described. If the end goal is to affect clinical care, it is worth having these points in mind throughout the process."

The checklist grew out of a workshop, which NCI convened on June 23-24, 2011.

"We wanted to get all of the players together to discuss this, to understand that there are problem areas in this process, but we can address them," McShane said. "That's why we thought it was important to bring in all the experts we brought into this paper, covering all these five domains in the checklist: assays, specimens, statistical issues, the trial design issues, the regulatory, ethical and legal issues."

"Everybody had to be talking to one another. This couldn't be just statisticians jumping up and down on the stage, screaming that everybody is doing the statistical modeling wrong. And it couldn't be a pathologist saying that these specimens are no good. We had to all get together and understand the problems together and have that communication going.

"Even when we put together the workshop that created the seed for this paper, we wanted to make sure that we had all of those people involved."

NCI posted a draft version of the checklist on its website for public comment earlier this year (The Cancer Letter, Feb. 8), and submitted the accompanying papers to the journals. Since Nature couldn't accommodate the length, a longer version was published by BMC Medicine which elaborates on the rationale for each checklist items and provides useful references to explain the type of information that is being requested.

Though NCI had weeks to prepare to roll out the publication, the press office ended up having to scrap its plans to issue a press release and arrange interviews when the government shut down, sources said.

At that time, the NIH press office routinely declined to respond to media inquiries not relating to the federal government shutdown. Happily for McShane, the government reopened on the day the papers were published.

NCI's 30 Criteria For the Use Of Omics-based Predictors

Source: *Nature*

Specimen Issues

1. Establish methods for specimen collection and processing and appropriate storage conditions to ensure the suitability of specimens for use with the omics test.

2. Establish criteria for screening out inadequate or poor-quality specimens or analytes isolated from those specimens before performing assays.

3. Specify the minimum amount of specimen required.

4. Determine the feasibility of obtaining specimens that will yield the quantity and quality of isolated cells or analytes needed for successful assay performance in clinical settings.

Assay Issues

5. Review all available information about the standard operating procedures (SOPs) used by the laboratories that performed the omics assays in the developmental studies, including information on technical protocol, reagents, analytical platform, assay scoring, and reporting method, to evaluate the comparability of the current assay to earlier versions and to establish the point at which all aspects of the omics test were definitively locked down for final validation.

6. Establish a detailed SOP to conduct the assay, including technical protocol, instrumentation, reagents, scoring and reporting methods, calibrators and analytical standards, and controls.

7. Establish acceptability criteria for the quality of assay batches and for results from individual specimens.

8. Validate assay performance by using established analytical metrics such as accuracy, precision, coefficient of variation, sensitivity, specificity, linear range, limit of detection, and limit of quantification, as applicable.

9. Establish acceptable reproducibility among technicians and participating laboratories and develop a quality assurance plan to ensure adherence to a detailed SOP and maintain reproducibility of test results during the clinical trial.

10. Establish a turnaround time for test results that is within acceptable limits for use in real-time clinical settings.

Model Development, Specification, and Preliminary Performance Evaluation

11. Evaluate data used in developing and validating the predictor model to check for accuracy, completeness, and outliers. Perform retrospective verification of the data quality if necessary.

12. Assess the developmental data sets for technical artefacts (for example, effects of assay batch, specimen handling, assay instrument or platform, reagent, or operator), focusing particular attention on whether any artefacts could potentially influence the observed association between the omics profiles and clinical outcomes.

13. Evaluate the appropriateness of the statistical methods used to build the predictor model and to assess its performance.

14. Establish that the predictor algorithm, including all data pre-processing steps, cutpoints applied to continuous variables (if any), and methods for assigning confidence measures for predictions, are completely locked down (that is, fully specified) and identical to prior versions for which performance claims were made.

15. Document sources of variation that affect the reproducibility of the final predictions, and provide an estimate of the overall variability along with verification that the prediction algorithm can be applied to one case at a time.

16. Summarize the expected distribution of predictions in the patient population to which the predictor will be applied, including the distribution of any confidence metrics associated with the predictions.

17. Review any studies reporting evaluations of the predictor's performance to determine their relevance for the setting in which the predictor is being proposed for clinical use.

18. Evaluate whether clinical validations of the predictor were analytically and statistically rigorous and unequivocally blinded.

19. Search public sources, including literature and citation databases, journal correspondence, and retraction notices, to determine whether any questions have been raised about the data or methods used to develop the predictor or assess its performance, and ensure that all questions have been adequately addressed.

Clinical Trial Design

20. Provide a clear statement of the target patient population and intended clinical use of the predictor and ensure that the expected clinical benefit is sufficiently large to support its clinical utility.

