THE CANCER LETTER

Vol. 37 No. 27
July 8, 2011

PO Box 9905 Washington DC 20016 Telephone 202-362-1809

Revamping Cooperative Groups

Advocates Call for Metrics, Action Plan In NCI's Redesign of Cooperative Groups

By Paul Goldberg

NCI should rely on prospectively chosen metrics as it proceeds to reorganize its cooperative groups, patient advocates involved in the groups said in a letter to Director Harold Varmus and Deputy Director for Clinical and Translational Research James Doroshow.

The institute should "define what constitutes success in terms of concrete endpoints and timeframes and decide how these will be managed," states the letter, dated June 30.

The letter, signed by 68 advocates who work with the cooperative groups, also urged NCI officials to respond with an action plan for implementation of the recommendations.

Institute officials have said that under the reorganization plan they would support no more than four adult cooperative groups. Currently there

(Continued to page 7)

NCI News:

Cruz-Correa, Cullen, Olopade, Samet and Sellers Appointed to the National Cancer Advisory Board

The **National Cancer Advisory Board** appointed five new members: **MARCIA CRUZ-CORREA, KEVIN CULLEN, OLUFUNMILAYO OLOPADE, JONATHAN SAMET** and **WILLIAM SELLERS**.

Cruz-Correa is associate professor of medicine at the University of Puerto Rico, Puerto Rico Cancer Center, and visiting assistant professor of medicine at Johns Hopkins School of Medicine.

Cullen is director and professor of medicine at the University of Maryland Greenebaum Cancer Center.

Olopade is director of the Cancer Risk Clinic at University of Chicago Medical Center, as well as associate dean for global health and professor of medicine and human genetics at the Pritzker School of Medicine.

Samet is professor and Flora L. Thorton Chair in the department of preventive medicine at the USC Keck School of Medicine, and director of the USC Institute for Global Health.

Sellers is vice president and global head of NIBR Oncology Research at Novartis Oncology.

They will serve on the board until 2016.

One slot on the board remains vacant. The administration has yet to appoint new members to the President's Cancer Panel.

The Duke Scandal:

NCI Official Tells Omics Panel About "Troubling Accusations"

By Taylor Doherty

Duke University researchers may have mishandled data in at least one of three discredited cancer trials, raising further concerns related to the Potti-Nevins Affair.

This acknowledgment by an NCI biostatistician followed a question from a member of the Institute of Medicine's Committee to Review Omics-Based Tests for Predicting Patient Outcomes in Clinical Trials.

The committee's task is to avoid repeating the mistakes that occurred at Duke—where the flawed genomic predictors were used to assign patients to different cancer treatments—and to define best practices in testing interventions based on genomics and proteomics.

"In those three Duke prospective clinical trials—based on the insights that you've provided to us throughout…that for the most reliable level of validation, it should come from a clinical trial where the study was conducted; the outcomes are recorded according to good clinical practice in a locked database, where that database is kept confidential from the investigators—do you have any insights as to whether or not that process was followed in those three Duke clinical trials?" asked IOM committee member Thomas Fleming, a biostatistician at the University of Washington.

"I am aware of allegations that they were not followed in at least one of the trials," responded Lisa McShane, the NCI biostatistician who has reviewed the research.

"Duke officials are aware of that and have investigated. I don't know the details of exactly what was found in the investigation, but that is a real issue.

"If you cannot rely on the data in the trial having been collected in a way that is free of errors—free of potential manipulation—that is a very serious problem."

McShane declined to elaborate on the details of the allegations, but noted that there is the possibility that people who should not have had access to the data, might have—which would open the possibility for data manipulation.

McShane urged the interested parties to request further information directly from Duke, because the university is in a better position to either confirm or refute the validity of the charges.

"There's quite frankly a bit of—not a bit, a lot of—detail in there. Names named, very troubling accusations made," McShane said. "And I would prefer not to release that, because it's so sensitive, but if you have no success getting it from Duke, I can certainly take it to the NCI leadership and we can decide what we think we could release."

McShane also outlined the many things that can go wrong in research that's searching for genomic signatures.

An external reviewer may have no way of knowing that a researcher chose to omit certain data points from the raw set, leaving open the possibility that a scientist might discard points that do not fit nicely with their model.

"This is really, really tough," McShane said. "This is why, when we went back to look at the cisplatin predictor, I pressed Potti on exactly how he went from the original 30 publicly-available cell lines to the 15 he used for his predictor. This can introduce a huge bias, and it's a bias that is almost impossible to detect."

Duke officials did not respond to questions from The Cancer Letter.

In a related development, The New York Times published a front-page story on the Duke scandal July 8: http://www.nytimes.com/2011/07/08/health/research/08genes.html

Follow us on Twitter: @TheCancerLetter

THE CANCER LETTER

® The Cancer Letter is a registered trademark.

Editor & Publisher: Paul Goldberg
Copy Editor: Conor Hale
Intern: Ridge Phelan Montes

Editorial, Subscriptions and Customer Service:
202-362-1809 Fax: 202-379-1787
PO Box 9905, Washington DC 20016
General Information: www.cancerletter.com

Subscription $395 per year worldwide. ISSN 0096-3917. Published 46 times a year by The Cancer Letter Inc. Founded Dec. 21, 1973, by Jerry D. Boyd.

Advocacy:

ACS CAN Urges President, Congress To Protect Cancer Program Funding

By Ridge Phelan Montes

The American Cancer Society Cancer Action Network, the society's advocacy organization, is requesting that White House and Congressional leaders ensure federal funding for cancer prevention and care programs, despite anticipated spending cuts.

Christopher Hansen, president of ACS CAN, sent a letter July 6 asking President Barack Obama and House and Senate leaders to fund three programs in particular: the Prevention and Public Health Fund, Medicare and Medicaid.

The Prevention and Public Health Fund, created through the Patient Protection and Affordable Care Act, provides communities and non-profits with financial support for tobacco control and other preventive programs.

"Prevention has the potential to transform our health system in new and innovative ways that will lead to a healthier population and lower health care costs," Hansen wrote in his letter.

Meanwhile, Medicare and Medicaid support nearly 50 percent of American cancer patients. "These individuals are generally our oldest, least healthy and most vulnerable citizens, and they have no alternative way of accessing affordable medical care," Hansen wrote.

