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Varmus: NCI Faces "Budgetary Disaster;" Flat Funds, Cuts Loom For Most Programs

By Paul Goldberg

NCI is facing a "budgetary disaster," Harold Varmus said at his second "town hall" meeting Jan. 10, six months after taking the job as institute director.

"When I was at this podium in July, I cautioned you not to expect miracles, like another doubling of the NIH budget, but I didn't expect a budgetary disaster," Varmus said, referring to his remarks July 12, 2010, the day he was sworn in by HHS Secretary Kathleen Sebelius (The Cancer Letter, July 16, 2010).

The institute has been operating on funds obtained through continuing resolutions, making do without increase over last fiscal year, and next

(Continued to page 2)

News Analysis:

Duke Deans Acknowledge Withholding Key Document From Outside Reviewers

By Keith Baggerly and Kevin Coombes

The Cancer Letter asked Baggerly and Coombes, biostatisticians at M.D. Anderson Cancer Center, to analyze the internal documents that were released by NCI for consideration by the Institute of Medicine committee reviewing the Duke scandal. The documents were released by the IOM to The Cancer Letter under the Public Access File procedures. Baggerly and Coombes spent four years investigating the too-good-to-be-true claims by Duke scientists.

We have been deeply involved in events leading to the IOM Review of the Use of Omics Signatures, and we are very familiar with the public information available.

We learned a great deal more from the first IOM committee meeting on Dec. 20, 2010.

At that meeting, Lisa McShane presented the NCI's view of the situation, mentioning several pieces of information previously known only to the NCI. Documentation (551 pages worth) was supplied to the IOM, and the IOM has now made these (and other) documents public (The Cancer Letter, Jan. 7).

Here, we present an annotated survey of the NCI documents (a timeline for the full set of events is available as a supplement) highlighting where various information can be found in the Public Access File (PAF) documents posted at *www.cancerletter.com/categories/documents*.

(Continued to page 6)

Reform of Groups, R01s, Genomics Will be Protected

(Continued from page 1)

year's outlook appears even more grim, as some conservative members of the House talk about rolling back appropriations to the 2008 level.

In a 45-minute-long speech, Varmus described the budget and his plans for redrawing the institute's priorities and broadening the scope of research it's now performing.

His plan: maintain the number of investigator-initiated grants, protect genomic research, and continue to revamp the clinical trials system. While these parts of the institute are likely to be shielded, most programs will see no increases, and cancer centers, intramural research, and noncompetitive grants may be cut.

Also, Varmus described his plans to formulate "provocative questions" that could stimulate high-risk research of the sort that generally doesn't succeed in standard peer review. In other new initiatives, the director said he has created the position of NCI associate director for cancer prevention and plans to expand the institute's international programs to increase its role in combating cancer in poor countries.

Varmus's first action as NCI director was to confront the Duke scandal, which threatens credibility of genomic research and public trust toward science (The Cancer Letter, June 16, 2010). As the scandal escalated last July, Varmus asked the Institute of Medicine to investigate both the Duke case and the underlying issues (The Cancer Letter, July 23, July 30, 2010; Jan. 7, 2011).

At the town hall meeting this week, Varmus addressed the broader issues arising from the case.

"We are trying to use the clinical trials system as a means of preparing the oncology community—including community docs—for the widespread introduction of molecularly-based therapies," Varmus said. "We are very conscious of the fact that this is not going to be an easy job, and that the standards for using molecular profiling to assign patients to therapies—or to place them in the right arms of a clinical trial—will require high standards. We've asked the IOM and its National Cancer Policy Forum, to undertake a study of how this is done, and that study is not only in operation already, but it has attracted quite a bit of attention."

The Budget

The text of Varmus's comments on the budget follows:

We are facing very, very difficult times. The problem that may be familiar to all of you can be summarized in three or four simple statements.

First, right now, NIH, and NCI, and all its components are operating under a continuing resolution until at least March 4. That means we are getting exactly the same amount of money from Congress as we got last year.

We have threats from some of the new members of the Republican leadership of the House to roll back to 2008 levels, and [it's not clear] how realistic those threats are for 2011, but they certainly are real for 2012, and we have to keep them in mind.

Although appropriation committees in both the House and the Senate in the last Congress approved increases, the hope of seeing that three-percent increase is vanishing. Maybe, eventually, there will be an appropriations bill that will give us some of that.

All of this adds up to uncertainty, and uncertainty complicates planning already made difficult by the prospect of not having more money than we did last year.

As you well know, all the institutes of the NIH have a large commitment base, and that commitment base is composed of the salaries that all of you have, the grants that we are already committed to, the centers, the contracts, intramural program, many things that already are expecting to receive at least what they received last year.

Some grants finish, and that creates some new money. Normally, NIH is sufficiently well respected by Congress that there is additional money on top of that as well, and we pay new grants out of all that.

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Editor & Publisher: Paul Goldberg

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Three Goals

Varmus presented a plan for managing the flat or declining budget, delineating protected programs from those likely to get cuts.

His comments follow:

I have three goals in this situation, other than just keeping the trains running.

First is to try to get to roughly the same number of new Research Project Grants as we did last year.

Last year, the number was 1,250. I view our new grants—especially new grants to new investigators—as the single best means to pursue new ideas.

If we have no new money—if we are operating under a continuing resolution the whole year—we need somewhere in the range of $100 million to $150 million of additional money gathered from some other part of our commitment base to achieve that.

Secondly, I want to be sure that our cancer genomics machines are full of fuel for this entire year and the foreseeable future. These are the reliable engines that are delivering discoveries that underlie much of what we are doing to develop new diagnoses, treatments, and prevention, and I want to be sure that those machines are running as close to full tilt as possible.

And thirdly, I want to be sure that we are paying for the critical changes that are going to have to occur in the clinical trials system. Some of them are cost-neutral, some of them have real costs, and we need to pay those.

How are we going to do this?

With a CR, we can't do all this without taking something out of the commitment base. So I am searching for dollars, with the help of many of my colleagues. Where am I looking? Well, first of all, it's fair to say that most programs will see no increase, but some programs are going to see some reductions.

I can't give you definite answers yet, because we don't know what the budget is actually going to be, so achieving the goals of funding an adequate number of grants, keeping genomics efforts in good health, and fixing the clinical trials system—we just don't know how much money we will need to get those things done.

But we are looking at all existing contracts, and elsewhere in our commitment base for places to cut.

There is some likelihood that we will be reducing payments to cancer centers, which have a fixed budget, but that budget can be cut by a modest degree, I believe, without fatal repercussions, and that will be less significant than failing to carry out the extra spending required to achieve an adequate number of grants.

We are having trans-NIH discussions—we do every year—about how much to spend on the noncompetitive renewal of grants. This is a very large fraction of any institute's budget, and even a small percentage reduction of a big number can generate many new grants. When you take NCI, it's 40 to 50 grants for every one percent that we don't spend on that number.

The expectation in good times is that we will increase most of the noncompeting renewals by about three percent. I think it goes without saying that any increase is unlikely for the continuing resolution, but there is consideration being given—not yet taken—for the possibility of making a one- or two-percent, or even three-percent, reduction below that level.

Likewise, intramural investigators can expect, for sure, that there will be no increase, and there could be a modest decrease. We will have to think about that as we get further into the year.

There is an additional issue: How do we conduct the awards process for new grants under these conditions? My colleagues on the science program leadership group are making a greater effort of stewardship of our new awards than has been done in the past.

This is more work for the scientific program leadership, but I think it's very much worthwhile. I realize that everybody in the extramural community wants to know whether he or she will get paid based on the priority score.

This year at least—and probably not in my tenure here—[there will not be] a simple payline.

Applications that have very high scores, seven or better, are virtually certain to be paid. But then you have to expect that there is a declining likelihood of funding down to 15th percentile, or even lower, depending on category of applications.

As you well know, there are applicants for new grants who have had previous grants, there are applicants who are first-time principal investigators, and there are some who are early-stage investigators who are within ten years of their last degree, and there are people who are applying in areas that are particularly high priority, applying for RFAs, applying for areas that are under-supported, and what I envision as a zone of uncertainty.

We are trying to award almost as many grants as last year in a responsible manner, and that manner in my view can't be one that's robotically responsive to priority scores under these circumstances.

Provocative Questions

Over the past six months, the institute has been trying to zero in on "provocative questions" and ways to fund research that would address them.

The opening lines on the institute's new website

on provocative questions offer the following definition of the initiative:

"The provocative questions project is intended to assemble a list of important but non-obvious questions that will stimulate the NCI's research communities to use laboratory, clinical, and population sciences in especially effective and imaginative ways. The questions should not be simple restatements of long-term goals of the National Cancer Program, which are to improve the prevention, detection, diagnosis, and treatment of all forms of cancer."

The website, http://provocativequestions.nci.nih.gov/?cid=Bq_nci, was launched on the day of the town hall meeting.

In his remarks, Varmus further described his rationale for the program:

We all recognize that there are some big questions that are restatement of our goals:

How do we treat cancer? How do we prevent it? How do we diagnose it?

But there are more subtle questions that build on findings that are ignored, findings that are not fully exploited, new technologies that allow us to go back and explain a phenomenon that had been mysterious in the past.

This exercise, which I called big questions, and which we now call provocative questions, perhaps is most easily exemplified by a question like "why does chemotherapy actually cure some cancers, like testicular cancer or a few others?"

We've made a lot of progress in trying to bring the community together to think about provocative questions. I've been helped in this exercise by a small leadership group that consists of [NCI Depity Director] Doug Lowy, Ed Harlow [head of the Department of Biological Chemistry and Molecular Pharmacology at Harvard Medical School], and Tyler Jacks [director of the David H. Koch Institute for Integrative Cancer Research at the Massachusetts Institute of Technology], in addition to myself.

We had our first workshop in October.

About 30 investigators, most of them interested in the molecular biology of cancer, but people from other fields as well.

That group had a very good day of animated conversation. They reached some consensus on five potential provocative questions that might guide our work in the future.

Many other questions were aired and discussed and might become lead candidates for being highly featured provocative questions in the future.

The group also felt it needed to reach out to a much wider constituency, many other disciplines.

And to do that we now have scheduled for early February three additional workshops, one on clinical and translational research, one on population-based research, public health, behavioral research and epidemiology, and then a third on a wider range of basic science, chemistry, engineering, informatics, and other disciplines.

Funding Provocative Questions

During the question-and-answer period, a member of the audience asked how the provocative questions initiatives would be funded.