21. Determine whether the clinical utility of the omics test can be evaluated by using stored specimens from a completed clinical trial (that is, a prospective–retrospective study).

22. If a new prospective clinical trial will be required, evaluate which aspects of the proposed predictor have undergone sufficiently rigorous validation to allow treatment decisions to be influenced by predictor results; where treatment assignments are randomized, provide justification for equipoise.

23. Develop a clinical trial protocol that contains clearly stated objectives and methods and an analysis plan that includes justification of sample size; lock down and fully document all aspects of the omics test and establish analytical validation of the predictor.

24. Establish a secure clinical database so that links among clinical data, omics data, and predictor results remain appropriately blinded, under the control of the study statistician.

25. Include in the protocol the names of the primary individuals who are responsible for each aspect of the study.

Ethical, Legal and Regulatory Issues

26. Establish communication with the individuals, offices, and agencies that will oversee the ethical, legal, and regulatory issues that are relevant to the conduct of the trial.

27. Ensure that the informed consent documents to be signed by study participants accurately describe the risks and potential benefits associated with use of the omics test and include provisions for banking of specimens, particularly to allow for 'bridging studies' to validate new or improved assays.

28. Address any intellectual property issues regarding the use of the specimens, biomarkers, assays, and computer software used for calculation of the predictor.

29. Ensure that the omics test is performed in a Clinical Laboratory Improvement Amendments-certified laboratory if the results will be used to determine treatment or will be reported to the patient or the patient's physician at any time, even after the trial has ended or the patient is no longer participating

in the study.

30. Ensure that appropriate regulatory approvals have been obtained for investigational use of the omics test. If a prospective trial is planned in which the test will guide treatment, consider a pre-submission consultation with the U.S. Food and Drug Administration.

Exit Joseph Nevins

Duke Genomics Scientist Retires

(Continued from page 1)

A search of Duke's faculty directory lists Nevins as retired and located off campus. No phone number is given.

The problems with genomics studies at Duke have prompted NCI and the Institute of Medicine to formulate guidelines for proper conduct of studies based on genomics analysis. The controversy also triggered a lawsuit against Duke and was the subject of a 60 Minutes feature.

Duke officials declined to comment on the status of an ongoing misconduct investigation stemming from the affair. Similarly, it is not publicly known whether the investigation is related to Nevins's retirement.

Nevins and Potti were business partners as much as they were colleagues, garnering millions of dollars in grants as well as investments in their company, CancerGuideDX, which controlled the predictor model the team developed.

The Duke trials enrolled 117 cancer patients who were assigned to therapy based on a genomics analysis that was later found to be fraudulent.

The scandal exploded after The Cancer Letter reported that Potti had inflated his credentials, falsely claiming to have been a Rhodes Scholar (The Cancer Letter, July 16, 2010).

The clinical trials were subsequently stopped, leading to a wave of retractions in the world's premier scientific journals, including The New England Journal of Medicine, Nature Medicine, JAMA, The Journal of Clinical Oncology, and The Lancet Oncology.

Even as retractions accumulated, Nevins remained a stalwart supporter of his protégé, and vigorously defended Potti's work.

In an interview with The Cancer Letter early in the controversy, Nevins said the Duke results had been confirmed by researchers at the European Organization for Research and Treatment of Cancer and were published by Lancet Oncology in December 2007.

"Data was made available to us, blinded," Nevins said to The Cancer Letter at the time. "All we got was the gene expression data. We ran the predictions and sent it back to the EORTC investigators, including the statisticians in the EORTC group.

"They took the results, analyzed it in the context of the clinical responses in that study, and did further analyses with respect to evaluating developing combined probability measures. Even if you just look at the predictions for single agents in that study that came from our predictions—that was completely blinded to us—there is a clear ability to predict in the two arms of the trial with the individual predictors." (The Cancer Letter, Oct. 2, 2009).

The study, it turned out, was not blinded, Duke's European collaborators of the Duke team said to The Cancer Letter at the time. The data originally sent to Duke had never been masked in any way. (The Cancer Letter, Oct. 23, 2009)

Indeed, the specimens were labeled according to whether each was a responder or non-responder. This was confirmed by details The Cancer Letter obtained from the European researchers.

