THE CANCER LETTER

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The Duke Scandal:

Nevins Says Duke Did "Very Good Job" Of Handling Crisis, Cites "Data Corruption"

By Paul Goldberg

In his first public comment on the scientific scandal in his lab, Duke genomic scientist Joseph Nevins refrained from criticizing his one-time protégé Anil Potti—or even mentioning him by name.

Testifying before a committee of the Institute of Medicine March 29, Nevins said that "data corruption" had produced incorrect results, leading to a wave of retractions in the world's premier scientific journals.

Errors occurred when data used to develop a model for predicting patient

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Guest Editorial:

Fukushima Not A Repeat of Chernobyl: A Doctor's Analysis of Nuclear Accidents

By Robert Peter Gale

The author led the international medical team responding to the Chernobyl accident. He develops new cancer drugs at Celgene and teaches in Los Angeles and London.

FUKUSHIMA, Japan—Twenty-five years ago, the Chernobyl nuclear power station in Ukraine exploded—killing 31 people and contaminating substantial areas of Ukraine, Belarus and Russia. It sent shockwaves around the world. We now face another global nuclear event: a potential meltdown at reactors at the Fukushima Daiichi nuclear power station in Japan.

There are substantial similarities and substantial differences between the Chernobyl and Fukushima-type reactors. The Chernobyl reactor was a RBMK-type boiling water reactor with a graphite moderator. Because of its huge size it was not possible to place it within a containment structure. RBMK-type reactors can produce weapons-grade plutonium as well as electricity, which accounts for their large size.

The Fukushima units are also boiling water reactors, but are much smaller, cannot produce weapons-grade plutonium (they do produce some plutonium as a consequence of fissioning uranium), and are within two containment structures: a steel vessel and a secondary containment building. There are several other important technical differences between these reactors

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Nevins: Duke Data Problems Are Part of Advancing Science

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response to therapy were commingled with data used to validate the predictor, he said.

Addressing the IOM Committee on the Review of Omics-Based Tests to Predict Patient Outcomes in Clinical Trials, Nevins refrained from criticizing his collaborators, the Duke administration—and himself.

Pressed by committee members, Nevins declined to comment on matters involving Potti's conduct and chose not to answer a question related to clinical trials that sought to test the controversial findings developed in his lab.

"Data corruption of the form that I just described is not something that one generally anticipates," said Nevins, the Barbara Levine professor of breast cancer genomics, whose center at the Duke Institute for Genome Science and Policy was abolished in a recent reorganization (The Cancer Letter, Jan. 28).

The scandal that has led to retractions in The New England Journal of Medicine, Nature Medicine, The Journal of Clinical Oncology and The Lancet Oncology exploded after The Cancer Letter reported that Potti had inflated his credentials, falsely claiming to have been a Rhodes Scholar (July 16, 2010).

Problems with Potti's credentials apparently prompted a thorough review of scientific work conducted by the Duke team and led to formation of the IOM committee focused on clinical applications of genomics and proteomics (The Cancer Letter, July 30, 2010).

Nevins's remarks were consistent with earlier efforts by the Duke administration to portray the scandal as a dispute between scientists where reasonable people can agree to disagree.

Errors can occur in the process of scientific search, Nevins said to the committee. "People are exploring different parameters, exploring ways to try to address how can I tease out information that would allow me to build the predictor that has some promise that we might go forward with," he said.

Nevins acknowledged that the work emanating his group generated controversy, as outside scientists pointed out what appeared to be a multitude of errors. However, Duke administration's response to criticism from the outside was appropriate, Nevins said to the committee.

"I think we did a pretty good job," Nevins said. "I think we had an integrated group of individuals providing the appropriate expertise. I think you can always do better. And I think we could do better, particularly in having individuals with the right expertise, particularly the statistical expertise, involved essentially as co-investigators, not providing just advice and expertise when needed, but working with a cancer biologist, working with the clinical researchers as co-equals."

The methods for testing the hypotheses in the clinic were sound as well, Nevins said.

"The studies and the infrastructure that was put together to carry out those studies was not flawed," he said. "We anticipated clinical questions in a very careful way. We put together studies that I think were well designed. We put together an infrastructure to ensure that they were run in a very robust way."

Duke conducted three phase II studies that relied on genomic predictors to determine the treatments that would be received by over 100 patients. According to FDA officials, studies that rely on biomarkers to select therapy must be conducted under an Investigational Device Exemption license from the agency, the device equivalent of the Investigational New Drug license.

The Duke studies had no such clearance.