Varmus's answer follows:

Some people have said that we ought to have an RFA for every question. Some people said, "Let's just throw questions out there and let them guide people who are applying for their own R01s."

I think we will probably end up with something in-between.

I can imagine having either program announcements with special review or RFAs that are designed to solicit responses to sub-collections of provocative questions.

That would mean having special study sections, hopefully composed of very mature people who are going to be asked to evaluate proposals that are going to be inherently risky, because provocative questions are, by their very nature, likely to be hard questions to answer.

I do think that eventually the provocative questions exercise is going to have a real payoff, because they are going to be intrinsically difficult to answer. We are gong to have to do something in a directed way to get applications from people who want to address these questions specifically.

It's easier to say, "I am going to do genomic analysis of a tumor" than to take on a difficult question that has gone unanswered for a long time, even though the payoff might be great.This is a way of encouraging inherently high-risk, high-reward science, and whether we assign some specific dollars to these programs or simply provide special review and special encouragement remains to be seen.

Prevention and Global Health

Varmus has created the position of Associate Director for Prevention in the Office of the Director, and is interviewing candidates for that job.

"I do think that there are amazing new opportunities created by our understanding of cancer on the genetic level," he said. "Environmental influences that manifest

themselves through genetic change are going to provide opportunities in the arena of prevention.

"Unfortunately, the public discourse on cancer tends to be focused on the cure. But the fact is that there is no gratitude from people whose cancer has been prevented, because they don't know who they are.

"But the idea of preventing cancer is inherently a more sensible one, and a more cost-effective one, in general, than treatment."

Also, the search for director for the new Center for Global Health has been narrowed down to a small number of candidates.

"I hope to be interviewing [candidates] over the course of the next couple of weeks," Varmus said, describing the center as "a distinct place to organize our thinking and our actions about the role of cancer in global health."

Varmus described his vision for the center's focus:

There doesn't have to be concern that this will be an activity that takes away from our focus on the domestic aspects of cancer. The NCI clearly spends a fair amount of money abroad.

Mainly, we undertake basic science studies in collaborations with colleagues in Canada, or France, or UK. Then we have other projects that are much more clearly in the global health arena, because they involve spending money on a project in China that addresses the genetic and environmental causes of esophageal and gastric cancer in China.

What's missing, in my view, is deliberate and well-planned effort to think about where we can make real advances at not exorbitant cost against the disease that afflict patients in poor countries.

It's been traditional to think that that's too difficult, too expensive, not appropriate, but we all know that work that [NCI Deputy Director] Doug [Lowy] has been involved in developing HPV vaccines has enormous potential for reducing the burden of cancer morbidity and mortality, because in those countries, unlike our own, cervical cancer is the largest cause of mortality from cancer among women.

Likewise, efforts to control smoking can be applied to poor countries. What needs to be done, in my view, is to bring someone who is highly knowledgeable in the practice of medicine in poor countries into the NCI, and to begin to look through countries one by one to identify the major burdens posed by cancer in those countries, to think about the health systems that exist in those countries, the kind of opportunities for making advances at low cost.

Other Recruitments

Edward Harlow was named special assistant to the director. In addition to his position at Harvard, Harlow serves as chief scientific officer at Constellation Pharmaceuticals Inc. of Cambridge, Mass.,

"Ed is going to be here two or three days a week, helping me with a variety of scientific issues, provocative questions enterprise, evaluation of biomarkers and proteomics," Varmus said.

The institute is recruiting deputy director for clinical and translational research. "We have several excellent candidates, who are being reviewed over the course of the few weeks in front of us, and I hope to have an announcement to make very soon," Varmus said.

Varmus said he is about to make an offer to a candidate for the job of director of the Center for Cancer Genomics, which amalgamates all activities in cancer genomics.

In another appointment, John Czajkowski was named executive officer, a position also known as deputy for management. His most recent job was at the Office of the Inspector General at the U.S. Department of the Treasury, where he served as director of the Office of Management.

"John has very quickly learned what our problems are, engaged with a lot of people throughout the NCI and I am sure that we are all going to find that he is a delightful person to work with and very committed to making the NCI a very efficient place to spend money," Varmus said. Jason Donaldson, former acting executive officer, has stayed on as a deputy.

Rick Borchelt, a science journalist and writer, was hired "to provide me on advice on public relations in general, and particularly to provide me with advice on public relations in general, and particularly helping us with the Bypass Budget narrative," Varmus said.

The Bypass Budget, one of the quirkier aspects of the National Cancer Program, allows the NCI director to bypass the HHS hierarchy and communicate his professional judgment of opportunities in cancer research directly to the President.

"It has a questionable level of authority when it goes to Congress, especially in the current economic climate," Varmus said. "But it does allow us to describe for the nation and the world what kind of progress is being made in cancer research.

"This year, we've elected to highlight six cancers, to talk about the kinds of progress that's occurring in prevention and diagnosis and treatment and basic understanding, how patients and doctors and scientists are collaborating to make these advances."

Biostatisticians Review 550 pp Of NCI Documents on Duke

(Continued from page 1)

We have partitioned our survey into two sections, the first dealing with Duke's use of genomic signatures to predict prognosis (deciding who should be treated), and the second dealing with Duke's use of genomic signatures to predict chemosensitivity (what we should treat them with).

In the first case, we focus on the Lung Metagene Score (LMS), introduced by Potti et al. (NEJM, 2006), and the associated clinical trial, Cancer and Leukemia Group B 30506. Few details of this story were known previously.

We now know that there were serious problems almost from the beginning.

In the second case, we focus on the cell line-based approach for deriving drug sensitivity signatures, introduced by Potti et al. (Nat Med, 2006). More is publicly known about the problems associated with these; what was not known was what role, if any, the NCI was playing in attempting to assess and govern their use.

We now know the NCI blocked the use of this approach in a cooperative trial (CALGB 30702), prompting Duke to begin its review in late 2009. NCI we now know, was actively investigating the use of the cisplatin and pemetrexed signatures when other events brought about the re-suspension and eventual termination of the three clinical trials Duke was running.

In both instances, we summarize what was known publicly, highlight what was not clear, walk through what the new documents show, and mention how our own views have changed in light of this information.

We found reading through NCI documentation actively frightening, because the NCI repeatedly found that the signatures failed to work as advertised, but Duke was still actively pushing them into clinical trials. Common themes include lack of reproducibility, lack of clarity, lack of attention to experimental details (e.g. blinding), and waste of resources. At a minimum, these points reinforce our belief that the supporting data and code should have been made public from the outset.

The LMS and CALGB 30506

What Was Publicly Known Before IOM Meeting

The LMS NEJM paper was big news. The claims in the paper by Potti et al in the Aug. 10, 2006, paper were dramatic. Using microarray profiles of tumors from early-stage NSCLC patients, they claimed to be able to predict which patients were likely to recur, and would thus benefit from chemotherapy as opposed to observation. ASCO's survey of clinical cancer advances for 2006 (Ozols et al, JCO, 25:146-62, 2007) classed this as one of "the most significant advances on the front lines of cancer." As of the start of 2011, the paper had been cited 369 times (Google Scholar).

Duke wanted to use the LMS to guide patient allocation to therapy. Duke Medicine's news and communications office released a press statement Aug. 9, 2010, noting that "the test's promising results have initiated a landmark multi-center clinical trial, to be led by Duke investigators next year. Patients with early-stage non-small cell lung cancer, the most common and fatal form of cancer, will receive the genomic test and its results will determine their treatment."

CALGB 30506 did not use the LMS for allocation, but only for stratification. According to the description first posted to www.clinicaltrials.gov (as NCT 863512, March 17, 2009), "patients are stratified according to risk group (high vs. low) and pathologic stage (IA vs. IB). Patients are randomized to 1 of 2 treatment arms within 60 days after surgery." In short, the LMS was being used as a balancing factor only, to ensure that high risk (by LMS) patients are equally randomized to all therapies, and the same for low risk patients. Treatment does not change based on LMS status.

Duke continued to talk as if the LMS was guiding therapy, but the NCI objected. As recently as July 2009, Jolly Graham and Anil Potti stated (Curr Oncol Rep, 11:263-8; PAF 15) that "in this study, patients who undergo resection of early-stage disease will receive further adjuvant chemotherapy if they are predicted to be at high risk of recurrence." The NCI felt sufficiently strongly about this that members of its Cancer Therapy Evaluation Program wrote an erratum (Curr Oncol Rep, PAF 16) stating that "for no patient enrolled in the trial is therapy directed or influenced by the lung metagene model" and that "the NCI does not consider the lung metagene model to be sufficiently validated at this time to direct patient treatment".

After the Baggerly and Coombes 2009 article, the NCI decided to re-evaluate the performance of the LMS. Baggerly and Coombes (Ann App Statist, 3:1339-54; available online September 2009) reported major data errors coming from the Potti/Nevins group affecting genomic signatures of sensitivity to various chemotherapeutics. These signatures were assembled from cell line data following Potti et al (Nat Med, 12:1294-300, 2006), which used a different strategy than the LMS (which didn't use cell lines). Duke suspended

enrollment in the clinical trials associated with the chemosensitivity approach and began an internal review (The Cancer Letter, Oct. 2, 2009). Despite the differences in modeling strategies, the NCI was sufficiently concerned that "When the issues came up with the review by Duke of their studies, we decided to review the LMS score in the trial we sponsored" (The Cancer Letter, May 14, 2010).

The NCI and CALGB then pulled the LMS from CALGB 30506. After the NCI review—and even though the LMS was only being used for stratification and not to guide therapy—"We have asked [CALGB] to remove the Lung Metagene Score from the trial, because we were unable to confirm the score's utility" (CTEP Director Jeff Abrams, in The Cancer Letter, May 14, 2010).

Some data were used without permission and inaccurately labeled. It was later noted by David Beer, PI of the Director's Challenge Consortium for the Molecular Classification of Lung Adenocarcinoma, the source of some data used for validation in the Potti et al NEJM paper (The Cancer Letter, July 30, 2010) that he had previously denied permission for his data to be used in the NEJM paper until after the NCI Director's Challenge paper was published. "When the NEJM paper subsequently appeared, and I saw that they used part of the data … Jim Jacobsen of the NCI and I contacted the editor of the NEJM and Dr. Nevins. The editor said that he could not retract the paper, and Dr. Nevins said he didn't want to, either." He further noted that "there were also numerous errors in the clinical data as listed in their paper".