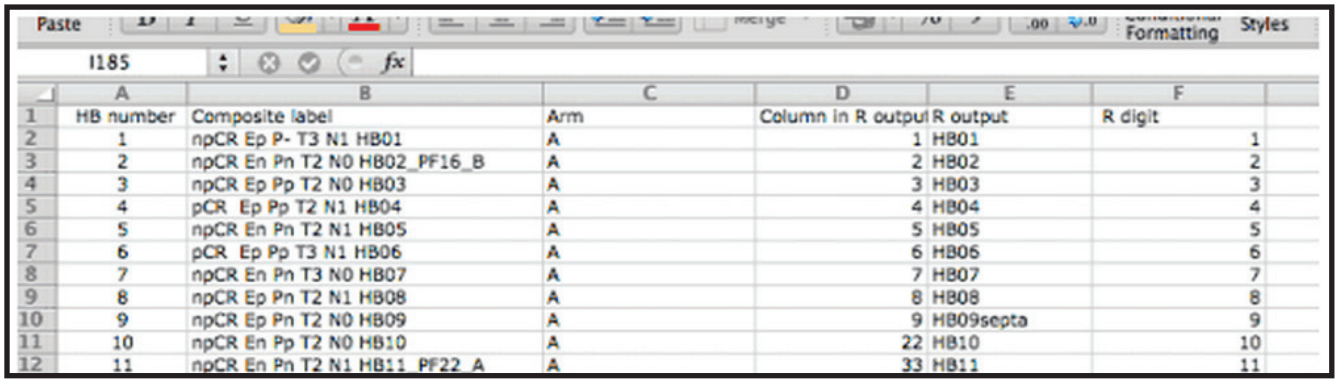
"Many subsequent problems might have been avoided, including perhaps initiation of treatment trials based on flawed analysis and conclusions, if proper attention had been paid to this claim of 'blinded validation,' because blinded hypothesis-testing using totally independent data is such a powerful tool to demonstrate that a result is real," said David Ransohoff, a cancer screening researcher and subspecialist/gastroenterologist at the University of North Carolina. Ransohoff worked with the Institute of Medicine committee that was appointed to examine the lessons learned from the Duke affair.

"The claim of blinded validation using EORTC data effectively silenced many observers, even though the paper itself did not contain the word 'blinding' and the paper's text said that the authors, including Nevins and Potti, 'had full access to the raw data.'

"Observers were left to speculate that that full access had happened following some initial blinded analysis," Ransohoff said to The Cancer Letter. "It turned out, though, that the data had been fully identified when initially sent from Europe, making blinding virtually impossible in the first place.

"In retrospect, it is interesting that none of the authors wrote a statement about blinding in the article itself and that reviewers and journal editors did not require it."

Testifying before the IOM committee in March 2011, Nevins alluded to "nonrandom data corruption,"



	A	B	C	D	E	F
1	HB number	Composite label	Arm	Column in R output	R output	R digit
2	1	npCR Ep P- T3 N1 HB01	A	1	HB01	1
3	2	npCR En Pn T2 N0 HB02_PF16_B	A	2	HB02	2
4	3	npCR Ep Pp T2 N0 HB03	A	3	HB03	3
5	4	pCR Ep Pp T2 N1 HB04	A	4	HB04	4
6	5	npCR En Pn T2 N1 HB05	A	5	HB05	5
7	6	pCR Ep Pp T3 N1 HB06	A	6	HB06	6
8	7	npCR En Pn T3 N0 HB07	A	7	HB07	7
9	8	npCR Ep Pn T2 N1 HB08	A	8	HB08	8
10	9	npCR Ep Pn T2 N0 HB09	A	9	HB09septa	9
11	10	npCR En Pp T2 N0 HB10	A	22	HB10	10
12	11	npCR En Pn T2 N1 HB11_PF22_A	A	33	HB11	11

Nothing Left to Chance: The top of the data set that Duke researchers used to validate their predictor model. In a 2009 interview with The Cancer Letter, Nevins said the validation was blinded. It was not. The data set is posted on The Cancer Letter website.

which rendered the results null and void. Given the data corruption, he said that some of the papers needed to be retracted (The Cancer Letter, April 1, 2011).

During the presentation, Nevins seemed to avoid mentioning Potti by name. He refrained from criticizing his collaborators, the Duke administration—and himself.

Less than a year later, Nevins said that Potti had manipulated data that laid the foundation for Duke's clinical trials of the technology (The Cancer Letter, Feb. 17, 2012).

"There was no explanation other than there was a manipulation," Nevins said in an interview with 60 Minutes. "A manipulation of the data, a manipulation of somebody's credentials and a manipulation of a lot of people's trust… It simply couldn't be random. It simply couldn't be inadvertent. It had to have been based on a desire to make something work."

Duke is facing a lawsuit brought by patients involved in the clinical trials.