"There wasn't an IDE," Nevins said unapologetically. "This was in 2005 and 2006, and it was the view of the group that it [the research] didn't represent a significant risk and the form of the study didn't demand it, in good part because of the design of the studies that were using acceptable therapies. We

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could have easily run these studies and observational studies, collected samples for analysis, and a lot of discussion that we are having here probably would be moot.

"At the time, the view was—and the IRB shared the view—that the nature of the studies didn't pose a risk and didn't demand an IDE," Nevins continued. "It did set this up in what we believe was an appropriate assay environment that I think was done in a way that was very appropriate."

FDA officials recently conducted a two-week audit at Duke, and the agency has said repeatedly that such studies require IDE clearance.

"The initial decisions were such that the IRB was comfortable with how the trials were set up based on the science," Nevins said at the IOM meeting.

While this statement appears to be correct, internal Duke documents obtained by The Cancer Letter point to concern and vigorous internal debate over the need for regulatory clearance of the three studies (The Cancer Letter, Jan. 28).

Nevins returned repeatedly to the notion that the experience had teaching value.

"What it had the effect of doing is generating data as a result of that study that then becomes useful for advancing the field," he said about one of the aspects of the scandal. "Even if the science didn't work as you anticipated, you come out of it with data that you can do something with."

Nevins avoided uttering the name Potti even when he discussed authorship of papers that have been retracted.

The challenge that faces the IOM committee is "making sure that good science, good publications aren't thrown out just because of one name on a paper, for instance," he said.

Nevins said he is concerned about medical literature that makes partial use of retracted data.

"We have one particular example of a paper that I think 95 percent of it is just fine," Nevins said. "That particular figure had almost no bearing on the overall thrust of the paper. Should a paper like that be removed? Or is that something that should be corrected and noted?"

Duke Submits New Document

In preparation for the meeting, Duke officials developed a lengthy memorandum laying out their version of events.

The document, posted at http://www.cancerletter.com/categories/documents, offers a description of Potti's role in contributing to "data corruption" that afflicted the group's research.

An excerpt from the document follows:

While a fellow in medical oncology, Dr. Potti's studies in the Nevins group culminated in 2006, with the publication of a study in Nature Medicine that described the development of gene expression signatures that could predict tumor sensitivity to various standard chemotherapies (Nature Medicine, 12:1294-1300 (2006)).

This work made use of publicly-available data from a panel of cancer cell lines (the NCI-60 panel) to derive training sets for various chemotherapies involving cells resistant or sensitive to the drugs that then allowed the development of gene expression signatures that were purported to have validated in additional publically available datasets including several from human tumor samples.

Although this work made use of methodology developed in the Nevins/West collaboration, Dr. [Mike] West [the Arts & Sciences Professor of Statistical Science and the Duke Department of Statistical Science] was not actively involved in providing statistical expertise on the development of the chemotherapy sensitivity predictors.

Dr. Potti carried out an additional study to derive gene expression signatures from lung tumor samples focused on prognosis in lung cancer that resulted in the development of a multi-gene predictor of lung cancer recurrence (the lung metagene score).

This work was published in the New England Journal of Medicine in 2006…

Further analyses revealed corruption of multiple datasets compiled by Dr. Potti that had been used as sources of validation of the various chemotherapy sensitivity signatures. These included data derived not only from Duke sources, but also publicly available data.

As an example, a dataset of 133 samples from a neo-adjuvant breast cancer study at MD Anderson involving patients treated with the combined regimen TFAC was used for validation of an adriamycin signature. The clinical annotation that was assumed to be used by Dr. Potti included 34 responders and 99 non-responders, the same distribution as reported by MD Anderson.

However, a detailed comparison of the two datasets revealed that the response information was reversed for 24 cases with 12 labeled incorrectly in each direction. In this case, the corrupted data yielded positive validation results whereas the accurate data did not provide evidence for validation.

Similar findings of corruption of data in key validation datasets were observed in other instances.

As a result, three publications were retracted, a manuscript describing the methods for implementing signatures in the clinical trials that was under review was removed from further consideration, and other publications are currently being analyzed.

Dr. Potti issued his resignation statement on November 19, 2010, and a statement of responsibility for the problems with the work. A research misconduct investigation is in progress…

There are many lessons to be learned from this experience, but the immediate lessons that Duke and the IGSP have learned are that all data and methods for clinical research must be assessed at multiple levels and that quantitative expertise is needed for complex analyses; furthermore, for translation to clinical trials these analyses must be done using systems that maintain independence between the data generation and the analysis and enable replication of the results, along with documentation of all changes to data and analyses.

The IGSP is committed to ensuring full publication of data and methods going forward and would note the Gatza 2010 publication as an example of that commitment.