What Wasn't Publicly Known

Why was the LMS only used for stratification? The Potti et al NEJM paper claimed that the performance of the LMS had already been validated in blinded test sets. Thus, it wasn't clear why the next step didn't involve prospective testing of treatment allocation.

What did the NCI investigate when it performed its re-evaluation? The NCI simply stated that it had "decided to review" the LMS. It was not clear what such a review entailed.

What caused the NCI to pull the LMS from CALGB 30506? The NCI stated it was "unable to confirm the score's utility", but even so, according to The Cancer Letter story (May 14, 2010), the "NCI's decision to eliminate LMS… is all the more remarkable, because the assay was not used to select patients for therapy … which means there was no plausible risk to patients."

Did the problems identified apply to the underlying paper as well? Even with the withdrawal of the LMS from 30506, it was unclear to what extent the NCI's concerns governed the use of the LMS in the trial as opposed to the base findings from the NEJM paper.

What the Documents Released by NCI Show

1. The NCI's initial evaluation (2006-2008)

The NCI had questions about data quality and blinding from the outset. A background overview assembled by CTEP in early 2008 (PAF 12, p. 17) notes that "it became apparent that there were numerous data accuracy problems with the version of the CALGB "validation" data used in the NEJM paper. Through the several-month process of making corrections and re-performing analyses, it also became apparent that the Duke investigators had access both to the microarray-based predictions and the clinical data for the NEJM "validation" sets. … All parties agreed that a completely new validation should be performed before launching a new trial that would base patient treatment decisions on the predictor."

The LMS initially failed in pre-validation. In the NCI's evaluation of the LMS on a new set of Director's Challenge samples that the Duke investigators had not seen (PAF 12, p. 20), "on the independent set of validation samples not seen before… the predictor failed completely, with some nearly significant trends in the wrong direction."

Success was achieved only after the Duke investigators made modifications. Several post-hoc analyses were performed by Duke (PAF 12, p. 21). In post-hoc analysis 4, the Duke investigators pursued normalization of the test data by batch. According to the NCI, (PAF 12, p. 22) "The NCI understanding was that the only change from the first set of predictions (which failed to validate) and the new set of predictions was the normalization step.… No other changes to the prediction algorithm were to be made. For example, it is NCI's understanding that there was no recalculation of weights used to define the metagenes after the data had been renormalized." With this modification (PAF 12, p. 22) "the difference in survival finally reach (sic) statistical significance (p=0.0478) in the stage IB subgroup (this time in the correct direction)… Interestingly, the dramatic separation in survival curves based on LMS risk prediction previously seen for Stage IA patients (the initial basis for the trial) disappeared when the LMS predictor was applied to the completely independent validation set… regardless of method of analysis."

Modification details were not sent to the NCI at the time. It's important to note that (PAF 21, p. 4) that

"during this pre-validation attempt, all microarray data preprocessing and risk prediction calculations were performed by Dr. Potti or members of his group. Neither NCI nor the CALGB Statistical Center had access to the computer software for running the predictor, but the Potti/Nevins group assured all parties that no changes had occurred in the form of the predictor between observation of the initial failed results and observation of the subsequent promising results."

The NCI encountered problems reproducing other genomic signatures. In November 2007, while consideration of 30506 was under way, the NCI became "aware of concerns about [the] chemosensitivity paper by Potti et al. (Nature Medicine 2006)" (PAF 3, p. 5, referring to Coombes et al, Nat Med, 13:1276-7, 2007). The NCI notes (PAF 3, p. 5) "Many groups (including NCI) [were] unable to reproduce [the] results."

The NCI would only approve the LMS for stratification, not to guide therapy. In the above situation, the NCI noted (PAF 12, p. 24) "we have many remaining concerns about the readiness of the LMS predictor for use in directing therapy in a large phase III trial as proposed". Consequently (PAF 21, p. 4) "as a condition for approval of the trial, NCI insisted on a trial design change in which the LMS predictor results … could not be used in any way to determine patient therapy … the LMS predictor would be used only as a stratification factor."

2. The NCI re-evaluation of whether the LMS worked at all, in light of similar problems reported by Baggerly and Coombes (November 2009-March 2010).

The NCI tried to check the Duke modifications, and insisted on running the LMS code themselves. On Nov. 16, 2009, the NCI asked Duke (through CALGB) to supply the code and data illustrating the improvement in the pre-validation results that drove the trial approval (PAF 12, pp.17-29). Duke supplied a collection of materials on Dec. 15, 2009 (PAF 12, pp. 30-45).

When the NCI applied the modifications, they didn't see improvements in the performance of the predictor. One of the NCI's re-analysis findings (PAF 11, p. 2, Feb. 10, 2010) was that "in none of the analyses performed during this re-evaluation using the prescribed methods of data pre-processing and risk prediction using the TreeProfiler application could promising predictor performance be demonstrated. In particular, no evidence could be found that pre-processing the microarray data separately by lab would produce an improvement in predictor performance as dramatic as that observed in the pre-validation."

When the NCI ran the code, they found the output was stochastic (i.e. random) –predictions could change simply depending on when the code was run. Another finding of the NCI re-analysis was that reruns of the same patient array data gave different risk predictions apparently depending on when the code was run (PAF 11, p. 1): "The percent of discordant risk group predictions from one run to another under identical conditions was observed to be about 20% on average, but discordant rates as high as 40% were observed for some pairs of runs." When predictions from the NCI's model runs were compared with the revised Duke predictions used to justify the trial (PAF 11, p. 13) "The percent concordance … ranged from 46% to 52% with mean 49%."

This stochasticity violated the NCI's definition of a "locked-down" prediction rule–for a locked-down rule, the same input (patient measurements) should always produce the same output (assessment of whether the patient was high or low risk). The idea that the same array profile could be, to paraphrase the 20% average discordance noted above, low-risk Monday through Thursday and high-risk on Friday was not acceptable to the NCI, which noted (PAF 11, p. 1) "This behavior is inconsistent with the assertions made during the pre-validation that the predictor was completely locked down and did not change throughout the entire exercise."

Duke argued the stochasticity was independent of being locked-down. In their response to the NCI's re-analysis, Nevins et al claimed (PAF 13, p. 2, March 8, 2010) that "in our opinion, the variability that is seen in run-to-run of TreeProfiler is independent of whether the predictor was completely locked down. All of the critical parameters (e.g. number of clusters, trees, thresholds, splits, etc) for running the software have been fixed and not changed throughout this process… Once again, we have been completely transparent throughout this process."

The NCI disagreed emphatically. In its reply to Duke's response (PAF 14, p. 1-2, March 26, 2010), the NCI notes: "You propose an alternative definition of "locked down," which allows LMS probability values to change dramatically every time the computer program is run, even when it is run using identical data and settings.… In the NCI letter to Dr. Harpole dated Jan. 7, 2008 (see Appendix H), NCI again states its understanding of the locked down status of the predictor (page 6, 2nd paragraph) and you voiced no disagreement with that statement. Example sentences from the NCI letter include "No other changes to the prediction algorithm were to be made. For example, it is NCI's understanding that there was no recalculation of

the weights used to define the metagenes after the data had been renormalized." As the weights would change from computer run to computer run just like the LMS probability values do, it appears that you agreed with a standard definition (and not your proposed alternative definition) of "locked down" in January 2008."

The NCI believes the NEJM paper is misleading. The NCI also states (PAF 14, pp. 1-2): "We maintain that your proposed definition is inconsistent with the impression provided in your NEJM paper … for which you state in your response you also used the TreeProfiler program. Your proposed definition is also inconsistent with agreed upon terms communicated during the NCI pre-validation. … In the NEJM paper (upper left column, page 573), you state that "the dominant metagenes that constituted the final model are described in the Supplementary Appendix." In addition, on page 575 of the NEJM paper (top right column), you state "further confirmation that the lung metagene model represents the biology of the tumor was provided by the finding that the metagenes with the greatest discriminatory capability included genes … for example, the BRAF, … and MYC signaling pathways." Any references to specific metagenes or to a "final" model are meaningless because the entire model would change if the TreeProfiler program was run again on any other data or even run again on the same data."

The NCI believes it was misled when approving the trial. The NCI's summary (PAF 14, p. 2) states: "The evidence, in our view, indicates that either the LMS predictor was not locked down, or inaccurate statements were made about what predictor was actually used to generate the reported results."

The NCI raised concerns with CALGB leadership about the irreproducibility of the results. After responding to further points in the Duke response, the NCI letter concludes (PAF 14, p. 5) "Because we were unable to reproduce your results, despite our discussions and your input, we will now contact CALGB leadership to pursue the issues with them."

Conclusions

Duke and CALGB should be thankful that the NCI prevented them from using the LMS to guide treatment.

One reason we objected to many of the chemosensitivity signatures was that "sensitive" and "resistant" labels were often reversed in the training data, so that if the method worked, their guidance would be at odds with the truth. Here, given that the NCI was unable to reproduce reported "improvements," our best estimate of performance is the NCI's completely blinded assessment, in which the predictions almost achieved significance going the wrong way. If the LMS had been guiding treatment, Duke might have to prove the LMS was completely ineffective to avoid claims of patient harm.

CALGB 30506 was potentially a much larger trial than those already terminated. Duke recently terminated the three clinical trials it was running where the Potti/Nevins genomic signatures were being used to guide patient treatment. Between the three of them, these trials involved about 110 patients. In CALGB 30506, there were "approximately 1,500 patients pre-registered, 1,300 randomized" as of the NCI's re-evaluation (PAF 11, p. 1). These figures were goals; as noted in a letter to the editor from NCI official Lisa McShane (The Cancer Letter, Jan. 14), "current accrual figures reported by CALGB to NCI on January 7, 2011, are 128 patients pre-registered with 24 patients fully registered."

The stochasticity of the LMS means that nobody could have reproduced it. David Beer noted: "We examined as best we could the metagene score in our Shedden et al., Nature Medicine paper, published in 2008. We were not able to repeat the type of astoundingly good discrimination between high- and low-risk individuals that was published in the Potti et al., NEJM paper using this method, in part because of lack of sufficient details provided in their paper." (The Cancer Letter, July 30, 2010). If they were trying to reproduce the numbers reported to be sure they were using the method correctly (something we often do), they would undoubtedly have been frustrated; the stochasticity virtually guarantees that different results would be obtained, and without being able to compel production of the raw data and code (which the NCI did) they could never be certain whether the problems lay with the approach itself or simply with their implementation of it. According to the NCI, there are problems with the approach.