Plaintiffs claim that they were subjected to "improper and unnecessary chemotherapy, and improper treatment of the plaintiffs' cancers based upon falsified medical research submitted to the United States government and its entities, various peer reviewed medical and scientific journals and to the wider public," according to the lawsuit.

"Plaintiffs' claims are based, in part, upon information and belief that all defendants have engaged in a systemic plan to develop for-profit cancer test for the primary purpose of generating billions of dollars in revenue; and that rather than actively protecting the safety and right of patients in proper clinical trials, they chose a path of conduct that was evasive, deceptive, misleading and fraudulent by falsely representing that the delivery of chemotherapy agents to human subjects was based on valid science, when in fact they either knew or should have known that it was not."

Five individuals, including Nevins and Potti, are named as defendants, along with Duke and the Duke University Health System.

"Duke University and/or DUHS withheld information from the plaintiffs regarding the fact that receiving chemotherapy at a particular stage of plaintiffs' cancer may not be beneficial to him or her and that he/she could appropriately decide to forego such treatment and all of the pain, injury and suffering caused by the administration of chemotherapy," the lawsuit stated.

The university did not notify the participants of the problems in the clinical trials, according to the lawsuit. The next hearing has not been announced.

The complaint is available on The Cancer Letter website.

Duke confirmed that Nevins was employed from June 1, 1987 to Aug. 31, 2013, and declined further comment. "It is Duke's policy not to provide information about personnel matters," university officials said.

The Duke Scandal

Nevins is a recognized leader in gene regulation and oncogenic mechanisms.

He served as chair of the department of molecular genetics and microbiology, and then as the Barbara Levine Professor of Breast Cancer Genomics. Nevins was also the founder of Duke's Center for Applied Genomics and Technology.

Nevins's career was going well.

Then, in 2006, Nevins and Potti published two papers—in Nature Medicine and NEJM—claiming to have produced two predictor models.

The promise of the studies the Duke team had published was extraordinary—by designing systems capable of predicting response and therefore enabling

oncologists to assign patients to optimal therapy, the entire enterprise of cancer treatment could be pulled up a notch.

On the down side, a bad biomarker can be more harmful than a bad drug: patients may end up assigned to ineffective therapy, denying them the opportunity to receive more effective therapy.

But the team's results were compelling, and journal after journal published their papers.

Things would have continued to go well were it not for John Minna, a lung cancer expert at UT Southwestern, an institution that participates in the lung cancer SPORE grant with MD Anderson.

Sometime after the 2006 Nature Medicine paper came out, Minna asked the SPORE's statistician, Kevin Coombes, to look into it. Coombes brought in his colleague, Keith Baggerly, also of MD Anderson.

Baggerly and Coombes started their efforts to check the Duke team's claims after oncologists at M.D. Anderson asked whether the approach was ready for use in the clinic.

Practicing a subspecialty they call "forensic bioinformatics," Baggerly and Coombes devoted about 1,500 hours to recreate the Duke team's work step-by-step, and found that the Duke team made multiple errors.

From 2007 to 2009, they documented these errors and presented critiques to journals that have published papers by the Duke team (The Cancer Letter, Oct. 2, 2009).

In September 2009, they published a paper in a journal called the Annals of Applied Statistics, where they claimed that patients enrolled in Duke clinical trials could be harmed by reliance on the Nevins-and-Potti predictors to choose therapy.

"Patients in clinical trials are currently being allocated to treatment arms based on these results," Baggerly and Coombes wrote. "However, we show in five case studies that the results incorporate several simple errors that may be putting patients at risk."

One example was an "off-by-one" error, where gene probe identifications were mismatched with the names of genes. Rows were literally off by one space, which rendered a table meaningless. The Duke group acknowledged this mistake and others in a letter published in the November 2007 issue of Nature Medicine.

Duke researchers said that their errors were minor and had no bearing on the findings.

"We stand by our work," said Potti, then a medical oncologist and an assistant professor. "Yes, we have made mistakes, and, actually, we've learned from those mistakes. Because we recognized that the mistakes were manual mistakes—mistakes of cut-and-paste—we have automated the entire process."

In the Duke clinical studies "there is no manual error possibility," Potti said in an interview at the time.

The Annals of Applied Statistics invited the Duke researchers to respond to the Baggerly and Coombes paper in writing, but they declined.

After the Baggerly and Coombes paper, Duke suspended two of its randomized clinical trials, then suspended the third. The Institutional Review Board started a review.

By January 2010, Duke's review of the scandal was completed. The Cancer Letter asked for a copy of the review, but Duke refused to reveal the details.

"The reviewers concluded that 'the approaches used in the Duke clinical predictors are viable and likely to succeed,' and 'we believe the predictors are scientifically valid,'" said a statement from Duke.