"Problems Could Have Been Addressed Earlier"

Errors in the group's work came to the attention of scientists thanks to efforts of two biostatisticians at MD Anderson Cancer Center, Keith Baggerly and Kevin Coombes. Baggerly testified at the March 29 meeting of the IOM committee,

The Cancer Letter asked Baggerly and Coombes to assess the explanation in the Duke document and in the Nevins testimony.

The text of their critique follows:

Dr. Nevins implied that these issues of data corruption could not have been identified earlier. As we understand it, data corruption refers to the mislabeling of validation data. In our second letter to Nature Medicine, which the editors showed to Drs. Potti and Nevins in June of 2008 (and based on whose "detailed response" they decided not to publish our letter), we documented sample mislabeling of the posted data purportedly used as the test data for the docetaxel signature.

This mislabeling was data corruption. The response to this criticism in our June 2008 letter was that the docetaxel data were removed from the web with no comment.

We also suggested (in 2007) that the validation data for adriamycin were mislabeled; in their rebuttal Drs. Potti and Nevins refer to "the acute lymphocytic leukemia dataset in which the labels are accurate—full details are provided on our web page."

We showed these labels were wrong in our unpublished June 2008 note to Nature Medicine. Potti et al published a correction in August 2008, but (as reported in our 2009 Annals of Applied Statistics paper) the new data used in the correction were mislabeled again.

Dr. Nevins also said he "initially thought that the disagreements were about the statistical methods used to evaluate the data not the validity of the studies. He believed that Duke researchers in his group at the IGSP addressed those concerns by adjusting their methodology." (The Duke Chronicle, March 31, 2011).

As noted in [NCI biostatistician] Dr. Lisa McShane's presentation to the IOM Committee on Dec. 20, 2010 (beginning 48 min, 45 sec into the MP3 recording available from http://www.cancerletter.com/categories/documents for the Jan 28, 2011 issue):

"It is amazing how throughout this process people still kept thinking that it was just debates about statistical issues. It really wasn't debates about statistical issues. It was just problems with data and changing models."

We are glad to see the problems acknowledged now. But one reason the IOM Committee may be able to provide useful guidance is that the problems could have been acknowledged and addressed much earlier.

Fleming: Corruption Not Random

At the IOM meeting, Thomas Fleming, professor of biostatistics at the University of Washington, seemed similarly unconvinced by Duke's historical exegesis.

"Thanks for giving us the insight into how some of this evolved," Fleming said to Nevins at the March 29 meeting.

"You had mentioned that one key aspect was that there was a failure to keep the separation of training and validation sets. And what you did to address that was to bring a reference set to keep them separate.

"And when you did the analysis in the validation set, you saw a nice association that existed between the signature score and response status. But then you discovered that there were 12 responders who were really non-responders and 12 non-responders who were responders."

NEVINS: "The evidence that I was showing you of achieving validation with that methodology was flawed."

FLEMING: "So when you correctly coded people according to their true response, what happened to the

association?"

NEVINS: "It went away."

FLEMING: "Completely?"

NEVINS: "Yes."

FLEMING: "Because if it was at random that the miscoding occurred, the association should be attenuated, but it would still exist. It would still be at least half. To go away completely, it would happen if there was not a random miscoding but a specific miscoding where the people called non-response had high scores and the people called response particularly had low scores. Which leads me to the second question: how did the 24 people get miscoded, because it doesn't seem to be at random, from what you are telling me?"

NEVINS: "So I can't really speak to the first part. Did it absolutely go away, etc. I probably can't speak exactly as to the ones that were mislabeled. I don't have that in my head right at this point in time. With respect to the very last point you raised, I can't address it.

"And I can't address it for reasons of an ongoing investigation. I just can't get into the position of speculating on how it happened. All I am doing is saying this is what we see."

FLEMING: "At least there is evidence here as to whether this it was at random. And it appears you are telling me that it wasn't at random. So it would be worth someone pursuing that to try to get some clues about whether this was intentional."

"Dismissive Nature" of Duke's Response

Gilbert Omenn, chair of the committee and director of the University of Michigan Center for Computational Medicine and Biology, asked Nevins to put this detail in historical perspective.

"Maybe what you can tell us, Joe, whether that information on the clear non-randomness was shared with the external advisory board, with the subsequent Duke investigation, the IRB, and all the other players who have been brought into this over the last four years," Omenn said.

NEVINS: "So we didn't recognize that until fairly late in the game, and that recognition was what stopped things.

"That recognition was what retracted papers. That recognition was what stopped the trials. That information absolutely has been shared with an appropriate body. Was it non-random? Was it not non-random? What are the implications of that?"