The stochasticity may explain inconsistencies within the paper. Figure 2A of the NEJM paper shows a heatmap of "Metagene 79", which is used in later panels to stratify the samples. Visual inspection of the heatmap shows about 30 genes. Supplementary Table 2 for the NEJM paper lists 19 probesets for "Mgene 79". If this is the result of simply rerunning the algorithm, we must agree with the NCI that "Any references to specific metagenes or to a "final" model are meaningless."

Some of the reported results are "too good" if the results are as unstable as reported. Low- and high-risk Kaplan-Meier curves in the NEJM paper are extremely well separated. As a test, we approximated the curves shown in Figure 5A and simulated what

might be encountered in practice by either leaving a given patient's classification alone (80% chance) or swapping it (20% chance). We then computed the p-value associated with the "simulated" split. Out of 100000 simulations, we got values more extreme than the one published only 62 times, for a p-value of 6.2e-4. If TreeProfiler is as unstable as it was in the NCI's hands, it would appear they got a very "lucky" figure.

The paper needs to be reproduced or retracted. In the July 30, 2010, issue of The Cancer Letter, Jennifer Zeis, a spokesman for NEJM, stated that "If Duke's investigation yields findings relevant to Dr. Potti's 2006 NEJM article, we will take the matter under consideration then." With the NCI, which was able to compel production of the raw data, willing to assert that the NEJM paper is misleading, this bar has been met and surpassed.

Chemosensitivity Signatures: CALGB 30702, Duke Review, and Cisplatin/Pemetrexed

What Was Publicly Known Before IOM Meeting

Duke was conducting three trials in which therapy was guided by genomic signatures of sensitivity to various chemotherapeutics. These signatures, derived from cell lines, were introduced by Potti et al. (Nature Medicine, 12:1294-300, 2006) and Hsu et al (Journal of Clinical Oncology, 25:4350-7, 2007). In late 2009, according to the www.clinicaltrials.gov database, Duke was using genomic signatures to guide therapy selection in three trials: NCT 509366 (comparing cisplatin with pemetrexed in lung cancer), NCT 545948 (comparing pemetrexed and vinorelbine in lung cancer), and NCT 636441 (comparing docetaxel and adriamycin in breast cancer). The first two were apparently Duke/pharma collaborations; the third was funded by the Department of Defense.

After the Baggerly and Coombes 2009 article reported major inconsistencies in the published studies that provided the basis for using the signatures, Duke began an internal investigation and suspended trial enrollments. In mid-September 2009, Baggerly and Coombes (Annals of Applied Statistics, 3:1309-34, 2009) was published online, describing problems with the data used as the basis for the trials. The article shows (p. 1334) "in five case studies that the [Duke chemosensitivity] results incorporate several simple errors that may be putting patients at risk" because some of the errors noted, such as reversing the sensitive and resistant labels in the training data, could result in sensitivity predictions pointing the wrong way. After the article was covered in the press (The Cancer Letter, Oct. 2, 2009), Duke noted that it was "working to engage independent experts in this field to fully explore these questions (The Cancer Letter, Oct. 9, 2009). In the meantime, NCT 509366 and NCT 545948 suspended enrollment by Oct. 6; NCT 636441 by Oct. 19 (The Cancer Letter, Oct. 9, 23, 2009).

Problems with blinding were publicly reported while the investigation was underway. At the outset, Duke researchers Joseph Nevins and Anil Potti described the problems as "clerical errors" and argued they had nonetheless gotten the approach to work in a blinded validation, which would constitute a very stringent test (Bonnefoi et al., Lancet Oncology 2007; referenced in The Cancer Letter, Oct. 2, 2009).

However, this claim was disputed by their coauthors, who said the study had never been blinded because they had sent the Duke investigators, at the start, both array and clinical data; since Duke knew the patient outcomes, the study was never blinded (The Cancer Letter, Oct. 23, 2009).

New data for cisplatin and pemetrexed was posted while the investigation was underway. We showed that all of the validation data contained in the cisplatin and pemetrexed dataset was wrong, and reported this to Duke on Nov. 9, 2009. In early November 2009, Duke investigators posted new data for the cisplatin and pemetrexed signatures to the web (http://data.genome.duke.edu/JCO.php). The cisplatin and pemetrexed dataset included 59 array profiles for ovarian cancer samples that had been used to validate the performance of the predictors. We showed that 43 of these samples were mislabeled; for the other 16 samples the genes were mislabeled so badly that the sample identities could not be confirmed. We sent a report outlining these and other problems to Duke deans on Nov. 9, 2009, and received acknowledgment that the report had been received. We sent the same report to the NCI's CTEP on Nov. 10, 2009.

The cisplatin and pemetrexed data were then removed from the web. The dataset was removed from the Duke web site by Nov. 16, 2009. Copies of the data and our report are available from http://bioinformatics.mdanderson.org/ReproRsch-All/Modified/index.html.

When the review was concluded (January 2010), Duke decided to restart the trials. Neither the reviewers' report nor new data were made publicly available. Duke also made no comment about the problems (mispreporting of blinding, and mislabeling

of validation samples) reported mid-investigation. Duke did acknowledge having sent a copy of reviewers' report to the NCI. We objected to the trials being restarted without such clarification, and made the Baggerly and Coombes report, which had previously only been shown to Duke and to CTEP, public by announcing it in the press. On Jan. 29, 2010, Duke announced it was in the process of restarting all three suspended clinical trials, noting that the results of their review "serve to strengthen the confidence in this emerging approach to personalized cancer treatment" (The Cancer Letter, Jan. 29, 2010). When asked whether the report or raw data justifying these conclusions would be made public, Duke stated "While the reviewers approved of our sharing the report with the NCI, we consider it a confidential document", noted that Nevins and Potti were preparing "additional manuscripts for the peer-reviewed literature", and indicated that the data and methods would be made available when these new papers were published. We objected that the trials should not be restarted before data supporting this action was provided, and publicly described the errors we had seen with the cisplatin and pemetrexed validation data, which we had previously only described to Duke and to CTEP, and posted the Baggerly and Coombes report to the web, noting "We are asked to trust that they got the data right "this time" when we have empirical evidence they got an important piece of it wrong."

A redacted copy of the reviewers' report obtained under FOIA (May 2010) showed that the reviewers themselves had been unable to understand the methods from the literature, or from data they were shown at Duke, and showed no mention of the new problems identified with blinding or mislabeling, or of the Baggerly and Coombes report, which we had supplied to the deans in November 2009, a month before the reviewers' report was written.

In early May, The Cancer Letter obtained a redacted copy of the reviewers' report from the NCI under FOIA. We noted (The Cancer Letter, May 14, 2010) that "the committee explicitly notes (twice!), that the underlying scientific methodology has not yet been published," and that "the committee *expected* this additional information would be made available, as they note that "In our review of the methods... we were unable to identify a place where the statistical methods were described in sufficient detail to independently replicate the findings of the papers.

Only by examining the R code from Barry were we able to uncover the true methods used … The one area that they [the Duke investigators] have not been fully responsive and *really need to do so* is in clearly explaining and laying our [sic] the specific statistical steps used in developing the predictors and the prospective sample assignments." Further, we noted that "given that additional problems [blinding, mislabeling of validation samples] arose even during the course of the investigation, we fear similar errors in data supplied to the committee might invalidate many of their conclusions. *The report makes no mention of these new problems."* This omission led us to question whether the reviewers ever saw the Baggerly and Coombes report, which we supplied to Duke on Nov. 9, 2010, over a month before the Dec. 22, 2009 date on the reviewers' report.

In July 2010, after revelations that Dr. Potti might have embellished his CV with claims including being a Rhodes scholar, Duke launched new investigations and resuspended trials. The July 16th issue of The Cancer Letter reported on several irregularities with Dr. Potti's CV, including that he had claimed to be a Rhodes scholar on various grant applications. The following week, Duke announced that the trials were being resuspended (The Cancer Letter, July 23, 2010). After reviewing the situation, Duke's Provost acknowledged (Duke News release, Aug. 27, 2010) that they had found "issues of substantial concern".

Several months later (October 2010), Nevins began to retract some of the papers in question, starting with Hsu et al. (JCO, 2007), listing problems identical to those we had described in the Baggerly and Coombes report as the rationale. In a letter to coauthors of Hsu et al. (JCO, 2007) sent Oct. 22, 2010, (The Cancer Letter, Oct. 29, 2010) Nevins notes "It is now clear to me upon re-evaluation of the data associated with the tumor samples that there are two problems with this dataset. First, there are 16 samples that do not match with the gene expression data from any of the ovarian samples that we have in our database. At this point, I cannot identify the origin or nature of these samples. It is possible they are from a set of non-ovarian samples or it is possible that they are ovarian samples that are permuted in a way that I cannot trace. But given that I cannot identify the nature of these samples, the associated clinical outcome labels are of no meaning. Second, for the remaining 43 samples that are clearly from the ovarian database, the tumor ID labels for these samples are incorrect. In a large number of these cases, the misidentification results in reversal of the clinical annotation of response vs. non-response." The problems listed are exactly those we had identified and forwarded to the Duke deans, and that the investigators had already

acted on (by withdrawing cisplatin and pemetrexed data from the web) in November 2009, almost a year earlier.

Statements by Duke suggest that the reviewers never saw the Baggerly and Coombes analysis. A Duke spokesman stated that while the raw data containing the errors had been supplied to the committee, those errors had gone undetected because the data "integrity" was not questioned (The Cancer Letter, Oct. 29, 2010) "Regrettably, the data sets that are the source of the retraction request are a subset of the same data that were provided by Drs. Potti and Nevins to external reviewers in early 2010 and were the basis for their review". Further, (the News & Observer, Oct. 30, 2010) "Sally Kornbluth, Duke's vice dean of research, said last year's investigation of Potti's work did not "drill down" to re-check the actual data that were used to form his calculations. She said that review team was "not aware that there were data integrity issues with the work." As a result, the reviewers did not catch the problems that have now led to Nevin's (sic) request for a retraction."

Duke terminated the clinical trials. On Nov. 9, 2010, the Duke Chronicle reported that Duke had terminated the three suspended clinical trials.