According to Hansen, 60 percent of cancer deaths are preventable through effective prevention, earlier detection and better access to care. In past years, federally supported research and prevention programs helped reduce death rates, Hansen wrote, and that "further progress is dependent upon federal leadership and financial support."

"We know that the deficit talks will require cuts in spending," Hansen wrote, "but when it comes to deciding what is important, we hope you will agree that a full scale effort against cancer, a disease that kills more than half a million Americans every year, should be priority number one."

The complete letter follows:

Dear President Obama, Leader Reid, Leader McConnell, Speaker Boehner, and Leader Pelosi:

As the representative of millions of cancer patients and survivors throughout the United States, the American Cancer Society Cancer Action Network (ACS CAN) is mindful of the necessity of reducing the federal deficit and the difficulty of the task you face in coming to such an agreement over the next several weeks. That is why we are asking you to make the fight against cancer a national priority.

Cancer continues to kill more than 1,500 Americans every day—over 570,000 each year. It strikes one in every two men and one in every three women—our parents, our children, our friends and loved ones.

Even so, we are making progress against the disease thanks to federally supported research and prevention programs. Past bipartisan support for cancer research and cancer prevention and early detection has resulted in reduced rates of death from the disease and corresponding increases in cancer survivorship.

Advances in genomic research have given scientists an understanding of why different cancers occur, leading to new discoveries about how to turn off the genes that control tumor growth.

Real breakthroughs are happening, such that today nearly one in twenty Americans is a cancer survivor, thanks in large part to the scientific advances made possible and supported by the taxpayers. Further progress is dependent upon federal leadership and financial support, and we urge you to make cancer research and prevention funding the highest priority.

We know that sixty percent of cancer deaths can be prevented through better prevention and early detection and access to health care. For example, the National Breast and Cervical Cancer Early Detection Program (NBCCEDP) has provided more than nine million mammograms and Pap tests to more than three million women and detected more than 47,000 cases of cancer over the past twenty years.

Because so many lives can be saved through tobacco control, better diet and exercise and access to early detection and treatment, we strongly support full funding of the Prevention and Public Health Fund. Prevention has the potential to transform our health system in new and innovative ways that will lead to a healthier population and lower health care costs.

It is important to note that approximately fifty percent of all cancer patients are served by either Medicaid or Medicare. These individuals are generally our oldest, least healthy and most vulnerable citizens, and they have no alternative way of accessing affordable medical care. The viability of Medicare and Medicaid needs to be protected to assure health care coverage for our nation's oldest and most vulnerable, and to maintain the commitment to all Americans that their health care is an important national priority.

Again, we know that the deficit talks will require

cuts in spending. But when it comes to deciding what is important, we hope you will agree that a full scale effort against cancer, a disease that kills more than a half a million Americans every year, should be priority number one. For cancer patients it's a matter of life or death, and we thank you for understanding the urgency of the fight.

Sincerely,
Christopher W. Hansen
President, ACS CAN

Letter to the Editor:

Henschke: I-ELCAP Conceived As "Data-Pooling Program"

To the Editor:

Your June 24 edition of the Cancer Letter not only again misrepresented I-ELCAP's work. It also missed a key opportunity to bring to the public's attention the threat that the Philip Morris lawsuit poses to academic freedom and cancer research.

First, prior to your publication, I clearly outlined to you the difference between the statements "10 percent of the consents have been documented historically" and "unable to locate 90 percent of the consent forms." You correctly quoted the confidential report, however, that written statement is very different from the one you attribute to an anonymous "individual involved with the review" that "I-ELCAP leaders acknowledged that they were able to locate only 10 percent of informed consent forms." That statement is filled with innuendo and implies that we were asked to locate additional informed consents and were unable or unwilling to do so—a flat out lie.

As you know, and have printed:

• I-ELCAP was conceived as a data pooling program with its own separate IRB approval and oversight;

• Such data pooling programs are **not required to review or obtain the consent forms** of participants at the collaborating institutions to report the data;

• All of our contributing institutions have their own IRB approval for performing screenings and are responsible for obtaining their own consents according to their own IRB requirements;

• There are **no requirements that the data pooling center maintain copies of the consents;**

• I-ELCAP's decision to voluntarily perform limited random sample audits of charts including consents at the contributing institutions as part of its overall quality assurance program in no way means anything was missing; and

• The I-ELCAP pooling center's only responsibility was to be certain that each collaborating institution had their own IRB approvals and to rely on their representation of having obtained consent consistent with their institutions' policy.

Second, your coverage of the Philip Morris subpoena completely missed the mark. Philip Morris, simply by use of invasive subpoenas, sought to destroy an ongoing research collaboration that now stands to address important outstanding questions that are being raised about screening for lung cancer. The potential for a giant tobacco company to destroy academic research just because it does not like certain results has enormous implications for society at large; and would have a chilling effect on research in general. This is the story that a newsletter dedicated to covering cancer should be writing.

I-ELCAP results, among other studies, are being used by plaintiffs as part of their basis for requesting medical monitoring. My colleague David Yankelevitz and I are not parties in that lawsuit nor have we been expert witnesses. Nonetheless, we were subjected to a highly intrusive third-party subpoena that requested all of our data and any correspondence relating to screening. It represented an all-out assault on academic freedom for researchers everywhere in the United States. In our case, it had the potential to destroy the only large scale, ongoing lung cancer screening research program in the U.S.

It would be a major betrayal of the multiple CT screening programs and thousands of screening participants for us to be forced to turn over their data. Imagine how a participant who is enrolled in the study, or an individual who lost a loved one to lung cancer, would feel to learn that the data they or their loved one contributed was now being used to defend the industry that likely caused the disease. How could they continue to participate in the study? Were Phillip Morris to be successful with this subpoena, the precedent it would set would endanger research in general, leaving it to the courts to decide who has access to data and when data can be snatched away simply because a large company decides that certain research may have a negative impact on their product.

I have to wonder why you have chosen to attack cancer research by mischaracterizing information rather than seizing this opportunity to shed light on a case that has the potential to seriously damage academia and

research in general. I would think this would be a topic of great interest to your readers in the medical community.

Although scientists can and should disagree with each other concerning their published works, I ask that the Cancer Letter exercise more objectivity and accuracy in its reporting. Moreover, when a tobacco company uses heavy handed tactics in an effort to discourage cancer research, I would expect that the Cancer Letter would recognize the potential threat, not just to I-ELCAP but to the entire scientific community.