The university restarted its three trials and CancerGuideDX, the Duke team's company, received $10.5 million in commitments, $2 million of which changed hands, according to a company press release issued at the time.

Then, on July 16, 2010, The Cancer Letter reported that Potti had falsified his credentials.

The Cancer Letter obtained two versions of Potti's biographies that were submitted to NIH—the documents show that Potti claimed variously to have won a Rhodes scholarship in 1995 or 1996 (The Cancer Letter, July 16, 2010).

He also made the Rhodes claim in an application that resulted in a $729,000 grant from the American Cancer Society.

Potti resigned from Duke in November 2010, and got a job at Coastal Cancer Center in South Carolina. That institution ended its relationship with him in February 2012.

"A recent 60 Minutes story concerning an investigation of Duke University's cancer research programs and Dr. Potti's work there prompted many concerned people to contact Coastal Cancer Center with comments and questions," said Lawrence Holt Jr., president of Coastal Cancer Center. "It has become obvious that this issue is going to take precious focus away from patient care. Coastal Cancer Center is staffed by incredibly caring people who want and need to concentrate on providing outstanding patient care.

"We received glowing references about Dr. Potti's character and skills from the highest ranks of the Duke

University School of Medicine and Duke University Medical Center," Holt said. "We were assured by Duke Medical's leaders that Anil was 'outstanding in all categories,' 'had excellent clinical skills' and that he had conducted himself at Duke with 'honesty, integrity and humility.'

"One Duke University director even went so far as to say he would be pleased to have Dr. Potti as the treating physician 'if my own family had unfortunately contracted a cancer,'" Holt said.

According to the statement, letters of recommendation came in from the chief of Duke Medical's Division of Medical Oncology, the director of Hematologic Malignancies Program, and several professors.

When Potti announced his resignation from Duke, Huntington Willard, director of the Duke Institute for Genome Sciences & Policy, wrote in an email:

"In a letter to me, [Potti] accepted full responsibility for a series of anomalies in data handling, analysis and management that have come under scrutiny in the past months," Willard wrote (The Cancer Letter, Nov. 19, 2010).

"As dismaying as this series of events is, it provides an opportunity for reflection about what we do and how we do it, and it offers important, if painful, lessons for us all."

Potti is currently employed as a hematology/oncology physician at the Cancer Center of North Dakota in Grand Forks.

Paul Goldberg contributed to this story.

The Shutdown

NIH Returns to Play Catch Up "After 16 Costly, Wasteful Days"

By Matthew Bin Han Ong

Sixteen days after hardline GOP lawmakers forced the U.S. government into a shutdown, a frenzied Congress voted late Wednesday night to reopen federal agencies and raise the $16.7 trillion debt limit—barely meeting a critical deadline set by the Treasury Department.

President Barack Obama signed the bill shortly after midnight, restoring government services and putting hundred of thousands of furloughed civil servants back to work Thursday morning, many of them in the Washington, D.C. region.

The measure only guarantees current-level funding through Jan. 15. Federal agencies might face another shutdown unless Congress resolves a continuing dispute on the deep automatic spending cuts known as the sequester.

The bill also raises the debt limit to a level the Treasury expects will last until Feb. 7, setting up a second confrontation over the national debt.

Economists estimate the shutdown cost the U.S. economy $24 billion, as well as 0.6 percent from the country's fourth-quarter growth of its gross domestic product, according to Standard & Poor's.

"One of the things I've said in this process is we've got to get out of the habit of governing by crisis," Obama said Wednesday night. "Hopefully next time it

won't be in the eleventh hour."

NIH staff is reporting to work on their regular schedules, and NIH is ramping up to full operation as quickly as possible to recover from the impact of the shutdown.

The NIH Clinical Center, which was forced to turn away patients during the shutdown, including children with cancer, is now fully operational—initiating new clinical protocols and resuming its normal patient admission process.

While the government was shut down, only a small number of new patients with life-threatening illnesses were admitted, and only one new clinical trial involving such patients was begun. Nearly 75 percent of NIH employees were furloughed (The Cancer Letter, Oct. 4).

The shutdown resulted in a profound loss of momentum, NIH officials said in a statement.

"While some basic and translational research projects involving large or unique investments of resources continued at a greatly reduced pace to protect these investments, the majority of research projects were placed on hold," they said.

"Hundreds of experiments will require starting over, which may take many months.

"While researchers with existing grants were able to draw down funds during the shutdown, NIH was not able to process new grant applications or make any new or continuing grant awards.

"All submission deadlines for grant applications that were scheduled in October are being rescheduled for November so that applicants can have access to NIH staff to assist with the application process.