Two major papers (Potti et al, Nat Med 2006 and Hsu et al, JCO 2007) have now been retracted, a third (Bonnefoi et al., Lancet Oncol 2007) has been the subject of an editorial "expression of concern", and Anil Potti has resigned. On July 23, 2009, the editors of the Lancet Oncology issued an "expression of concern" regarding Bonnefoi et al., 2007 (another of the chemosensitivity papers) because "on July 21 and 22, 2010, The Lancet Oncology was contacted by Richard Iggo and Hervé Bonnefoi on behalf of the 15 European co-authors of an article we published in December, 2007. The authors expressed grave concerns about the validity of their report in light of evolving events. … Repeated attempts by Iggo and colleagues to contact their co-authors at Duke University, NC, USA, who had been responsible for the statistical analyses in the report, had been ignored."

On Nov. 16, 2009, JCO officially retracted Hsu et al. (JCO, 2007). On Nov. 19, 2010, the AP reported that Anil Potti had resigned, and that Joseph Nevins "is asking the journal Nature Medicine to retract a paper he published with Anil Potti, the scientist who's stepping down. Potti's collaborator Joseph Nevins said some of the tests in the research they produced for that paper can not be duplicated."

What Wasn't Publicly Known

Why did Duke send a copy of the reviewers' report to the NCI? It was not clear to us, before Dec 20, 2010, why the NCI was receiving communications from Duke about the three ongoing trials, because, according to clinicaltrials.gov, none of the three Duke clinical trials were directly funded by the NCI. However, comments by Duke officials had suggested that the NCI had been in communication with Duke about the review. It was not clear who had initiated that communication, or why.

Did the NCI think the reviewers' report addressed the questions raised? Given that the NCI was communicating with Duke about the reviewers' report, and that, in our view, the reviewers' report missed some important problems (and given that the committee itself said that the underlying scientific methodology had not yet been published), we were curious about whether the NCI thought there were still problems. We knew that the NCI decided to pull the LMS from CALGB 30506 (a trial it funded) based on a re-evaluation triggered by our findings, but we weren't clear whether that represented the end of the NCI's involvement.

More broadly, we had no idea what questions the NCI was asking, and what steps it was taking to answer them. None of that was known before Dec 20, 2010. Between May 14 (when the NCI pulled the LMS) and July 16 (when the Rhodes story broke), we continued to believe that the Duke trials were based on irreproducible results, but were at a loss in terms of what to do by way of any further assessment. We were curious – but had no way of knowing -- if the NCI was pursuing any further kinds of inquiry.

What the Documents Released by NCI Show

1. The NCI's review of CALGB 30702 raised concerns re cisplatin/pemetrexed (July through November 2009)

CALGB 30702, proposing to use genomic signatures for cisplatin and pemetrexed to allocate patients to treatment arms, was initially rejected by the NCI at the start of 2009, but it was resubmitted mid-2009 and was under active consideration when the Baggerly Coombes article appeared. CALGB 30702, "Genome-guided Chemotherapy for Untreated and Treated Advanced Stage Non-Small Cell Lung Cancer: A Limited Institution, Randomized Phase II Study", proposed using the Potti/Nevins genomic signatures of sensitivity to several drugs (primarily cisplatin and pemetrexed) to guide the allocation of patients to doublet therapy combinations. The protocol was initially rejected by CTEP (which evaluates trial protocols coming from official cooperative groups) in January 2009 (PAF 5, p. 6), but CALGB resubmitted

the protocol (PAF 8) together with a response to the CTEP critiques (PAF 7) in July of 2009. At this point, CTEP was closely examining these specific signatures as they pertained to a cooperative group trial, before the publication of Baggerly and Coombes (2009).

The NCI saw problems in 30702 similar to those reported by Baggerly and Coombes. In the course of its review, CTEP became aware of several inconsistencies in the data and signatures as they appeared in multiple contexts (papers, websites, grant applications). In particular, its detailed review (PAF 9, p. 2, written in November 2009) notes that "Comparison of the published cisplatin and pemetrexed signatures (as reported in Hsu et al JCO 2007) to the ones described in the supplementary tables supplied in the investigators' response to CTEP show that the classifiers are not the same." The review further notes with respect to ERCC1 and ERCC4 (previously cited by Hsu et al (JCO, 2007) as providing biological plausibility for the cisplatin signature) that (PAF 9, p. 2) "the gene list provided in Table 7 or CALGB's response to CTEP does not contain the genes ERCC1 and ERCC4. If the Hsu et al version had changed, then the investigators should have fully acknowledged this and this paper should no longer be viewed as providing a 'validation.'" The review also notes changes in number, identity, and possibly sensitive/resistant direction of cell lines across studies, citing Baggerly and Coombes (Ann App Statist, 2009). Yet, as the NCI noted (Point 2 of PAF 9, beginning on p. 1) the CALGB resubmission (PAF 7, p. 17) states "Briefly, the identification and validation of each signature has been reported in four important manuscripts, and serve as the basis for the gene membership and parameterization of the predictive models". It then lists the four manuscripts (PAF 7, p. 17):

"1. Potti, A et al Nature medicine 2006

2. Hsu D et al JCO 2007

3. Bonnefoi H et al Lancet Oncol 2007

4. Salter K et al PLOSone 2008".

In its own analysis, however, the NCI disagrees that these four manuscripts provide an adequate basis for the signatures. (PAF 9, p. 2), "CTEP strongly disagrees with the premise that these publications represent validations of the signatures to be used in the proposed trial" and, citing the errors noted above, flatly states "the results in the Hsu et al paper cannot be viewed as a validation of these predictors."

Based on its analysis, the NCI rejected 30702 on Nov. 9, 2009. Per the cover letter (PAF 10), "We regret to inform you that the reviewers recommend disapproval of this study."

2. The NCI's interactions with Duke regarding the initial review (September 2009 through January 2010)

The Dec. 20, 2010, documents show that the NCI was concerned with the three trials based on its review of 30702, and on the awareness that these same signatures were guiding therapy in the three Duke trials. The NCI notified Duke of its concerns in late September-early October 2009, ultimately leading to the initial review. There are some slight discrepancies in the report as to the precise timing. According to Dr. McShane's overview (PAF 21, p. 2, see also PAF 20, p. 3) "The CALGB-30702 protocol mentioned a few trials that were already in progress at Duke University using some of these genomic predictors to determine patient therapy. A search of ClinicalTrials.gov identified several trials that appeared to be using these predictors for which NCI now had significant concerns. NCI CTEP contacted Duke University with its concerns at the end of September 2009." A recollection written by Duke deans Sally Kornbluth and Michael Cuffe (PAF 1, p. 1) notes "It was this claim of potential patient endangerment [raised by Baggerly and Coombes] that heightened our concerns about the use of the questioned genomic predictors in the three clinical trials. At the same time, similar concerns prompted the NCI to contact us in October, 2009, asking that we carefully consider the validity of the work and its extrapolation to the clinic."

Thus, the Duke review was initiated at least in part in response to the NCI's concerns. Again, per Dr. McShane's overview, the contact with the NCI (PAF 21, p. 2, PAF 20, p. 3) "led to suspension of three trials and initiation of an investigation by the Duke IRB with assistance from two external statisticians experienced in genomic data analysis and hired by Duke. … NCI had no knowledge of the details of the conduct of the review." The deans' recollection is consistent with this, though they emphasize (PAF 1, p. 1) "To be clear, at the time, Duke's institutional involvement in this situation was initiated by patient safety concerns, not by claims of clerical errors or by academic disagreements concerning the validity of statistical approaches taken by Drs. Nevins and Potti.

The reviewers finished their report Dec. 22, 2009. Duke forwarded the reviewers' report to the NCI on Jan. 7, 2010, and indicated it would be restarting trials. The review (PAF 3) was previously obtained by The Cancer Letter (May 14, 2010) in more redacted form under FOIA, and is discussed above. As noted, the review makes no mention of the Baggerly and Coombes analysis. Nonetheless, in email to the NCI, Duke stated

(PAF 4, p. 1) "Based on this review process, we believe that the trials are safe for patients, the scientific basis for these studies is valid, and we have every reason to hope that important results will be obtained. In light of these reviews, we are initiating processes to re-open enrollment in the involved trials."

The Duke deans re-emphasized that all data was provided to the reviewers. More recently (Oct. 28, 2010, according to the Public Access File List), the Duke deans stated (PAF 1, p. 4)

"An additional issue concerns the completeness of the data provided to the reviewers in order to conduct their review. It has been reported in a number of venues that the reviewers said they did not have sufficient data to fully evaluate the validity of the genomic predictors. However, the reviewers reported that they were provided with comprehensive access and data, but also acknowledged that the published work of Nevins/Potti did not contain sufficient information for others to be able to reproduce their work. At the time, we were assured that the reviewers had received unfettered access to the Nevins/Potti data and labs."

3. The NCI's examination of cisplatin/pemetrexed trials (NCT 509366, NCT 545948) covered by the Duke review (April through June 2010)

The NCI discovered it was providing support for one of the questioned trials. Following its review of CALGB 30506 (November 2009-March 2010), the NCI turned to a review of other grants it funded that involved the genomic signatures. A review of R01 CA131049-01A1 to Anil Potti (PAF 2) showed that it was providing funding for a clinical trial involving cisplatin and pemetrexed in which the cisplatin signature was being used for treatment allocation. On April 13, the NCI requested clarification of which trial this was (PAF 18, p. 1) "Please clarify how the clinical trial in the grant, noted in Aim 1, is related to the trial NCT00509366 (listed on clinicaltrials.gov.) If these trials are indeed the same, please explain, in appropriate detail: why the NCI is not identified as a sponsor of the trial on the website clinicaltrials.gov…" The NCI further noted (PAF 18, p. 2) "A <u>written</u> response to the above requests should be provided upon receipt of this letter (*i.e., immediately*)." (All emphasis theirs.) Dr. Potti immediately confirmed (PAF 18, p. 19) that the trial was indeed NCT 509366.

The NCI requested the raw data and code for the signatures described in R01 CA131049-01A1, the grant application indicating that these signatures were being used in NCT 509366. In their request, the NCI noted that they found the reviewers' report alone insufficient for them to assess the signatures' validity. The NCI also requested (PAF 18, p. 2) that Dr. Potti "Please provide the raw data, a detailed description(s) of the microarray data preprocessing steps descriptions of predictor building algorithms and computer source code need to re-derive the cisplatin and pemetrexed response predictors as they were used in the paper by Hsu et al (J. Clin. Oncol. 25:4350-4357,2007)", noting (PAF 18, p. 1) "We believe that you may have already assembled this material for the purposes of the independent review of some Duke trials initiated by the Duke IRB. Because NCI did not take part in the Duke IRB review of these classifiers and did not have access to the data provided to the independent reviewers, we deem it necessary to conduct our own independent review of any studies for which NCI has oversight or has supplied funding. This will allow us to confirm the documentation that you provided as justification for grant approval and funding."