Pressed by committee members, Nevins said the data corruption case he described in his presentation wasn't isolated.

"I used that as an example, but we found some additional examples," he said.

Nevins also declined to respond to questions about clinical trials of the technology, stating that he lacked detailed knowledge.

"You are not a clinician," Omenn said. "However, the trials we are asking about were stopped. And then they were restarted. That was probably not warranted in light of all the information on hand.

"One of the problem is the tone and dismissive nature of institutional responses to all of those criticisms.

"And reverberations for the whole community are serious. There are hundreds of other scientists who cited your work, so the lack of investigation when the things were brought up raises the question of how do you deal when something looks too good to be true."

This triggered the opposite of a mea culpa.

"I would suggest that the institution did a very good job of addressing this, of paying attention to the issues that were raised, to do an effective review based on what was provided in the course of that review, and I think that process was done in good faith," Nevins said.

"Yes, it was a very significant set of criticisms, and yes it was a process that was ongoing, but I think it's important to recognize that we [viewed] that we had addressed the vast majority of the issues. There were inconsistencies in data, there were issues about mislabeling things, but when we had evidence of validation performance of predictors, we had confidence. In some way you can view this as an aspect of scientific competition. We addressed it at the time based on what we saw and the way we felt was the most appropriate."

Perhaps the most controversial instance in the Duke scandal involves the decision by Duke officials to withhold a crucial document from outside experts who were asked whether trials should be restarted.

Here is the chronology:

In the fall of 2009, Baggerly and Coombes published a paper in which they argue that reliance on the group's predictor model to assign patients to treatment could cause harm (The Cancer Letter, Oct. 2, 2009).

Duke officials responded by halting the three trials and seeking guidance from outside advisors (The Cancer Letter, Oct. 9, 2009). However, Duke officials later acknowledged that the panel was not given a document in which Baggerly and Coombes point out the exact problem with data corruption that Nevins would acknowledge later The Cancer Letter, Jan. 14).

The external reviewers recommended restarting the trials, and Duke officials followed their recommendation.

The trials continued until The Cancer Letter reported irregularities in Potti's CV.

The document released by Duke officials March 29 reveals that the decision to withhold information from reviewers was cleared with Victor Dzau, the chancellor for health affairs.

The new document states:

On Nov. 9, 2009, Dr. [Sally] Kornbluth [vice dean, research at the Duke School of Medicine] received an email from Dr. Baggerly describing his analysis of supplementary data posted to a Duke web page that was in relation to the previously published JCO paper regarding the cisplatin and pemetrexed signatures.

He stated that since Drs. Potti and Nevins had said that they were preparing a paper clarifying their methods, and since this JCO paper was a subject of dispute, he assumed that there would be corrections regarding previously identified clerical errors.

Dr. Baggerly went on to document two primary issues–that the pemetrexed signature was reversed, and that many, if not all, of a collection of ovarian cancer samples were incorrectly labeled. This Duke web page had been used for the sharing of data by the investigators involved in developing the new manuscript, as well as preparing for the review.

Dr. Kornbluth forwarded Dr. Baggerly's communication directly to Dr. [John] Harrelson [chair of the IRB] so that it would be entered into the peer review process (with the assumption that this information would be provided to the external reviewers along with any other material prepared by Drs. Nevins and Potti).

Dr. Kornbluth also thanked Dr. Baggerly and informed him that the material he sent would be provided to the IRB.

Dr. Harrelson then forwarded the material from Dr. Baggerly to Drs. Nevins and Potti noting that he was not sure if this represented old information or whether there were any additional claims that they wanted to address in the response document being prepared for the external reviewers.

At this point, Dr. Nevins expressed his strong objection to Dr. Kornbluth and others on the leadership team, believing that this was an improper intrusion by Dr. Baggerly into an independent review process commissioned by the Duke IRB, that the pemetrexed issue was not new and had already been addressed, and that the issues relating to sample mislabeling had to do with data being assembled for the review involving work in the new manuscript in which there were changes in predictors for implementation of the trial.

Based on his commitment to fairness to faculty, Dr. Nevins' conviction and arguments, and in recognition of his research stature, Dr. Dzau concurred that the reviewers should examine the data independent of the Dr. Baggerly email.

It was believed that the conclusions of a thorough and objective review of all of the data would speak for itself. There was no other discussion on this point and Dr. Baggerly's communication was not further disseminated.

Baggerly, Coombes Unconvinced

Commenting on the presentation and the Duke chronology, Baggerly and Coombes said withholding their report from external reviewers was "the wrong thing to do."