I appreciate your time and, as before, I ask that you place your personal agenda aside and accurately report the facts.

Sincerely,

Dr. Claudia Henschke

Letter to the Editor:

Walker: Avastin Hearing Became Pazdur's "Kangaroo Court"

To the Editor:

As is typical of The Cancer Letter's Paul Goldberg, his coverage of Genentech's appeal of FDA's decision to rescind approval of Avastin for the treatment of metastatic breast cancer (MBC) provided background, insight, and a description of the proceedings that captured both the unique nature of the event and the actions of the "Avastin women." Those women came to the hearing on their own volition and at their own expense to be seen and heard by the FDA bureaucrats and panelists deciding their fate. As a patient advocate supporting those women and helping Terry Kalley (www.fameds.org), husband of one of the Avastin women prepare for and organize the rally, I became a subject of the story.

I am writing to clarify a few of The Cancer Letter's observations.

In the first version of the story released early on July 1, a sentence strongly implied that many members of the Abigail Alliance opposed the 1962 requirement that drugs demonstrate efficacy. The implication was followed by a link to a 2005 Cancer Letter story. I contacted Mr. Goldberg to inform him that the Abigail Alliance had never taken that position, and that in fact the 2005 story included extensive coverage and quotes (from me) regarding how the Abigail Alliance thought the FDA should apply the efficacy standard differently. Mr. Goldberg agreed to modify the sentence and re-issue the article.

For the record, the Abigail Alliance has always supported the need for safety and efficacy testing, and for standards to guide drug development and approval. Our opposition to FDA practices and policies have always centered on the inflexibility of the process toward progress delivery for those who can't wait. Our earliest proposals for FDA reform, dating back to 2001, included many of the proposals now entering the mainstream, such as modernizing FDA's regulatory science, reinvigorating Accelerated Approval for serious and life-threatening diseases other than HIV/AIDS, creating investigational drug access programs that would actually work for patients, and creating a new, early conditional approval mechanism to make the system more responsive to the many thousands now abandoned by it.

Then and now, we see the problems with our system and the many people and organizations inside and outside the FDA who fight to maintain the status quo, from the perspective of well-informed patients and family members being denied access to obvious medical progress. The clichéd "greater good" arguments used to defend obsolete regulatory and scientific approaches to drug development, approvals and availability, look a lot less "good" when one has become a member of the ever changing population of people who don't have time to wait for a plodding regulatory process to grind to its conclusion. As a result, we see the many problems with the system earlier than most—because we are being directly affected by those problems.

It has been a frustrating 10 years. It is very difficult to change the status quo at a place like the FDA, an opaque agency with an aversion to listening to the public, and an even worse record of responding. We learned early on that there are only two ways to get the attention of the FDA. Blindly support their efforts to maintain the status quo and hope they embrace you (but accomplish nothing except attracting funding from financial special interests thus converting from an advocate to a paid cottage industry), or openly and aggressively challenge them in ways they can't ignore. We chose the latter, because the status quo wasn't then and isn't now, acceptable.

It is encouraging to see others finally recognize that we have been right about some of the major problems at FDA. Last week BIO proposed that FDA should use a "progressive approval system" based on a "weight of evidence" approach, and this week Friends of Cancer Research said there should be an "expedited approval" pathway in a Congressional hearing. Those proposals sound a lot like the proposals we made in our Citizen's Petition submitted to FDA in 2003, pursued

in our Constitutional lawsuit between 2003 and 2008, and again proposed in the Access Act, introduced three times in Congress over the last several years. Some of our other important proposals are also popping up under new brands.

At no time did we ever propose or pursue elimination of the efficacy standard. Our current thinking on what Congress should do regarding the efficacy standard, and how best to modernize FDA's science, including the reasoning behind those proposals, can be found in our recent Food and Drug Law Institute Policy Paper (Vol 1, Issue 7, April 13, 2007) posted on our website at http://abigail-alliance.org/docs/FDLISteveWalker.pdf and at www.fdli.org.

The Cancer Letter correctly reported that I asked for a meeting with the Commissioner, but didn't know that I was asking on behalf of the Avastin women. Near the end of the hearing, when the direction of the panel was becoming clear, I asked them if they would like to meet with the Commissioner. They responded in the affirmative, and I left the seating area and eventually the hearing room to request (actually demand) that they be granted that meeting. To their credit, FDA officials quickly moved to request the meeting with Dr. Hamburg. When I returned to the hearing room, the Avastin women were standing, silently.

Ultimately, Dr. Hamburg (who was off campus) refused to meet with the women at any time, claiming that because a process was underway, she could not. The Avastin women were not then and are not now parties to the hearing process; consequently the Commissioner's refusal to meet with them seemed calculated and without a valid procedural basis. I asked for an explanation from an FDA attorney, and my request was refused. I was then told quite bluntly that no one at FDA would meet with the Avastin women—an unfortunately typical FDA response to the legitimate concerns and rights of patients with serious and life-threatening diseases.

Mr. Goldberg's account of my comments at the end of the hearing regarding its sham nature is accurate as far as it goes, but he did not link my comments to the reasons for them. On the previous day, I explained during the public participation session of the hearing that virtually every physician member of the Oncologic Drugs Advisory Committee (ODAC) is selected by the Office of Oncology Drug Products (OODP), directed by Dr. Richard Pazdur, including any Temporary Voting Consultants who sit for specific ODAC meetings. This clear violation of the intent of the Federal Advisory Committee Act (FACA) that advisory committees be free of undue influence from the agency, and agency personnel, asking them for advice, had long been a concern of the Abigail Alliance, and the subject of several efforts to address the problem with FDA, beginning in 2005.

The panel selected for the hearing included no physicians with expertise in breast cancer (a fatal flaw all by itself), and all but one of the physicians voting on the panel had previously voted to rescind approval of Avastin for metastatic breast cancer in July 2010. The fifth voting physician had been appointed to the ODAC by Dr. Pazdur in May, well after the hearing had been announced and scheduled, and "separation of functions" was initiated for the hearing by FDA. The ingrained and intentionally formed selection bias of the panel was obvious. They were there to rubber stamp Dr. Pazdur's decision.