In this investigation of the raw data and algorithms used to derive signatures, the NCI determined that some "rules" were not well-defined. In particular, there was no algorithm for choosing which cell lines to derive signatures. Data and code had been supplied on April 29, 2010 (PAF 18, pp. 22-38); some clarification was requested by the NCI on May 17, 2010 (PAF 18, pp. 5-8) and supplied on May 21, 2010 (PAF 18, pp. 39-47). One point of clarification involved the selection of cell lines used to construct the cisplatin signature, since only a subset of lines available from the source cited (Gyorffy et al, Int J Cancer, 2006) were used. In his communication of April 29, Dr. Potti noted "there is actually no `algorithm' to select the cell lines constituting the cell line based predictors. The selection is initially done manually based on in vitro drug sensitivity information and cell lines are chosen or excluded based on their biologic characteristics and whether or not certain cell lines appear as outliers in the model building process" (PAF 18, p. 23). In his communication of May 21, Dr. Potti acknowledges that this selection process may be subjective, but notes "But, as I am sure you will agree, the real test of the model is in independent validation and we have always tried to be as aggressive as possible in validating these in vitro based signatures in independent cohorts" (PAF 18, p. 40).

After independently trying to reconstruct the cisplatin and pemetrexed signatures from the data Dr. Potti supplied, using the code Dr. Potti supplied, the NCI reported problems similar to those reported in Baggerly and Coombes paper and the Baggerly and Coombes analysis submitted to Duke. The NCI completed its review of the cisplatin and pemetrexed data on June

10, 2010 (PAF 17). Using data and code supplied by Dr. Potti, they found (paraphrasing PAF 17, pp. 1-2)

1. They were unable to confirm that the cell lines reported were used to assemble the predictor,

2. They were unable to confirm the in vitro ovarian cancer cell line validation results reported,

3. In vitro validation results for lung cancer cell lines reported in the R01 application did not match those reported by the code supplied,

4. In vivo results for ovarian tumors differed from those reported earlier, and

5. There was a general problem of conflicting information from multiple sources.

The NCI concluded that the results could not be reproduced, using the data and algorithms Duke supplied. The NCI's report concludes (PAF 17, p. 26) "Although Dr. Potti has previously acknowledged errors in figures and gene lists, he has maintained that the actual predictors and the reported performance of those predictors were unaffected by those errors. The data, computer code, and instructions provided to us by Dr. Potti did not enable us to reproduce the results in the paper, and we do not know why or when the methods were changed. We also do not know if the version of the predictor supplied to us is the same version implemented in the trial, and if it is different, we do not know if the trial version was properly validated prior to its use in the trial to guide therapy."

The NCI met with Duke investigators to express concerns. The NCI saw problems with 30702, 30506, and cisplatin/pemetrexed as a set, and also noted misstatements in the reviewers' report. At the request of Duke administration (PAF 1, p. 4), a meeting was held at the NCI on June 29, 2010 to discuss the NCI's concerns about 30702, 30506, and the cisplatin and pemetrexed signatures (PAF 1, p. 4). Attendees included Anil Potti, Joseph Nevins, William Barry (statistician), Huntington Willard, and Sally Kornbluth from Duke and several NCI staff (PAF 1, p. 4, PAF 21 p. 6). Notes from the meeting (PAF 6) clarify that Barry, mentioned in the Duke external review (PAF 5), joined Duke in April 2007; both the 2006 Potti et al Nature Medicine paper and the 2007 Hsu et al JCO paper were submitted before he arrived. The NCI presentation at that meeting (PAF 5) outlined the problems the NCI had encountered with CALGB 30702, CALGB 30506, and with the cisplatin/pemetrexed predictors. Reversal and misspecification of pemetrexed cell lines was noted (PAF 5, p. 20), coupled with the observation that the pemetrexed signature was being used to guide therapy in NCT 545948 (PAF 5, pp. 21-22). If the signatures were reversed, the wrong treatment might be administered. Further, the NCI highlighted a quote from the reviewers' report (PAF 5, p. 22, PAF 3, p. 3) that "it does not appear the [pemetrexed] predictor the labels were reversed. In addition we agree with Nevins and Potti that since the profile is not used in any of the clinical trials patients are not being endangered" showing that the external reviewers were misinformed about whether the pemetrexed signature was being used to guide therapy.

Given that the NCI couldn't reproduce the cisplatin and pemetrexed signatures from the data provided, and likewise couldn't confirm the predictive accuracy of the reported signatures, the NCI thought that using the predictors to guide therapy was wrong. The NCI wanted justification ASAP, and mandated a search for the original data and code underlying the initial claims. As Dr. McShane notes in her overview (PAF 21, p. 6), "the [June 29] meeting concluded with NCI remaining unconvinced of the validity of the Duke predictors. Further, NCI directed that a search of original laboratory and computer records be initiated to produce evidence of the correct versions of the data with the expectation that this task would be performed in expedited fashion." As noted by Dr. Kornbluth (PAF 1, p. 4), "Dr. Barry was charged with the task of providing the NCI with the methodologies and data that would be necessary to fully reproduce the published work of Nevins and Potti, particularly the JCO paper of 2007."

Conclusions

The NCI appears to have been close to unilaterally terminating trials it now knew it was funding. Our reading of the NCI documents leading up to the June 29th NCI/Duke meeting suggests the NCI was getting set to take action on the trials involving cisplatin and pemetrexed if their concerns were not addressed quickly. Thus, had the Rhodes story not broken when it did, we don't think the trials would have continued much longer given that the science was faulty (and as evidenced by the recent retractions).

While the reviewers' report was positive enough to justify restarting trials, the reviewers were not informed about the Baggerly and Coombes analysis, and were apparently misinformed about which signatures were being used. We believe that the reviewers' report was insufficient for restarting trials, and Duke, Nevins and Potti should have known this. The tone of the reviewers' report is undeniably positive. It is also incomplete. We find it impossible to credit that if reviewers had seen the Baggerly and Coombes analysis they would not "drill down" enough to see problems

explicitly listed as itemized conclusions in the executive summary, especially now since the reasons given by Dr. Nevins for retracting Hsu et al (JCO, 2007) include the exact points we made in the Baggerly and Coombes analysis in November 2009. We know the Duke deans had the Baggerly and Coombes analysis before the reviewers' report was written, and since the website went down within a week of the Baggerly and Coombes analysis being sent, we likewise presume that Potti and Nevins saw it. Whether the committee saw this, we do not know. Was anyone charged with communicating this information to the committee? Likewise, as the NCI has noted, the committee was apparently misinformed in at least one respect, in that the pemetrexed signature was being used to guide patient allocation in one of the trials in question. To the extent that the committee was not, or mis-informed, it was not equipped to conclude (as Nevins et al wrote to the NCI, PAF 13, p. 1) "the methods being employed in the trials were sound and scientifically valid."

Errors identified in the Baggerly and Coombes paper and the Baggerly and Coombes analysis are neither trivial clerical errors nor "academic disagreements." Gross errors in raw data are inseparable from concerns over patient harm. We disagree with the viewpoint expressed by the Duke deans (PAF 1, p. 1) when they state: "To be clear, at the time, Duke's institutional involvement in this situation was initiated by patient safety concerns, not by claims of clerical errors or by academic disagreements concerning the validity of statistical approaches taken in previous publications by Drs. Nevins and Potti."

We see the objections raised in Baggerly and Coombes (2009) to be about gross and repeated mislabeling (and misrepresentation) of the raw data. These are not trivial "clerical errors"; neither are they abstruse arguments about "statistical approaches". Rather, they amount to repeated assertions that *the data's wrong*. In that light, it is not clear to us that these types of errors can be separated from patient safety concerns.

Cross-Connections

The same types of problems were seen both times. More knowledge of the problems in one instance might have better informed studies of the other. In neither case were the results reproducible. In both cases, major difficulties were encountered with identifying what data were used for training and validation, establishing that the labels were correct, and identifying the code used. To an extent, these commonalities were visible to the NCI, which was able to compel the production of data and code in both instances.

This is partly visible in the chronology, as the NCI reviewed CALGB 30702 (July-November, 2009), the LMS (Nov 09-Mar 10) and the cisplatin/pemetrexed signatures (Apr 10-Jun 10). Because the data and code were unavailable, the commonalities were not visible to others. We knew of problems with the chemosensitivity signatures, but lacked information about the data used to produce the LMS results (e.g., survival times), let alone the random seed required to obtain the exact results reported. One might wonder whether the external reviewers Duke contracted in late 2009 would have proceeded with their task differently had they known the NCI had raised similar questions about an entirely diffrent trial.

Common Themes

This appears to be a huge waste of resources. The papers describing the LMS and the chemosensitivity signatures made strong claims that have not turned out to be reproducible.

As a result, several clinical trials have had to be terminated or weakened. Had those papers not set an artificially high standard for the performance of genomic signatures, researchers might have developed different signatures and designed other clinical trials. The money that went to fund those trials and related grant proposals might have been spent on other projects with a better chance of long-term success. This says nothing about the dashing of patient hopes or the public's faith in genomic research.

The NCI decisions were absolutely correct. In retrospect, the NCI reservations about taking the LMS to a clinical trial, reservations about using the chemosensitivity signatures in CALGB 30702, and questions about the reproducibility of the chemosensitivity signatures appear well-founded. As Dr. McShane notes in her overview (PAF 21, p.7), "if we are going to move clinical tests based on omics technologies into clinical trials where they will have an impact on patient treatment and outcome, we need to instill more rigor into the development and validation process."

We note that the assessments of methods and data the NCI performed were not, at heart, complex – they were all focused on answering questions about "what, precisely, did you do, and what, precisely, were the results you obtained?"

The currently acknowledged problems are all of types we described. The problems the NCI encountered both with the LMS and internally with chemosensitivity

signatures parallel problems we encountered and described publicly: mislabeling of samples, predictions going the wrong way, difficulty reproducing results, questionable claims of blinding (Baggerly and Coombes, 2009, The Cancer Letter, Oct 23, 2009).

Ongoing validation attempts have so far resulted in two of the chemosensitivity papers (Potti et al, Nat Med 2006, and Hsu et al, JCO 2007) being formally retracted; further investigations are underway.