The two statisticians write:

Dr. Nevins should not have been allowed to block data from being seen by the external reviewers.

This is because (a) his contentions were wrong as a matter of fact, (b) it was the quality of his own work that was under review, and (c) the possibility of patient harm, which drove the review, should have compelled the IRB to make all data available to those conducting the review.

Dr. Nevins should certainly have been allowed to respond, and that response should have been forwarded to the reviewers along with our analysis, so that the reviewers would be fully informed. But Dr. Nevins should not have been allowed to prevent the topic from being discussed.

Points (b) and (c) above are qualitative statements, but point (a) requires proof. We had indeed earlier inferred sensitive/resistant label reversal in the signature for pemetrexed based on an improperly labeled heatmap published in Hsu et al (2007) (p.14 of the perspective).

One reason we worried about reversal was, as we documented in our Annals of Applied Statistics paper, that when we looked at 12 sources of information about the signatures used for 10 different drugs, we found "at least one sensitive/resistant label reversal for every drug checked more than once." (p.1327, section 6.1).

However, as noted in the report sent to Dr. Kornbluth, in this case the label reversal was not inferred from a heatmap, but rather from labels explicitly given to data columns posted on the web page, so this was a new finding. Our full report is available from http://bioinformatics.mdanderson.org/Supplements/ReproRsch-All/Modified/index.html.

With respect to the sample mislabeling, no preparation of data for the review could justify posting columns of data with incorrect sample labels affixed, which is what we reported.

Japan's Health Consequences Not As Vast As Chernobyl's

(Continued from page 1)

but they need not concern us here. Consequently, in trying to compare these accidents we need to consider several key variables: (1) how much fuel is contained in the reactor; (2) what type of fuel—uranium, or a mixture of uranium and plutonium; (3) how much of the fuel is expended; (4) how wmuch radiation is released from the reactor core; (5) what is the physical-chemical form of the released radionuclides; and (6) how much of the released radiation enters the environment where it affects biota, including humans.

In trying to estimate the potential health consequences of radiological releases at Fukushima versus Chernobyl, fundamental differences in containment and amount of radiation released are key.

Because the Chernobyl reactor core was not in a containment structure, and because the reactor had recently been refueled, a tremendous amount of radiation was released into the environment: predominately 131-iodine and 134- and 137-cesium (but also 90-strontium and 239-plutonium) were ejected into the lower troposphere and were spread by winds throughout the northern hemisphere (winds of the hemispheres do not mix). Rain was important in depositing the airborne radiation within the nuclear cloud throughout northern Europe. Eventually the radioactive cloud reached the US.

This northern hemispheric dispersion of radionuclides led to health consequences, most easily detected in Ukraine, Belarus and Russia, where about 6,000 excess cases of thyroid cancer were detected, mostly amongst young persons.

These thyroid cancers were predominately caused by 131-iodine in milk and dairy products (137-cesium may also have contributed). However, it is equally important to recall that there is, as yet, no convincingly-documented increase in leukemia or solid cancers at 25 years post-accident. This is an adequate observation period for leukemias but is incomplete for solid cancers.

Because leukemias are a harbinger of other cancers, the absence of an increase in leukemia-risk is encouraging. If we use data of cancer-risk derived predominately from the atomic bomb survivors, we would estimate 2,000-15,000 excess cancer deaths over 50 years, following the accident. This magnitude of increase is difficult to detect in the context of 42 million expected cancer deaths in Europe and the ex-Soviet Union in this interval.

Other concerns, like genetic abnormalities and birth defects have, fortunately, not materialized. But there are many collateral effects, including the evacuation and relocation of about 300,000 people.

Turning to Fukushima, we can use these data to make some estimates of likely health consequences. Assuming (rather optimistically) there is no further radionuclide leakage, the Fukushima accident has released about 10 percent as much 131-iodine and 137-cesium as the Chernobyl accident. Also, the dispersion of the release is far smaller. Finally, in contrast to Chernobyl, it has been possible to restrict consumption of contaminated milk and dairy products and to distribute non-radioactive iodine (KI) to block uptake of 131-iodine.

Based on these considerations, we might expect few, if any, cases of thyroid cancer, and about 200-1,500 leukemias and other cancers combined over the next 50 years.

During this interval, about 20 million Japanese will die from cancer unrelated to Fukushima. Thus the attributable risk of cancer from Fukushima should be <0.1 percent. This is obviously below our level of detection in epidemiological studies. Raising the price of a pack of cigarettes in Japan by 10 to 20 percent would result in a much greater reduction in cancer risk than the increase we can predict from the Fukushima accident.