Dr. Pazdur was the FDA official that decided in December to revoke approval of Avastin for MBC, based at least in part on the advice received from his ODAC in July 2010, and was the equivalent of the prosecutor at the hearing for the FDA. Under the separation of functions decision (which was supposed to render CDER an equal petitioner with Genentech at the hearing with no role in its planning or execution), every voting physician member of the panel had been appointed to ODAC by Dr. Pazdur.

Under the intent of FACA, ODAC members should not be selected by Dr. Pazdur or his office. That Dr. Pazdur probably didn't make the final selection of the five physicians on the hearing panel doesn't mitigate his influence in selecting all of his ODAC members based on his universally applied litmus test that only physicians highly likely to agree with his policies and positions receive his recommendation (in effect an appointment) for ODAC.

It was a sham hearing on a matter with life and death consequences for the Avastin women, and for thousands more, already diagnosed and not yet diagnosed, who weren't there. The panel selection rendered the hearing a kangaroo court.

I was also misquoted in the story. In my comments to the panel at the end of the hearing, I actually said, "This was a close call, and yet not even a dissenting thought, let alone a dissenting vote" or something very close to that (Mr. Goldberg misquoted me as saying it was "not" a close call). My point was that from a medical, scientific, regulatory and legal perspective, it really was a close call, which in a fair hearing with a panel that had not already made up its mind, would have prompted an active and open-minded debate on the merits. That debate would have included an

acknowledgment that the data were generally positive across all the trials, the FDA appeared to have in fact moved the goal posts, most of the modern medical world disagreed with FDA on this one, and while the trials may not have established clinical benefit to the point needed for regular (full) approval, the available evidence placed Avastin for MBC squarely within the standards for retention of Accelerated Approval.

The panel should have been instructed by FDA attorneys that leaving the drug on the market with an Accelerated Approval would fall squarely within the limits set by the statute, and that the FDA's position was based on policy crafted by FDA staff, not law or regulation. In fact, allowing more than "one bite at the apple" (the cliché batted around during the hearing by FDA and the panelists as some kind of heinous violation) was in fact quite legal, reasonable, within the intent of the law, and probably appropriate in this case. What would the votes have been if the panel had been properly instructed on any of this?

Lives really are at stake here, and based on the facts, it is more likely than not that FDA's rigid, policy-based decision is medically and scientifically wrong; an extreme position forced forward in a sham hearing lead from the top levels of the agency. It is now up to Commissioner Hamburg to make the final decision based on a deeply flawed hearing process.

Steven Walker is a co-founder of the Abigail Alliance for Better Access to Developmental Drugs.

Paul Goldberg responds: The Cancer Letter did modify the article soon after it was posted to describe Mr. Walker's position on efficacy with greater clarity. Also, Mr. Walker is correct that at the meeting he referred to the vote as "a close call." Someone was talking over him, and I misheard him.

Revamping Cooperative Groups:

Patient Groups Write Two Letters Stating Positions on Reform

(Continued from page 1)

are nine are in operation.

On the same day, patient advocates involved in the Children's Oncology Group wrote a separate letter, urging Varmus and Doroshow to learn from the experience of the four children's groups, which merged into a single administrative entity a decade ago.

"Some of us did experience the consolidation of the four legacy pediatric cancer research organizations into COG and hope that lessons from that experience can be applied to the [current] implementation," COG advocates wrote.

In May, the Coalition of Cancer Cooperative Groups submitted a joint letter to NCI, proposing eight "guiding principles" for change (The Cancer Letter, May 20). The letter was signed by the chairs of all 10 groups. The chairs had previously endorsed the recommendations for restructuring the clinical trials system made by the Institute of Medicine in September 2010.

The June 30 letters were submitted as part of the public comment period for the NCI Funding Opportunity Announcement that will be presented at the next meeting of the Board of Scientific Advisors, Nov. 7-8. The next update on the subject is scheduled for the July 13 meeting of the NCI Clinical Trials and Translational Research Advisory Committee.

COG doesn't have to go through consolidation.

However, the group is affected by changes that are mandated by NCI as part of the broad reorganization effort.

"Although [COG] will not be directly impacted by the implementation, we are keenly aware that ultimately any slowing of progress in the adult clinical trials could adversely affect clinical research in children," said the COG advocates' letter, signed by six advocates.

COG is switching to the Medidata Rave data capture system, which NCI has acquired for use in cooperative group trials. Also, the pediatric group could end up being affected by changes in the biospecimens banks.

Originally, NCI officials said the five cooperative groups would be supported by no more than three grants for biospecimen repositories. However, that plan was shot down by the Board of Scientific Advisors in March, and it appears that it has been tabled by NCI until the FOA for reorganization of the groups is approved (The

Cancer Letter, March 11).

The idea of reliance on metrics was proposed by Michael Katz, a business consultant and chair of the Patient Advisory Board of the Coalition of Cancer Cooperative Groups. Katz, a multiple myeloma survivor, is vice president of the International Myeloma Foundation.

Patients are in a position to speak more freely than researchers and group chairs, Katz said to The Cancer Letter.

"There are things in that letter which others would agree with but would be uncomfortable saying in public," Katz said. "We are not the ones that are out there applying for the grants. There is a competitive grant cycle that's about to begin, where only some people will remain standing. Advocates are not going to be influenced by considerations around funding and not try to be politically correct."

Katz said he hopes that NCI would respond with an action plan sometime next month. "We think we are entitled to a response as the ultimate beneficiaries of the system," he said. This conversation should take place before the institute starts finalizing the funding opportunity, he said.

As it stands, Katz said he is not convinced that the consolidations of the groups in recent months have been optimal. "When someone important like NCI says something like, 'There is going to be four groups instead of nine,' stuff begins, even though it hasn't been formally decreed yet," he said. "All this irreversible stuff is happening without any foresight and forethought about whether it's the right way to do it."

Katz describes his repeated suggestions that scientists rely on metrics of performance as something of a "personal theme." He had proposed metrics for evaluating the effectiveness of central IRBs.

"In my day job I am a management consultant," Katz said. "We always rely on metrics to figure out where the problems are and what solutions are appropriate. It's bizarre to me, because when it comes to conducting a scientific experiment, metrics are everything. There is such an incredible amount of rigor around defining endpoints, and exactly what you are going to do, and how you are going to measure, and what constitutes equipoise, and when you need to stop a trial or modify a dose.

"But when they are working on the system they are running, they don't see that. People that are so skilled and so rigorous in protecting human subjects in clinical trials and verifying that they have found out quality information you can act on don't have that sense at all in working on their own systems.