The data and code should have been available from the outset. We are all too aware that reconstructions of the type evidenced here are time-consuming tasks. We thank the NCI for undertaking them. That said, it is not clear to us that verifying the basis for a phase II or phase III trial (the Duke and LMS trials, respectively) should require NCI compulsion of the data and code. In our view, these should be available in checkable form before the trials are begun. As the IOM committee deliberates about what should be required for the use of omics signatures in clinical trials, we hope they will keep these cases and principles in mind.

Duke Withheld Information from Reviewers

Summarizing the Duke review, the university's deans Kornbluth and Cuffe noted (PAF 1, p.4, Oct. 28, 2010): "An additional issue concerns the completeness of the data provided to the reviewers in order to conduct their review. It has been reported in a number of venues that the reviewers said they did not have sufficient data to fully evaluate the validity of the genomic predictors.

However, the reviewers reported that they were provided with comprehensive access and data, but also acknowledged that the published work of Nevins/Potti did not contain sufficient information for others to be able to reproduce their work. At the time, we were assured that the reviewers had received unfettered access to the Nevins/Potti data and labs."

The deans were recently asked about this point by reporter Eugenie Reich, of Nature. As posted on Nature's blog on Jan. 5, 2011, "Kornbluth responds that the review was conducted under the auspices of the Duke Institutional Review Board, which did receive a copy of the document from her.

But, she explains in a statement sent together with Cuffe, the board, in consultation with Duke's leadership, decided not to forward it to the reviewers, "it was determined that it would be best to let the data, publications, etc., speak for themselves and not bias the independent investigation for or against any party.

In retrospect, we did not realize that the data provided by our investigators were flawed (as the public record now shows), rendering an outside review addressing the methodology flawed as well. In hindsight, we would have ensured that the IRB provided all communication with Dr. Baggerly, recognizing the risk of bias. We've learned considerably from this process and are introducing key changes in the way we deal with research that will be translated to the clinical arena as a result," they say."

More recently, in a Nature news feature (Jan. 13, 2011, posted online Jan.11), further clarification was provided about who saw the Baggerly and Coombes analysis: "Kornbluth and Cuffe admit that, in consultation with John Harrelson, who was acting as chairman of Duke's Institutional Review Board, they decided not to forward the latest communication from Baggerly and Coombes to the rest of the board or the external reviewers."

We don't see how providing our report would have biased the investigation. Our report was not an ad hominem attack. We named specifics that could be checked to see if they were right or wrong, as facts. These included the problems noted, a year later, by the senior author in calling to retract the results. Withholding this information from the investigators made it harder for them to do their jobs properly.

The Duke statement indicates that "in retrospect, we did not realize that the data provided by our investigators were flawed (as the public record now shows)." We are at a loss to explain how this was missed. The cover letter accompanying our report was roughly 700 words, and explicitly states (with respect to the validation data), that:

"1. The sensitivity labels are wrong.

2. The sample labels are wrong.

3. The gene labels are wrong.

"All are 'wrong' in ways that could lead to assignment of patients to the wrong treatment."

The bulleted points above were extracted verbatim from the conclusions section of our full report's executive summary and linked to patient assignment specifically so that this point would not be missed. What else should we have said to highlight that the data were flawed?

Further, we see no justification for citing a review produced in ignorance of the facts as a validation of the approach, let alone claiming (The Cancer Letter, Jan. 29, 2010) that the "detailed external investigation and confirmation of the scientific methodology serve to strengthen the confidence in this evolving approach to personalized cancer treatment."

Letter to the Editor

NCI Biostatistician Clarifies Points Raised Jan. 7 Issue

To the Editor:

Two points in The Cancer Letter coverage of the Duke scandal Jan. 7 may be confusing to readers and would benefit from clarification:

--The description of the CALGB-30506 trial as a "large (> 1000 patients) trial;" the trial size should be understood as the *planned* sample size. The trial is still in accrual phase, so the number of patients currently enrolled has not reached the final size. The current accrual figures reported by CALGB to NCI on Jan. 7, 2011, are 128 patients pre-registered with 24 patients fully registered.

--The Cancer Letter's description of my quote as pertaining to "the model Duke researchers used to select therapy for lung cancer patients" could have inadvertently caused some confusion.

The quote pertained to an earlier version of the Lung Metagene Score (LMS) predictor that had been used in a pre-validation exercise in 2007 that was conducted as part of the decision-making process for approval of the CALGB-30506 trial.

The NCI would like to clarify that the version of the LMS predictor actually used in the trial apparently had been locked down to remove the random behavior prior to initiation of the trial. However, due to the randomness in the earlier version, we are unable to link the version of the predictor that was in use in the trial to a predictor that has been validated.

Further, it is important to emphasize that results of the LMS predictor were kept blinded in the CALGB-30506 trial, and no patient's therapy was influenced by those LMS results. The material excerpted from my prepared testimony that is presented in The Cancer Letter article on page 6 near the bottom of the right column ("An additional surprising and important finding . . .") accurately describes the situation in more detail.

Lisa McShane
NCI Biometric Research Branch

Correction

The Cancer Letter erroneously referred to the three Duke trials as "randomized." The phase II trials were multi-arm, but not randomized. Treatment was determined on the basis of genomic predictors.

In the Cancer Centers:

Michigan's Zhang Wins "Protein Science Olympics"

YANG ZHANG, of the University of Michigan, took top honors in the **Critical Assessment of Techniques for Protein Structure Prediction**, a biennial scientific competition to test protein structure and function prediction methods. Zhang's lab was ranked No. 1 in both protein structure and function prediction among more than 200 groups.

The winning team included Zhang, graduate student Ambrish Roy, and postdoctoral fellows, Dong Xu, and Jian Zhang. Zhang's lab also won CASP protein structure prediction competitions in 2006 and 2008.

"CASP is the Olympics of protein science, and Zhang is like a three-time Olympic champion," said Gilbert Omenn, director of the U-M Center for Computational Medicine and Bioinformatics.

For the competition, scientists were given the amino acid sequence of more than 100 unknown proteins and directed to predict what the detailed three-dimensional shape of each protein is and what the molecule does in living cells.

The ability to predict the three-dimensional protein structure from amino acid sequence by computer is extremely helpful to health research and the drug-discovery industry, and could make research more cost-effective.

"Many proteins, especially those embedded in the cell membrane, are difficult or even impossible to solve using current experimental techniques," said Zhang, associate professor of computational medicine and bioinformatics at the U-M Medical School. "Computational methods provide a possible avenue to deal with these molecules."

The focus of Zhang's U-M lab is to develop computer algorithms to predict three-dimensional structures of protein molecules from amino acid sequences. Approximately 15,000 registered scientists from 89 countries use the lab's on-line system and algorithms to generate protein structure and function modeling for their own research.

CLAIRE VERSCHRAEGEN was named interim director of the **Vermont Cancer Center**. She was also named professor and chief of hematology-oncology at the University of Vermont and Fletcher Allen Health Care.

Verschraegen specializes in rare cancers, such as mesothelioma, metastatic melanomas, sarcomas, and

gynecologic malignancies, as well as the study of new anticancer drugs and treatments for solid tumors.

Verschraegen will relocate from the University of New Mexico Cancer Center, where she is a professor of medicine in the Division of Hematology and Oncology, and director of translational therapeutics and clinical research. She also oversaw the Clinical Protocol and Data Management Core at the UNM Cancer Center, which received NCI designation in 2005. She is the principal investigator for the New Mexico Minority-based Community Clinical Oncology Program.

CLAYTON SMITH was named director of the Hematologic Malignancies Program at the **University of Pittsburgh Cancer Institute** and director of Leukemia and Stem Cell Transplant Clinical Services with UPMC Cancer Centers.

Smith served as the director of the Leukemia/Stem Cell Transplantation Program at the British Columbia Cancer Agency and as an associate professor of medicine at the University of British Columbia in Vancouver.

EDWARD SAUSVILLE, associate director for clinical research at the University of Maryland Marlene and Stewart Greenebaum Cancer Center, was named an editor in chief of the journal **Cancer Chemotherapy and Pharmacology.**

Sausville, who joined the Greenebaum Cancer Center in 2004, previously, served as associate director of the NCI Developmental Therapeutics Program.

He succeeds the late **Merrill Egorin**, of the University of Pittsburgh Cancer Institute, who was the editor in chief for more than 20 years.

VANDERBILT-INGRAM CANCER CENTER received two Early Detection Research Network awards from NCI. The awards support early detection of lung and colon cancers.

Pierre Massion, associate professor of Medicine and Cancer Biology, has been awarded $3 million over five years for the creation of the Vanderbilt Clinical Validation Center.

Daniel Liebler, the Ingram Professor of Cancer Research and professor of biochemistry, pharmacology and biomedical informatics, and David Tabb, assistant professor of biomedical informatics and biochemistry, have been awarded $3 million over five years for the creation of the Vanderbilt Biomarker Development Laboratory.

The BDL will be established within the Jim Ayers Institute for Precancer Detection and Diagnosis. The institute is dedicated to biomarker development.

Massion and his colleagues will recruit Nashville-area patients at high risk for lung cancer for a screening trial called the "Nashville Early Diagnosis Lung Cancer Project," and will evaluate a set of biomarkers to determine whether the molecular signatures are helpful in early diagnosis of lung cancer. Biomarkers may be found in blood, urine or tissue samples from patients.

Otis Rickman, director of bronchoscopy, and **Ronald Walker**, professor of clinical radiology and radiological sciences, will participate in the lung cancer study.

Massion's group will be collaborating with Liebler and Tabb who will develop and apply new proteomics methods and informatics tools to identify proteins which may be useful as biomarkers for lung and colon cancer. This multidisciplinary approach will take advantage of Vanderbilt's growing expertise in biomarker research in cancer.

The NCI grants are matched by institutional support from Vanderbilt, including funds from the Clinical and Translational Science Award, the Thoracic Oncology Center, Vanderbilt-Ingram Cancer Center and the Ayers Institute.

UNIVERSITY OF COLORADO CANCER CENTER researcher **Carol Sartorius** received a $1.25 million grant from the NCI to investigate the role of stem-like cells in estrogen receptor-positive breast cancer.

Sartorius, associate professor of endocrinology at the University of Colorado School of Medicine, was the first person to show that the hormone progesterone regulates a stem-like cell phenotype in breast cancer. In a July 28, 2010, paper in Breast Cancer Research Treatment, Sartorius and UCCC breast-cancer researcher and clinician **Peter Kabos**, assistant professor of medical oncology at the SOM, identified a pool of cells that lose lose both estrogen and progesterone receptors and gain expression of the protein cytokeratin 5. They showed that cells expressing cytokeratin 5 tend to survive treatment and endocrine therapy.