There is, however, an important caveat to the above discussion: the spent fuel assemblies stored atop each reactor at the Fukushima site. These fuel rods still contain radioactive materials and are stored under water to prevent excess heat production. There is no containment structure surrounding these pools.

Consequently, loss of water or a rupture in one of these pools could release radioactive materials directly into the environment and substantially alter the above calculations. I doubt this will happen. Another consequence of the accident is that about 120,000 people have been displaced, but many may be able to return within one to two years, if not sooner.

As for acute radiation syndrome, at Chernobyl the use of advanced medical techniques—like sophisticated antibiotics and anti-virus drugs, transfusions of blood components, genetically-engineered hormones and bone marrow transplants—save about 85 percent of persons exposed to more than 1 Gy of acute whole-body radiations.

This has led to recommendations for a medical strategy to deal with future nuclear accidents. Fortunately, there has been no need to test these recommendations until now. No worker so far at Fukushima has received

a radiation dose greater than 250 mSv.

The global confusion and hysteria over these accidents makes it clear that policymakers and the public be educated on what radiation from an accident at a nuclear power station can—and, more importantly, cannot—do. For example, on the short-term it is almost all better to remain at one's home or office ("shelter-in-place") than evacuate. And people in the U.S. should not be buying and taking KI tablets. Response to such an event requires a solid, well-informed command and control structure and a panel of credible, independent medical experts to provide information and instructions and information to the public in settings where government credibility is often severely compromised.

Most accidents at nuclear plants involve few workers. There are extensive guidelines for dealing with these incidents that work reasonably well. There are also well-established command and control procedures and experienced personnel who rehearse potential incidents. Unfortunately the high standards, at least on paper, in most developed countries, like Japan, may not apply to all stations—especially those in developing countries, where many nuclear plants are planned or are currently being developed, such as in China or Indonesia.

Because an accident anywhere is an accident everywhere, developed countries should offer expert medical and accident-planning advice to their neighbors. This is being done by the International Atomic Energy Agency. As always, prevention of accidents at nuclear power stations is preferred to medical interventions.

The major issues with an event at a nuclear plant for the public are political, psychological and economic—not medical. As we have seen in Japan, a major natural disaster can disrupt the safety measures at almost all nuclear power stations. Are there adequate numbers of trained emergency personnel at nuclear power plants, especially those in geographically and/or politically unstable regions? In earthquakes of extraordinary magnitude, the widespread destruction, floods or tsunamis, fires and loss of life make the potential effects of a radiation release of less real impact.

In summary, there is suddenly renewed concern regarding potential accidents at nuclear power stations. Dealing effectively with these concerns requires diverse strategies, including policy decisions, public education, and as a last resort, a medical response. It is important to keep long-term risk-benefit ratios in mind.

As alarming as the news sounds, there are unlikely to be major health consequences of current events at nuclear power stations in Japan. Their magnitude will certainly be less than the consequences of continued dependence on fossil fuels for electrical generation. We should not let one event, no matter how dramatic, to alter our long-term calculus. On the other hand, we clearly need to increase our emergency preparedness at nuclear power stations if we want public acceptance of continued use or expansion of nuclear energy.

Clinical Research

Groups Respond To Proposal From Cancer Center Directors

The chairs of clinical trials cooperative groups said they were mostly in agreement with the plan for reform proposed by directors of the cancer centers.

Last month, center directors submitted a white paper, titled "Building an Integrated National Cancer Clinical Trials Program: Proposal for Re-Organization from NCI Cancer Center Directors." (The Cancer Letter, March 25).

The directors argued that they are entitled to a voice because they provide support for group activities—from payment of salaries of group investigators, to shouldering costs associated with enrolling patients in group trials.

The white paper urges NCI to focus on science, as opposed to organizational structures.

"We believe that the effort to reorganize our national clinical trials system is best done by first focusing on the development of multi-institutional, multi-disciplinary (medical oncology, radiation oncology, surgical oncology, gynecologic oncology, pediatric oncology, imaging, prevention, survivorship, etc.) disease-specific scientific working groups or 'teams,' who together focus on the design and development of large national phase III and possibly large randomized phase IIb clinical trials," the document states.

The document presents three approaches for structuring the teams.

NCI is advancing a plan to fund no more than four cooperative groups focused on adult cancer. Now, with mergers in process, there are five.

Finally, the center directors call for creating a single "common national infrastructure to drive national phase III and randomized IIb clinical trials."

"This common infrastructure could be in an extramural setting, or in an institutional or industry setting, or partially at NCI, and would provide fully integrated IT support; tissue banking; finance and administration; interfacing and negotiating with pharmaceutical companies and institutions; contracting

and legal services; statistical support for clinical trial design and analysis, etc.," the report states.