"In business, or in this type of research enterprise, the kind of precision brought to the trials is not feasible. When measuring market share or profitability, critical measures for business, there are almost always issues getting the exact data. One needs to rely on estimates and do a bit of reasonability testing to get metrics that are useful.

"Unfortunately, this disdain for the use of what in business we call 'professional judgment' and the obsession with perfect data often means that the leaders of our national cancer research enterprise are flying blind for want of acceptable instrumentation."

The cooperative group advocates letter doesn't propose specific metrics. The COG letter does.

They are:

• The development of all key clinical trials;

• Maximizing patient enrollment in clinical trials;

• Special development of clinical trials for rare tumors;

• Increased diversity in the participation in clinical trials, particularly under-represented minority communities.

• Faster development of trials and the careful review of procedural hurdles that slow approval.

The COG letter also disagrees with two of the recommendations of the coalition letter:

• Be quicker to course-correct/adapt and more transparent and flexible, reflecting the lessons learned in prior implementations

• Clarify plans to address IOM recommendations relative to NCI's role in the clinical trials enterprise

The COG advocates say their experience with consolidation more than a decade ago isn't exactly parallel to that of most adult groups today. The four children's groups merged on their own, with no mandate from NCI, and no additional financial assistance from the institute.

"When the four groups came together to form COG, they had to meld four different cultures in a very quick time and not hurt accrual," said Joan Darling, chair of the COG Patient Advocacy Committee. "It's very difficult to do, and we wanted to remind NCI right upfront that they needed to make space for that. We worked very hard at it, but it turned out to be a lot harder than the four legacy groups anticipated."

Some problems were practical.

"None of the patient enrollment methods could handle the scale-up in the number of patients," Darling said to The Cancer Letter. "Getting a new method for enrolling patients was crucial and it wasn't built into the

merger system. It took much more time than anybody anticipated, because one of the group enrollment systems could easily be scaled up to handle the increased number of patients."

The merger will likely be more challenging than anyone anticipates, said Rebecca Pentz—and cost more money than anyone anticipates, said Darling. Pentz is professor of hematology and oncology in research ethics at Emory University Winship Cancer Institute and COG representative to the Coalition of Cancer Cooperative Groups.

"We are not close enough to the process to know what exactly the technical or cultural issues will be, but they will be there," Pentz said. "It's not easy to consolidate nine groups down to four, I think they should talk with people like Greg [Reaman, the first COG chair], who went through it, people who understand the actual details that went into making it work."

Robert Comis, president and chairman of the Coalition of Cancer Cooperative Groups and chair of the Eastern Cooperative Oncology Group, voiced cautious support for the idea of reliance on metrics in reforming the groups.

"I think we should all thank the patients and patient advocates who work with us directly in the cooperative group system for their continued efforts and their strong support, as evidenced by the recent letters," Comis said in an email. "I don't think there is any other NCI structure that has such broad and deep involvement of advocates in the clinical research process. The cooperative group advocates have worked with us through the many reviews over the years: Armitage/ Implementation Committee in the 90s; the Clinical Trials Working Group in the 2000s; and now, through the implementation of the IOM Committee Report.

"Cooperative Group advocates have developed a track record as a strong voice for an evidence-based approach to change. As a very recent example of their effectiveness in this area, they made a case with the NCI that certain adjustments in the Central IRB process would lead to a much more streamlined, and more responsive, CIRB. The NCI has now implemented those recommendations, which have proven to be successful.

"I'm sure that as we move forward with the restructuring of the cooperative group system, their help and support and strong voice for reasoned change will help us all."

Follow us on Twitter: @TheCancerLetter

Letter From Patients Involved With Adult Cancer Cooperative Groups:

Dear Drs. Varmus and Doroshow,

We are writing to you as advocates working in the US Cancer Cooperative Groups to express our thoughts and concerns about the IOM/NCI clinical trials implementation. The NCI-funded Cooperative Group system is a national treasure. We need to be both bold and careful as we move forward to make it better, because breaking it would be a tragedy for all cancer patients, current and future.

As advocates, cancer survivors and people touched by cancer, we share with you nine recommendations concerning this transformation initiative and respectfully request that NCI respond to these with an action plan:

1. Incorporate into the implementation plan tangible patient and scientific outcomes as primary endpoints

2. Integrate instrumentation, transparency, and accountability (i.e., clear metrics with targets, timeframes and responsible parties) into the management of this implementation

3. Define what constitutes success in terms of concrete endpoints and timeframes and decide how these will be managed

4. Avoid allowing the pace of change to get ahead of rational design and planning for the implementation. If the design is not vetted or the metrics are not in place, move the implementation date(s) back until there is a solid design and clear metrics to guide the implementation

5. Be quicker to course-correct/adapt and more transparent and flexible, reflecting the lessons learned in prior implementations

6. Incorporate milestones with go/no-go decision points and pilot programs for the more challenging elements of the new operating model

7. Clarify plans to address IOM recommendations relative to NCI's role in the clinical trials enterprise

8. Incorporate enforcement of NIH Policy and Guidelines on the Inclusion of Women and Minorities in Clinical Research as prescribed in the NIH Revitalization Act of 1993, PL 103-43 into the change program

9. Meaningfully involve the cooperative group advocates as full partners in the implementation and beyond

The remainder of this letter provides the background and rationale for these recommendations.

There are lessons learned from prior initiatives that should be applied to this transformation

As many of us have been involved in clinical trials for many years, we are also cognizant that this is not the first effort to restructure and reengineer the system. There are clear lessons learned that we all need to keep in mind as we approach this critical, game-changing transformation.

Previous efforts have been fraught with false starts, unintended consequences and stillborn constructs. Protocol development pipelines, patient accruals and, consequently, the pace of science and improvement of patient outcomes were all impacted as some changes were fine-tuned and others were aborted. The current change program is far more aggressive than prior efforts and has incredible potential. Many of the same people who were involved in prior restructuring initiatives are involved in the present effort—at NCI, within the groups, at contractors supporting on-going operations and change management. Much has been learned from the prior initiatives. However, we expect that there will be challenges as this effort moves forward and we all need to keep a close eye on key metrics and be ready to fine tune the strategy and implementation.