Sartorius said the grant will allow her to figure out how these cytokeratin 5-expressing cells are regulated in ER+ breast cancer, how they make the tumor more drug-resistant. She will collaborate with UCCC researcher **Dan LaBarbara**, assistant professor of pharmaceutical sciences at the University of Colorado School of Pharmacy, to figure out whether the cells can be targeted with novel drugs.

Sartorius is also working with UCCC researcher

Jennifer Richer, associate professor of pathology at the SOM, who is an expert in the role of microRNAs in breast cancer.

They received a $375,000 Idea Grant from the **Department of Defense** to narrow down which of a group of microRNAs are involved in changing cells from being differentiated to being stem-like. Kabos will also collaborate on the DOD grant.

FOX CHASE CANCER CENTER has recruited three staff members.

• **Marcia Boraas** returned to Fox Chase as an attending surgeon in the department of surgical oncology. She specializes in treating patients with breast cancer, as well as those who may be at high risk of the disease and patients with suspected breast cancer.

Boraas returned to Fox Chase after seven years at the University of Pennsylvania, where she served as an attending surgeon and clinical associate professor. She began her medical career at Fox Chase in 1983 after completing residency in general surgery and clinical fellowship at the Hospital of the University of Pennsylvania.

• **Zeng-Jie Yang** joined Fox Chase as an assistant professor in the Cancer Biology Program. Yang comes to Fox Chase from the Department of Pharmacology and Cancer Biology at Duke University, where his postdoctoral research primarily focused on the origins of medulloblastoma.

• **Andy Andrews** joined Fox Chase as an assistant professor in the Cancer Biology Program. Andrews comes to Fox Chase after concluding a postdoctoral fellowship at the University of Colorado in the lab of HHMI Investigator Karolin Luger. He studies epigenetics, changes in gene expression controlled by mechanisms outside of the underlying DNA sequence.

Patient Advocacy:

Bill Clinton Praises NBCC Goal To End Breast Cancer by 2020

FORMER PRESIDENT BILL CLINTON endorsed the **National Breast Cancer Coalition's** campaign to end breast cancer by 2020.

"The stakes are too high, the losses have been too great to let another decade go by…. And if I know anyone who can do this, it's you," Clinton says in a video clip displayed on the NBCC website http://www.stopbreastcancer.org/2020/president-clinton-nbcc.html

During his presidency, Clinton established the National Action Plan on Breast Cancer and appointed NBCC President to serve as its co-chair. President Clinton later worked with NBCC on the Department of Defense Breast Cancer Research Program and legislation such as the Centers for Disease Control Breast and Cervical Cancer Treatment Act.

In 2005, President Clinton and NBCC launched the Virginia Clinton Kelley Fund to honor the memory of his mother.

THE NATIONAL PATIENT ADVOCATE FOUNDATION has created a **Comparative Effectiveness Research Database**, which is available to the public on its website, www.npaf.org.

The database compiles comparative studies funded by NIH and the Agency for Healthcare Research and Quality. The majority of reviews are funded through the $1.1 billion in CER funding allocated by the American Recovery and Reinvestment Act, which was signed into law in February 2009.

The NPAF CER Database includes 224 NIH CER projects along with a separate database which lists 49 NIH CER cancer-related studies. Each project title contains a link to the NIH RePORTER website, which holds additional information on each individual project.

The database also includes 72 ARRA-funded grants and 280 non-ARRA-funded grants under AHRQ's Effective Health Care Program, which funds individual researchers, research centers and academic organizations to work together with AHRQ to produce effectiveness and CER for clinicians, consumers and policymakers.

The Federal Coordinating Council for CER defined CER as "the conduct and synthesis of research comparing the benefits and drawbacks of different interventions and strategies used to prevent, diagnose, treat and monitor health conditions in 'real world' settings.'

Professional Societies:

Kornfeld, Rothman, Schekman Win Edmund B. Willson Medal

THE 2010 E.B. WILSON MEDAL of the American Society for Cell Biology was awarded to **Stuart Kornfeld** of the Washington University of St. Louis, **James Rothman**, of Yale University School of Medicine, and **Randy Schekman**, of the University of California, Berkeley.

The medal, the society's highest honor, is named after Edmund Beecher Wilson, credited as America's first cell biologist, and recognizes far-reaching contributions to cell biology over a lifetime in science.

THE ASCO CANCER FOUNDATION appointed **Gabriel Hortobagyi** to its board of directors and reappointed **Sandra Swain** and **John Glick** to serve additional three-yeat terms.

As the philanthropic arm of the American Society of Clinical Oncology, the foundation seeks support for programs including thematic and Annual Meetings and ASCO's patient website, Cancer.Net. The foundation finances the society's state affiliate program and international courses and fellowships. The foundation's grants and awards program promotes career development of clinicians and researchers. Over the past 27 years, the foundation paid out $67 million in research grants.

Hortobagyi, a past president of ASCO, is a member of the faculty at M.D. Anderson Cancer Center, where he is chair of the Department of Breast Medical Oncology.

Glick, a past president of ASCO, is the vice president of the University of Pennsylvania Health System and associate dean for resource development and professor at the University of Pennsylvania School of Medicine.

Swain is the medical director for the Washington Cancer Institute and Washington Hospital Center and a professor of medicine at Georgetown University. Swain led intramural breast cancer clinical research effort at NIH. A member of the ASCO board of directors, she was recently elected to serve as ASCO president, beginning in 2012.

THE AMERICAN SOCIETY OF HEMATOLOGY announced the 2011 Scholar Award recipients. The program supports hematologists who have chosen a career in research by providing partial salary or other support during the critical period required for completion of training and achievement of status as an independent investigator.

The awards are for a two- to three-year period, totaling $100,000 for fellows and $150,000 for junior faculty. The recipients are: **Omar Abdel-Wahab** (Memorial Sloan-Kettering); **Karen Bunting** (Weill Cornell Medical College); **Brian Edelson** (Washington University School of Medicine); **Hiyaa Ghosh** (Columbia University Medical Center); **Andrew Muntean** (University of Michigan); **Mary Philip** (University of Washington); **Jonathan Thon** (Brigham and Women's Hospital); **Jennifer Trowbridge** (Dana-Farber Cancer Institute); **Pieter Van Vlierberghe** (Columbia University Medical Center); **Anil Chauhan** (University of Iowa); **Jill Johnsen** (University of Washington); **Michael Kharas** (Brigham and Women's Hospital); **George Murphy** (Boston University School of Medicine); **Daniel Starczynowski** (University of Cincinnati); **Catherine Yan** (Beth Israel Deaconess Medical Center); **Samantha Jaglowski** (Ohio State University); **Holbrook Kohrt** (Stanford University); **Veronika Bachanova** (University of Minnesota); **William Savage** (Johns Hopkins University).

The Joanne Levy Memorial Award for Outstanding Achievement, given to the current ASH Scholar with the highest scoring abstract for the ASH annual meeting, went to **Grant Challen**, of the Baylor College of Medicine.

THE AMERICAN CANCER SOCIETY gave national awards to five individuals:

• **Olufunmilayo Olopade** received the Distinguished Service Award in recognition of major contributions and commitment in the field of cancer. She is the American Cancer Society clinical research professor of medicine and human genetics, University of Chicago Pritzker School of Medicine. By establishing and maintaining a database of high-risk individuals, Olopade has been able to examine the contribution of BRCA1 and BRCA2 mutations in diverse populations and her laboratory was the first to describe recurrent BRCA1 mutations in extended African American families with breast cancer, a study she has extended to the founder population of African Americans in West Africa.

• **Peter Sheldon** and **Karen Moffitt** were awarded the National Volunteer Leadership Award in recognition of their volunteer service to the society. Sheldon, of Lansing, MI, has been acrive with the s for over 20 years and was involved in the launch of the American Cancer Society Cancer Action Network. Moffitt, of Tampa, has advocated for millions of dollars in state and federal support for cancer research in Florida.

• **Sister Mary Scullion**, of Philadelphia, received the Humanitarian Award for her efforts to begin an internationally recognized organization addressing the prevention of homelessness and alleviation of poverty. She is a founder of Project HOME (Housing, Opportunities, Medical Care and Education).

• **Anthony Back**, of Seattle, received the Pathfinder in Palliative Care Award for his innovative contributions to the advancement of the field of palliative care. Back is the director of palliative care and the program on cancer communication at the Seattle Cancer Care Alliance. He has developed creative OncoTalk and OncoTalk Teach programs to improve doctor-patient communication.

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COMPREHENSIVE CANCER CENTER
UNIVERSITY *of* CALIFORNIA · IRVINE
A National Cancer Institute-Designated Comprehensive Cancer Center

DEPUTY DIRECTOR POSITION AVAILABLE

The University of California, Irvine is recruiting a physician scientist for a tenured position at the associate or full professor level who will also be the Deputy Director of the Cancer Center. We are seeking an experienced translational scientist with an established research program focused on either basic/translational investigations or clinical/translational science. This is a senior leadership position within a National Cancer Institute designated Comprehensive Cancer Center. Responsibilities of the selected individual would include:

(1) Conducting a translational research program with external peer-reviewed funding.
(2) Bridging basic, clinical and cancer control research among the 6 research programs with the goal of facilitating translational programs, P0-1s, SPOREs and similar multi-investigator grants and contracts.
(3) Providing senior leadership for the physician-scientists and clinical investigators in the Center.
(4) Managing the clinical research infrastructure within the center.
(5) Representing the Cancer Center throughout the campus and greater community.

As the current long-term Director has announced his departure from this role following the next CCSG review, responsibilities of the Deputy Director will expand in the near future to include transitioning the Center with new leadership.

Applicants must hold an MD or equivalent degree, be board certified in their cancer related sub-specialty, and be eligible to obtain an active license to practice medicine in the state of California.

For more information, contact Krista Hollinger, MPH at kholling@uci.edu.

Application Procedure: Interested candidates must submit a cover letter, curriculum vitae, statement of research, statement of teaching, and contact information for 3-5 references via the University of California's Academic Personnel RECRUIT system at http://recruit.ap.uci.edu. Please reference OEOD# 5012.

The University of California, Irvine has an active career partner program and an NSF ADVANCE Program for Gender Equity and is an Equal Opportunity Employer committed to excellence through diversity.