The system would be run by a single governing body at the NCI. This structure could include NCI leaders, center directors, advocates, and the industry.

The centers' white paper was co-authored by six center directors: William Dalton, of H. Lee Moffitt Comprehensive Cancer Center and Research Institute; Steve Rosen, of Northwestern University Robert H. Lurie Comprehensive Cancer Center; Craig Thompson, of Memorial Sloan-Kettering Comprehensive Cancer Center; Donald Trump, of Roswell Park Cancer Institute; George Wilding, of University of Wisconsin Carbone Cancer Center; and Cheryl Willman, of the University of New Mexico Cancer Center.

In their March 15 letter to James Doroshow, director of the NCI Division of Cancer Treatment and Diagnosis, the group chairs wrote:

Thank you for forwarding the document…entitled "Building an Integrated National Cancer Clinical Trials Program: A Proposal for Re-Organization from NCI Cancer Center Directors" for our review.

[We] would like to take this opportunity to present an initial response to this proposal.

As cooperative group chairs, we see the role of our organizations as inextricably linked with the NCI-funded cancer centers. To achieve research results that truly benefit our patients, the cooperative groups and the cancer centers must be fully aligned, such that these publicly-funded organizations provide a continuum from laboratory research to practice-changing phase III clinical trials.

At the present time, researchers residing in the cancer centers are the major scientific leaders of the cancer cooperative groups. The cooperative groups also derive substantial support from the cancer centers, as the cancer centers subsidize clinical trials accrual costs, and the cooperative groups leverage cancer center resources to achieve other needs such as core laboratory and biorepository infrastructure support.

Finally, cancer center researchers provide substantial support to cooperative group research because they serve as the PIs of R01, P01, and SPORE grants that use the cooperative group infrastructure to achieve their research aims. We therefore understand that any re-structuring of the cooperative group system must maintain and, ideally, enhance the close relationship between the cancer centers and the groups.

The proposal for re-organization, submitted by cancer center directors, brings some interesting new perspectives to the discussion, and a number of these are already in agreement with the approach initiated by the cooperative groups.

We agree that cancer clinical trial development is predominantly disease-oriented and multi-modality. As a result, researchers within a given disease must work together across all institutions (cancer centers, SPOREs, cooperative groups, etc.) to develop and prioritize high-impact studies.

We also agree upon a need to achieve a coordinated approach to trial development and prioritization that permits competition of ideas, arrives at a consensus concerning which best ideas move forward, and eliminates competition for operational structures/resources. Any re-structuring of the cooperative group system should enhance this activity.

We are pleased to find that the cancer center directors are actively engaged in the process of improving the nation's cancer clinical trials system, and welcome the opportunity to work together with them to achieve our common goals.

We also call upon the NCI to provide both programmatic and financial support that will make this collaboration possible.

CMS News:
CMS Coverage Memorandum To Pay for Provenge On-Label

The Centers for Medicare & Medicaid (CMS) issued a proposed decision memorandum today to cover on-label use of Provenge (sipuleucel-T) under a national coverage determination.

Provenge, an autologous cellular immunotherapy treatment for metastatic prostate cancer, is labeled for use in men with asymptomatic or minimally symptomatic metastatic castrate resistant prostate cancer. A course of treatment with the agent costs $93,000.

The CMS determination provides reimbursement for the labeled indication and allows local contractors to decide on coverage on off-label uses.

CMS will accept public comments on this proposed decision for 30 days. A final decision will be announced within 90 days.

The proposed decision is posted at: http://www.cancerletter.com/categories/documents.

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Cancer Death Rates Declined From 2003 to 2007, Report Says

Death rates from cancer in the U.S. continued to decline between 2003 and 2007, the most recent reporting period available, according to the latest Annual Report to the Nation on the Status of Cancer.

The report, by the NCI, the North American Association of Central Cancer Registries, the Centers for Disease Control and Prevention, and the American Cancer Society, found that the overall rate of new cancer diagnoses for men and women combined decreased an average of slightly less than 1 percent per year for the same period. The latest drop continues a pattern that emerged in the early 1990s.

The report said that, for the first time, lung cancer death rates decreased in women— more than a decade after rates began dropping in men.

Childhood cancer incidence rates continued to increase while death rates in this age group decreased.

Overall cancer incidence rates in men were essentially unchanged. There was a very small uptick in prostate cancer rates, and if these rates were excluded from the analysis, there would be a continued decline in overall male incidence rates.