Recent events bode well for the success of this effort

We note the success in initiating rigorous deadlines for various stages of protocol development and their positive impact on lead times. We also note the initiation of a parallel process for protocol activation for sites not using the NCI Central IRB (CIRB) and the positive impact on activation times at sites not using the CIRB. Remarkably, there has also been a concomitant, dramatic reduction in CIRB throughput times. These successes demonstrate the power of good metrics and clear targets in driving tangible results, as well as the importance of addressing these issues early in the change process (these metrics and targets were not introduced until over eight years after the CIRB was instituted.) Also encouraging are public statements by NCI openly acknowledging that, in order to fund an orderly transition, costs will likely rise before they fall.

Recent events also suggest that the effort is resulting in potentially precipitous actions

The pace of change is getting ahead of design of the new model and plans to manage the transition and measure its effects. We cite two examples here to illustrate this concern:

• Declaration of the intent to move from ten adult groups to four has resulted in the existing groups deciding to consolidate ahead of the implementation (anticipatory consolidations.) There is some merit to allowing marketplace forces to build the appropriate alliances. However, there has been no analysis to determine which of the existing groups would most appropriately be consolidated to best leverage existing resources and position the system to meet the challenges of the future. And, there is still much uncertainty about whether the result will preserve the most valuable elements of the existing groups, especially the focus of some of the groups on specific cancers and populations (e.g., the Gynecological Oncology Group, GOG) and therapies not directly related to drug therapy (e.g., radiation and surgery.) This uncertainty stems largely from ambiguity about how the funding opportunities will be structured and the constraints being put into place by anticipatory consolidations

• National Disease Site Steering Committees appear to have been deployed without explicit metrics or evaluation programs in place to measure their effectiveness.

There is much discussion about negative impacts on the protocol development pipeline. Unfortunately, the data is largely anecdotal and there is little or no objective data available to confirm or refute the concerns that have been raised.

This transition should be viewed as one would view a prospective clinical trial

In our view, an undertaking of this magnitude and complexity on such a critical resource is best viewed as analogous to conducting a clinical trial on patients with a terminal disease (e.g., cancer.) There is no one "right answer" and, while there is great potential, there is also the potential for disastrous impacts on the science and patient outcomes. When initiating a transformation of an organism as massive, complex and precious as the NCI-funded clinical trials enterprise, one should ask many of the same questions that an IRB would ask in reviewing a cancer clinical trial. Unfortunately, the answers to those questions for this effort are cause for concern:

• The transformation is essentially a single-armed trial with an ambiguous schema – If scientists identify a new molecule with an exciting mechanism of action in vitro, the molecule would be taken through Phase I and Phase II trials to establish dose and efficacy in vivo. The investigators would then be required to show that the new treatment is superior to the standard of care in a randomized Phase III trial. Large-scale business transformations with far less at stake and similar

issues about the feasibility of rigorous multi-phase trials substitute financial and operations modeling to choose among available alternatives and develop clear implementation plans.

This effort appears to be going straight to implementation without adequate solution design, business case (cost/benefit) analysis, or migration planning

• There is no dose modification plan—Clinical trial protocols make explicit provisions for adapting the treatment plan in response to adverse events (e.g., reducing doses in the event of dangerous cytopenias.) There does not appear to be any explicit criteria for what would constitute a dangerous or unanticipated consequence that would require adaptation of the implementation program. This, coupled with the lack of metrics and clear endpoints is deeply concerning

• The data monitoring plan is weak—While there is a stated intent to manage performance to reach a higher level, ambiguity surrounding metrics and the lack of baselines and targets threatens to confound this intent. Essentially, we have no effective way of measuring performance levels for the status quo and no definition of what constitutes success (i.e., the targeted level of improvement.) It is important to note that metrics played a crucial role in recent successes with protocol development timeframes and CIRB throughput. Metrics can be difficult to develop and often aren't perfect, but they inform action and provide clear incentives and feedback

• Reliance on secondary endpoints—Trials are ideally designed to achieve primary endpoints that indicate clinical benefit, such as overall survival. Secondary endpoints, like response rates, are viewed as not necessarily indicative of true clinical benefit and are frowned upon where there are primary endpoints that can readily be measured. There is a presumption of benefit from reducing the number of groups from ten to four. However, there is no evidence that there will be benefits. We have not seen analyses to project the magnitude of any benefits and what specifically will be required to achieve them. Similar assumptions are made relative to consolidation of decision-making into national committees. However, there is no evidence that this will be the case and no metrics defined to assess the effect on outcomes

Some redundancy may be required to achieve an optimal result

When manufacturing Toyotas or purchasing computers, there are clear economies of scale. Redundancy is anathema, a good and evil issue. In a creative process subject to serendipity and dependent on creative development and testing of hypotheses, competing (i.e., redundant) efforts are often necessary to hedge against the risk of failure and to avoid stifling innovation. Centralized planning and prioritization for scientific research has value to focus investment of scarce resources. However, it needs to accommodate independence of thought and innovation, and extend to the entire portfolio of research, which includes cancer centers and R01's.

It is unclear how NCI plans to address the IOM recommendations that relate to changes at NCI

The IOM report suggested numerous changes to NCI's management of the clinical trials enterprise. Examples of these changes include:

• Re-evaluating NCI's role in the clinical trial system and shifting from hands-on leadership and oversight to funding the clinical trials process

• Allocating a larger portion of the NCI research portfolio to the Clinical Trials Cooperative Group Program

• Enhancing trial participant diversity through support for Minority-Based Community Clinical Oncology Programs, Patient Navigator Research Program and other NCI programs. Our constituents ask that NCI Enforce NIH Policy and Guidelines on the Inclusion of Women and Minorities in Clinical Research as prescribed in the NIH Revitalization Act of 1993, PL 103-43

• Increasing the per case reimbursement rate and adequately funding the costs of conducting trials

• Mandating the submission of annotated bio-specimens In some areas, it is unclear if NCI plans to or is able to proceed with the recommended changes (e.g., funding/reimbursement.) In others (e.g., leadership/oversight), the direction appears to be counter to the IOM recommendation. It is important that these issues be dealt with early in the transition as they could have a significant impact on the ultimate outcome.

Cooperative group advocates should participate as full partners in the transition

As cooperative group advocates, we represent the patient and consumer communities. Most of us are cancer survivors and all of us have been touched by cancer. We work directly with the Cooperative Groups and NCI to design, conduct and evaluate clinical trials. Many of us have professional experience in related fields that we bring to bear in our advocacy work. We are committed, knowledgeable and have a unique point of view. We should be full partners in this implementation.