"Hundreds of peer review meetings that had been scheduled in October must now be rescheduled, and there will be some delays in grant awards. Specific dates will be shared with the research community through the NIH Guide for Grants and Contracts."

In an email to staff and grantees Oct. 11, NCI Director Harold Varmus said the shutdown was felt most acutely by staff and investigators in the intramural program, but the effects on the extramural research community would worsen if the shutdown persisted.

"NCI's Division of Extramural Activities has postponed until undetermined dates several site visits to evaluate re-competing centers and large grant applications, and it has postponed more than a dozen meetings to review grant applications," Varmus wrote.

"Thus, the NCI's grant review cycle could be significantly delayed, threatening a smooth restart of NCI's support of extramural research, even if the NIH reopens relatively soon.

"This situation could have serious effects on the review and funding of virtually all NCI programs, including NCI-designated Cancer Centers, program project and SPORE grants, training awards, and individual research project grants."

Professional Societies: No More Shutdowns, Please

Congress must avoid a repeat of this debacle at the end of the short-term deal, said Jon Retzlaff, managing director of office of science policy and government affairs at the American Association for Cancer Research.

"While we are relieved that the shutdown is finally over and that many of our nation's talented and dedicated scientists and clinicians are back conducting the research that so many patients are dependent on, we are concerned that we may see this indefensible situation repeat itself in three months," Retzlaff said to The Cancer Letter.

"If our policymakers are going to be able to move beyond this latest fiasco and begin supporting some of our nation's priorities, such as the medical research that is funded by the NIH, it is going to require that Congress work in a constructive, bipartisan fashion to find a more balanced approach to address the federal deficit and prevent sequestration from occurring again in January 2014.

"Congress cannot continue to look at the domestic discretionary pot to come up with their deficit reduction," Retzlaff said.

The government shutdown brought into focus the importance of funding for biomedical research, said Clifford Hudis, president of the American Society of Clinical Oncology.

"Now, our colleagues at NIH and the FDA can continue with their critical life-saving medical research and the advancement of safe and effective drugs into practice," Hudis said in a statement to The Cancer Letter. "Patients can again enroll in clinical trials at the NIH Clinical Center.

"NIH grant administrators can continue to schedule reviews of grant applications submitted by researchers around the country who are finding ways for all of us to lead healthier and longer lives.

"NIH programs to train the next generation of researchers can continue. FDA staff can resume monitoring drug shortages and drug safety, and reviewing new drug applications.

"Clearly, federal funding for biomedical research pays for a lot of work that improves the health of

Americans and contributes to economic growth for the U.S.," Hudis said. "Now, it's time for Congress and the Administration to work together to pass a budget that will enhance our country's commitment to individuals with cancer."

In the short term, the biggest impact of the shutdown will be the disruption to the grant funding cycle, said Carrie Wolinetz, president of United for Medical Research.

"Rescheduling cancelled study sections and Council meetings, and getting grants reviewed by the new deadlines will be a monumental undertaking, and it's hard to see how there will not be some delay in the next round of extramural funding," Wolinetz said in a statement to The Cancer Letter.

"But the aftermath of the shutdown is minute in comparison with the continuing impact of sequestration and the prospect of further cuts to come when the current continuing resolution expires in January."

In a statement to research advocates, Research!America President Mary Woolley wrote:

"After 16 costly, wasteful days, the government has been funded through Jan. 15 at post-sequestration, FY13 levels—hardly adequate for providing the solutions the American public awaits.

"A bicameral, bipartisan budget committee has been charged to develop a long-term deficit reduction plan by Dec. 13. If these marching orders sound familiar, they should: We've been down this road before, only this time sequestration isn't the threat at the end, it's embedded in the negotiations.

"As tempting as it is to give in to brinksmanship fatigue and just tune out the process, advocates must seize the opportunity to make sure our issue remains front and center, that it becomes impossible for lawmakers to ignore.

"Sequestration must go; research and innovation must be an immutable national priority, supported at the level of scientific opportunity that will allow us to overcome health challenges and continue to drive the economy."

The text of Varmus's Oct. 11 email follows:

To NCI staff, grantees, advisors, reviewers and others:

I am writing to keep you abreast of the ways in which the National Cancer Institute (NCI) and its extramural and intramural research programs have been—and are likely to be—affected by the current shutdown of the federal government.

And I am also writing to ask for your help in responding to the difficult situation that we are likely to face when the government is reopened.

As you have doubtless seen in the media, if not experienced directly, the NCI, along with the rest of the NIH, has been obliged to place on furlough many valuable employees, presently about 80 percent of our staff.