We are grateful for the incredible progress that NCI has engendered by involving advocates in all key management functions in its research enterprise. However, this undertaking to transform the system has not met the high standards for advocate involvement that NCI has set.

• There was no cooperative group advocate on the IOM task force that developed the recommendations

• Meetings to present the program and work out details have excluded cooperative group advocates from key sessions, most notably from NCI's many meetings with the Cooperative Group Chairs

Advocates are passionate about the NCI-funded clinical trials system and have a huge stake in its success. This passion sometimes translates into controversy, which we believe is healthy as long as it remains constructive. We have much to contribute and ask that the NCI ensure that we are fully integrated into the implementation program and the ongoing efforts that will follow.

We respectfully request a response to the nine recommendations listed above

As concerned stakeholders and representatives of the patient and consumer communities, the ultimate beneficiaries of the clinical trials enterprise, we respectfully request a timely response in the form of an action plan to the nine recommendations listed above. We believe these are critical to ensure that the implementation delivers on its promise and that timely action is required. Your thoughtful response will facilitate consensus and demonstrate transparency on critical elements of the implementation.

There are over ninety advocates working within the US Cancer Cooperative Groups. Most of us are cancer survivors and all of us have been touched by cancer. All of us are passionately committed to the success of NCI-funded clinical trials. We work assiduously with NCI, the Cooperative Groups, advocacy organizations, the patient community and industry to improve NCI-funded clinical trials and we applaud the efforts of the Institute of Medicine and the National Cancer Institute to revitalize them. This letter represents the consensus of approximately 75% of our advocates, listed on the next page with their Cooperative Group affiliations.

Thank you for your attention. We look forward to working with NCI as we jointly pursue this exciting opportunity.

Follow us on Twitter: @TheCancerLetter

Letter From Advocates For Children's Oncology Group:

Dear Dr. Varmus and Dr. Doroshow:

We are writing to you as research patient advocates working in the Children's Oncology Group to express our thoughts and concerns about the Funding Opportunity Announcement and the related reconfiguration of the NCI clinical trials group (together, the "Implementation"). The NCI-funded Cooperative Group system is a crucial resource and key to continuing to advance new and better treatments to treat cancer.

Although the Children's Oncology Group will not be directly impacted by the Implementation, we are keenly aware that ultimately any slowing of progress in the adult clinical trials could adversely affect clinical research in children. Therefore, although we understand and applaud the goals of the Implementation, we are concerned that any remake of the adult Clinical Trial System not hobble the reconfigured Cooperative Groups and not distract them from developing new cures for cancer.

The composition of the cancer advocates in COG includes cancer survivors, parent and loved ones of cancer patients, nurse and ethicists. Some of us did experience the consolidation of the four legacy pediatric cancer research organizations into COG and hope that lessons from that experience can be applied to the Implementation.

1. We respectfully advance ten recommendations concerning the Implementation:

Incorporate into the Implementation tangible patient and scientific outcomes as primary objectives of the Implementation. We would expect those objectives to include:

• The development of all key clinical trials;

• Maximizing patient enrollment in clinical trials;

• Special development of clinical trials for rare tumors;

• Increased diversity in the participation in clinical trials, particularly under-represented minority communities.

• Faster development of trials and the careful review of procedural hurdles that slow approval.

2. Establish instrumentation, transparency, and accountability (including, clear metrics with targets, timeframes and responsible parties) into the management of all aspects of the Implementation.

3. Define what constitutes success of the Implementation in terms of concrete objectives and

timeframes and how they will be managed and achieved.

4. Avoid allowing the timetable for the Implementation to precede rational design and planning. If the design is not vetted or the metrics to manage the Implementation are not in place, suspend implementation dates until there is a solid design and clear metrics to guide the Implementation.

5. Respond quickly with needed course corrections where appropriate; adopt flexibility and transparency in the design of the Implementation and incorporate consultation with and participation on an ongoing basis by the Cooperative Group leadership, PIs and other and members of the Cooperative Groups including patient advocates at every stage of the Implementation process. Continue to consult with the past and present leaders and membership of the Children's Oncology Group and the NCI staff who dealt with the COG consolidation to determine what worked best (and what did not) in that earlier process.

6. Incorporate milestones with go/no-go decision points and pilot programs for the more challenging elements of the new operating models.

7. Support funding and logistical support to the consolidation of the Cooperative Groups contemplated by the Implementation, including assistance with mediating conflict and organizational integration, with focus on steps to ensure that any interaction in Cooperative Group core functions caused by consolidation is mitigated and that the disruption of new and ongoing clinical trials is minimized.

8. Clarify the plans to address IOM recommendations relative to NCI's role in the clinical trials enterprise.

9. Incorporate enforcement of NIH policy and Guidelines on the Inclusions of Women and Minorities in Clinical Research as prescribed in the NIH Revitalization Act of 1993, PL 103-43 into the Funding Opportunity Announcement and all aspects of the Implementation.

10. Enlist the cooperative group advocates as full partners in the development of the Implementation, in the reconfiguration of the cooperative groups and in the transformed groups.

Note that except for Recommendations 5 and 7, and for the objectives in Recommendation 1, we have adopted the foregoing Recommendation in whole or in part from the *Cooperative Group Advocates' Public Comment Regarding Reconfiguration of the Cooperative Group Program*, dated June 30, 2011, addressed to Dr. Varmus and Dr. Doroshow and executed by over 60 adult patient advocates.

We appreciate your consideration of these recommendations, respectfully request that they be included in the public comments on the development of the Funds Opportunity Announcement and the reconfiguration, and that you consider them in the development of the Implementation.

Sincerely,
Joan Darling, Chair, COG Patient Advocacy Committee
John Mussman, COG Patient Advocate, COG Representative to Coalition of Nation Cancer Cooperative Groups
Rebecca Pentz, COG Patient Advocate, COG Representative to Coalition of Nation Cancer Cooperative Groups
Jay B. Long, COG, Patient Advocate
Anne Lown, COG, Patient Advocate
Peggy Kulm, COG, Patient Advocate

Copies of both letters are posted at:
www.cancerletter.com/categories/documents

In the Cancer Centers:

Pui Wins Henry Stratton Medal;
NCI DCEG Wins Epidemiology Award

CHING-HON PUI will recieve the **Henry M. Stratton Medal** from the **American Society of Hematology** for work that has advanced the research and treatment of pediatric leukemia.