While all components of the NCI have furloughed many personnel, most of those we have been able to exempt from furlough are in our intramural programs and needed to preserve ongoing research protocols, ensure laboratory safety, care for experimental animals, and, especially, serve our patients at the Clinical Research Center.

This situation has been hard for everyone, particularly for many of our trainees, who have been told to limit their activities on campus to those permitted during the shutdown. They, like regular staff members, are unable to travel to scientific meetings or to perform much of the research they came to NCI to do.

Although the shutdown has been felt most acutely by our staff and investigators in the intramural program, the effects on the extramural research community are likely to become progressively greater as the situation persists.

Presently, the vast majority of NCI's extramural staff is furloughed, which means that many NCI staff members are unable to provide their usual administrative and programmatic support services to extramural grantees.

Furthermore, many grantees, especially those responsible for planning collaborative work, including clinical trials, have been limited in their abilities to conduct important meetings that require NCI staff and support.

Still, we have been able to exempt from furlough some program officers who provide oversight and guidance for clinical trials that were initiated prior to the shutdown. Moreover, the length of the shutdown has not been great enough to affect most ongoing research activities at extramural sites.

Since the Payment Management System has remained operational, we also continue to process requests to obtain expected funds for most of the grants awarded to our extramural investigators. However, that may not be possible if an award was made with restrictive terms or if a request triggers a need for additional interactions.

Now that the shutdown is nearing the end of its second week, however, further consequences are coming into view. While grant applications can be

accepted and stored at Grants.gov, the NIH Office of Extramural Research has discouraged submissions, and applications will not be processed further until normal business operations are restored through Congressional appropriations. (See the OER's message at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-13-126.html).

Furthermore, NCI's Division of Extramural Activities (DEA) has postponed until undetermined dates several site visits to evaluate re-competing centers and large grant applications, and it has postponed more than a dozen meetings to review grant applications. Thus, the NCI's grant review cycle could be significantly delayed, threatening a smooth restart of NCI's support of extramural research, even if the NIH reopens relatively soon.

This situation could have serious effects on the review and funding of virtually all NCI programs, including NCI-designated Cancer Centers, program project and SPORE grants, training awards, and individual research project grants.

Questions or concerns about these matters should be sent to John Czajkowski, NCI Deputy Director for Management, or to Dr. Paulette Gray, Director of the Division of Extramural Activities.

Part of the reason I am writing at this time is to prepare you for the possibility that we at the NCI (and presumably others at the NIH) will be asking reviewers and advisors to adapt to abrupt and inconvenient changes in the scheduling of meetings to review grant applications and oversee programs.

These changes may require you to alter long-standing plans to attend worthwhile events. But avoiding a major crisis in grant-making and program development this year may be possible only if all members of the NCI communities are willing to help alleviate the consequences of the shutdown.

Needless to say, all of us at the NCI hope that the current situation is resolved quickly, but we have no way to know when the shutdown will end. In the meantime, I encourage all of you to monitor major media outlets regularly, as we do, for updates on the status of federal operations.

As long as the shutdown continues, the NCI will remain committed to advancing our common cause—research to control cancer—as best we can within the limits of the law. Your patience, persistence, and flexibility are very much appreciated during this unhappy and uncertain time.

In Brief

Barakat Named MSKCC Network Deputy Physician-in-Chief

(Continued from page 1)

Barakat serves as president-elect for both the Society of Gynecology Oncology and the International Gynecologic Cancer Society.

In his newly created position, Barakat will be responsible for implementing and expanding the recently announced Memorial Sloan-Kettering Alliance (The Cancer Letter, Sept. 27), as well as an expansion of the network's clinical research program and surgical service.

DAVID ALBERTS was named director emeritus of the **Arizona Health Sciences Center**. He was director of the University of Arizona Cancer Center from 2005 to 2013.

The title is retroactive to July 1 and will accompany his current title of regents professor of medicine, pharmacology, nutritional science and public health. **Anne Cress** was named interim director of the UA Cancer Center on July 19.

Alberts helped pioneer treatments for advanced ovarian cancers, including in vitro tumor cell chemosensitivity testing for personalized medicine strategies, intraperitoneal chemotherapy, and maintenance chemotherapy. Currently, he helps coordinate phase I and II and pharmacokinetic drug studies at the cancer center for molecularly targeted chemopreventive agents.

Alberts has served as chair of the FDA Oncologic Drugs Advisory Committee and as a member of the NCI's Board of Counselors to the Division of Cancer Prevention, as well as the Board of Scientific Advisors and the coordinating subcommittee of NCI's Clinical Translational Advisory Committee.