Pui is chair of the Department of Oncology at St. Jude Children's Research Hospital; co-leader of the hospital's Hematological Malignancies Program; medical director of the St. Jude International Outreach China Program; and holder of the Fahad Nassar Al-Rashid Chair of Leukemia Research.

The award honors senior investigators with well-recognized contributions to hematology, that have taken place over several years.

His work has shown that cranial irradiation, once regarded as a standard treatment for childhood acute lymphoblastic leukemia, can be omitted altogether, sparing patients from the side effects. His treatment approaches have resulted in cure rates approaching 90 percent in older adolescents with ALL.

Pui also helped found the International Childhood ALL Working Group to facilitate international research collaboration and has been helping developing countries access modern leukemia treatments.

TRISHA LOLLO has been named vice president of cancer services for the **Siteman Cancer Center at**

Barnes-Jewish Hospital and Washington University School of Medicine. She will take over the newly created position Oct. 3.

Lollo is currently the associate administrator of oncology services for the University of California, San Diego Health System, overseeing clinical care at two hospital campuses and the UC San Diego Moores Cancer Center.

Siteman Director Timothy Eberlein adds, "Trisha's operational expertise and experience is outstanding. She has an infectious enthusiasm and wonderful collaborative spirit. We will look to her to help Siteman reach a new level of accomplishment in the next decade."

Lollo will be responsible for strategic planning, budgeting and operational improvements. She also will promote research collaborations across organizational boundaries and foster multidisciplinary care efforts within clinical programs.

BRIAN SPRINGER joined the **Roswell Park Cancer Institute** as its new executive vice president.

Springer's work at RPCI will focus on oversight of administrative, scientific and clinical operations, but will also encompass strategic planning, application for renewal of the Institute's NCI core grant, and involvement in mission-driven programs such as technology transfer and diversity initiatives.

Springer was executive director of the Alvin J. Siteman Cancer Center at Barnes-Jewish Hospital and Washington University in St. Louis.

The **University of Kansas Cancer Center** merged with the **Kansas City Cancer Center,** an affiliate of the United Network of U.S. Oncology. The new organization will be part of the KU Cancer Center, but will maintain KCCC's existing relationships with community hospitals.

The KU Cancer Center and KCCC have jointly operated the region's only adult Blood and Marrow Transplant program since 2007, and the combined program will offer the region's only comprehensive breast cancer program.

Twenty-seven physicians from KCCC became members of the KU School of Medicine faculty in Internal Medicine and in Radiation Oncology. Non-physician staff members of KCCC are now employees of The University of Kansas Hospital. No jobs will be lost as a result of this merger.

Research will be the primary focus of the new organization, which will have 216 clinical trials underway.

Roy Jensen, director of The KU Cancer Center, said he expects the partnership to support the university's application for National Cancer Institute designation.

"With this merger complete, we will be able to report to NCI in our September application that we have significantly expanded the number of patients to whom clinical trials may be offered as a treatment option," Jensen said in a statement.

NAPOLEONE FERRARA won the 2011 Dr. Paul Janssen Award for Biomedical Research, awarded by Johnson & Johnson during the BIO International Convention in Washington, D.C.

Ferrara received the award in recognition of his research on angiogenesis. Ferrara's lab isolated and cloned vascular endothelial growth factor, and helped explore the role of VEGF and its receptors in the development of tumors. His findings led to the development of anti-VEGF compounds, including bevacizumab (Avastin) and ranibizumab (Lucentis).

Ferrara is currently a Genentech Fellow in tumor biology and angiogenesis.

JAMES CASSIDY was named head of translational medicine in the Oncology Discovery and Translational Area in Pharma Research and Early Development at Roche.

Cassidy was previously professor of oncology, head of the Department of Cancer Research, and head of the Division of Cancer Sciences & Molecular Pathology at the University of Glasgow, Scotland. His major research interests include telomerase, DNA repair, drug resistance and molecular pharmacology of anti-cancer drugs.

Cassidy, a fellow of the Royal Society of Edinburgh, chairs the West of Scotland Cancer Research Network and is a member of Cancer Research UK, American Society of Clinical Oncology, the American and British Associations for Cancer Research, Association of Cancer Physicians, and National Cancer Research Institute.

Cassidy is a member of the editorial boards of Cancer Chemotherapy and Pharmacology, Expert Reviews of Anticancer Therapy, European Journal of Cancer, Investigational New Drugs and the British Journal of Cancer. He is also the author of two theses, five books, several book chapters, and over 200 peer-reviewed papers and manuscripts.

NCI's DIVISION OF CANCER EPIDEMIOLOGY AND GENETICS received the **Alexander D. Langmuir Award for Training Program**

Excellence and Innovation. The award recognizes one degree program, training program or series of courses that has developed and implemented creative educational offerings in epidemiology.

The award honors Alexander Langmuir, who created the Epidemic Intelligence Service in 1949, a training and service program of epidemiologists at what became the CDC, and served as the center's chief epidemiologist until 1970.

Jackie Lavigne, chief of DCEG's Office of Education, accepted the award during a ceremony at the 3rd North American Congress of Epidemiology in Montreal.

FDA News:

FDA Will Slim Down Regulations For Common Diagnostic Devices

FDA proposed new policies regarding common diagnostic and radiology devices that have well-established safety and effectiveness profiles.

The agency will not enforce pre-market notification requriements for these devices, as long as they do not exceed certain limitations. It intends to exempt these devices from notification requirements in the future through regulatory processes.

The draft guidance lists 30 different device types, including urine and blood tests, alcohol breath tests, and blood clotting protein tests--as well as radiology device accessories, such as film cassettes, film processors, and digitizers. The FDA determined that these devices do not require stringent oversight, and that these changes would not compromise public health.

"The safety and effectiveness of these devices have been well demonstrated over the years," said Jeffrey Shuren, director of FDA's Center for Devices and Radiological Health. "By addressing the risk level of these devices, the agency is taking a smart regulatory approach that eases unnecessary requirements for manufacturers, while making sure the public has safe and effective devices."

FDA intends to continue to enforce all other applicable requirements, including registration and listing and Good Manufacturing Practices determined by the Quality System regulations. The draft guidance is open for comment for 90 days.

The draft guidance can be found here: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm262071.htm