ROBYN DIAZ was named chief legal officer and senior vice president of **St. Jude Children's Research Hospital**.

Diaz joined the hospital's Office of General Counsel as associate general counsel in August 2010 and was promoted to deputy general counsel in May 2012. Prior to joining St. Jude, Diaz was associate general counsel at MedStar Health and an attorney in the health care practice group at Crowell & Moring, LLP, both located in Washington, D.C.

Diaz served as an adjunct professor at the Georgetown University School of Nursing and Health Studies, teaching classes on law and health care

administration, and served as an academic preceptor to undergraduates in Georgetown's program in healthcare management and policy. She previously co-chaired the District of Columbia Bar Health Law Section Steering Committee.

THE ASSOCIATION OF COMMUNITY CANCER CENTERS honored 10 cancer programs with its **2013 Innovator Awards**.

The award recipients presented the details and outcomes of their programs at the ACCC National Oncology Conference in Boston. Many of this year's winning programs directly address issues highlighted in the Institute of Medicine report "Delivering High-Quality Cancer Care: Charting a New Course for a System in Crisis," published in September.

The award recipients are:

• **Avera McKennan Hospital and University Health Center and Avera Cancer Institute**, in Sioux Falls, S.D., for rural chemotherapy. The institute unified chemotherapy administration standards across 45 sites. Compliance across all sites that administer chemotherapy was achieved within nine months.

• **Baton Rouge General Medical Center and Pennington Cancer Center**, in Baton Rouge, La., for providing disaster charts and an informational security net for patients. Hurricane Katrina left cancer patients displaced and their treatments disrupted; the cancer center received patients with no records while their phone and fax lines were down and treating physicians were unreachable. The radiation oncology treatment team developed a portable electronic medical record that provides patients with their must-have documents in a universal format so that they may quickly resume care if displaced by a disaster.

• **The George Washington University and the GW Cancer Institute**, in Washington, D.C., for exceeding new accreditation standards for patient-centered care. A key goal identified in the recent IOM report is to "reduce disparities in access to cancer care for vulnerable and underserved populations." The GW Cancer Institute's Citywide Patient Navigation Network developed a program that helps patients navigate their cancer treatment. Lay navigators work with a social worker and nurse navigators to guide patients from screening through treatment and into survivorship care. The network served 2,840 D.C. area residents in 2012, of whom 86 percent were minority and nearly 30 percent were uninsured.

• **Gibbs Cancer Center & Research Institute**, in Spartanburg, S.C., for integrating palliative care into its medical oncology practice. This initiative added a half-day supportive care clinic into the medical oncology practice, expanding palliative care services beyond the inpatient setting, and increasing patient satisfaction and reducing distress symptoms.

• **Methodist Healthcare System and the Methodist Cancer Center**, of San Antonio, Texas, for emergent care for oncology patients through its Very Immunocompromised Patient Program. The center developed a process for rapid assessment and management of cancer patients with a low white blood cell count presenting to the emergency department. A kit educates patients on when to report to the ED and improves coordination of care with community-based physicians.

• **St. Luke's Mountain States Tumor Institute**, in Boise, Idaho, for improving oncology genetic counseling, and providing those living in rural communities access using a two-pronged approach—telehealth and weekly chart review.

• **Temple University Hospital and the Temple Cancer Program**, in Philadelphia, Pa., for creating transparency with an electronic dosimetry whiteboard. Treatment plan delays led to decreased patient satisfaction, care delays, low employee morale, and potential lost revenue. The whiteboard centrally displays the status of every case, allowing the staff to make process changes. The whiteboard led to improved patient satisfaction and employee morale as well as increased accountability.

• **Texas Health Harris Methodist Hospital and Klabzuba Cancer Center**, of Fort Worth, Texas, for community/corporate collaborations and mobile health outreach. When Klabzuba Cancer Center discovered that patients using mobile mammography services had unmet healthcare needs beyond mammograms, they adapted their mobile clinics to provide additional services including cancer, cardiovascular, and bone density screenings, pelvic and clinical breast examinations, and education for each service.

• **University of Texas Southwestern Medical Center and the Harold C. Simmons Comprehensive Cancer Center**, of Dallas, Texas, for CancerGene Connect, a virtual genetic counseling environment. Patients complete an online family and medical history that allows genetic counselors to calculate risk before the patient's visit.

• **Winship Cancer Institute of Emory University**, in Atlanta, Ga., for implementation of a community-based program for cancer survivors and caregivers. Winship implemented the community-based "Winship at the Y" program in collaboration with the YMCA of Metro Atlanta.