Other highlights include:

• In men, incidence rates have declined for cancers of the lung, colon and rectum, oral cavity and pharynx, stomach, and brain (malignant only) while rates have risen for kidney, pancreas and liver cancers, as well as melanoma of the skin.

• In women, incidence rates decreased for breast, lung, colorectal, uterine, cervical, bladder, and oral cavity cancers, but increased for kidney, pancreas, and thyroid cancers as well as for leukemia and melanomas of the skin.

• Among racial/ethnic groups, cancer death rates were highest among black men and black women, but this group also showed the largest decline for the period between 1998 and 2007 compared with other racial groups.

• For new cancers, black men had the highest incidence rates in the 2003 to 2007 period studied.

• Among women, white women had the highest overall incidence rates. Breast cancer was the most commonly diagnosed cancer among women regardless of race or ethnicity.

The differences and fluctuations in death rates by racial/ethnic group, sex, and cancer site may reflect differences in risk behaviors, socioeconomic status, and access to and use of screening and treatment.

In the special feature section, the report explores the diversity of brain tumors and other nervous system cancers beyond those that are identified as malignant, including those that are borderline and benign.

The researchers analyzed data between 2004 and 2007 and found that in adults, non-malignant tumors were about twice as common as malignant tumors.

"Our new data show that non-malignant brain tumors are far more common than malignant brain tumors, and affect different population groups," said Betsy Kohler, executive director of the NAACCR. "We hope that the collection of both malignant and non-malignant brain tumors by central cancer registries will continue to provide a significant source of information and insight to researchers."

The report notes that non-malignant tumors make up two-thirds of all adult brain tumors and one-third of childhood brain tumors, with meningiomas being the most common type of nervous system tumor in the U.S.

Changes in diagnostic techniques, including the introduction of computed tomography, or CT, scans in the 1970s and magnetic resonance imaging, or MRI, in the 1980s, have led to less invasive methods for diagnosing brain tumors, but also have had a strong influence on incidence rates over the past decades.

Newer molecular studies have improved classification of brain tumors for treatment and prognostic purposes.

In the discussion of trends in malignant brain tumor incidence is the relative stability of long-term trends for tumors of neuroepithelial tissue, which arise from glial (support) cells in the brain and other tissues.

Incidence rates for glioblastoma, the most common, as well as highly fatal, form of these malignant tumors, increased from 1980 through 1991, likely due to increasing use of aggressive diagnostic procedures in elderly patients, but since 1991 the rates have been stable. The report notes that the relatively low variation in incidence and mortality rates over the past several decades for brain cancers suggest that external risk factors in the environment do not play a major roles in this disease.

"The full repertoire of numbers reported today reflects the enormous complexity of cancer, with different trends for different kinds of cancers, important differences among our diverse people, and different capabilities to prevent, detect, and treat various cancers," NCI Director Harold Varmus said in a statement. "Moreover, as our population continues to age, we have an obligation to discover and deliver better ways to control all types of cancers."

Drug Approval News:

Sylatron Approved For Melanoma; Amgen Disputes EMA Opinion

FDA approved **Sylatron** (peginterferon alfa-2b) for treatment of melanoma with microscopic or gross nodal involvement within 84 days of definitive surgical resection including complete lymphadenectomy. Sylatron is sponsored by Schering Corp., a subsidiary of Merck.

Patients who had been adequately surgically resected for their primary cutaneous melanoma and affected regional lymph nodes were randomized (1:1) to receive either Sylatron or observation for a five year period.

The primary endpoint, relapse-free survival, was defined as the time to the earliest of local or regional recurrence, distant metastases, or death.

Based on 696 RFS events, an improvement in RFS for Sylatron-treated patients [HR 0.82 (95% CI: 0.71, 0.96); unstratified log-rank p = 0.011] was observed. The estimated median RFS was 34.8 months (95% CI: 26.1, 47.4) and 25.5 months (95% CI: 19.6, 30.8) in the Sylatron and observation arms, respectively.

Following 525 deaths on study, there was no difference in overall survival between the Sylatron and the observation arms [HR 0.98 (95% CI: 0.82, 1.16)].

The trial's stratification factors included: type of nodal involvement (microscopic versus gross), number of positive nodes (1, 2-4, 5 or more, or not assessed), Breslow primary thickness (less than 1.5 mm, ≥ 1.5 to 4 mm, ≥ 4 mm), ulceration of primary tumor (present or absent or unknown), sex and study center.

Patients were assessed for local and regional recurrence or distant metastases every three months for the first two years of treatment and subsequently every six months through the end of the trial.

A blinded, independent review committee reviewed the case report form data to determine the occurrence, and the date of loco-regional recurrence, or distant metastasis.

Safety was evaluated in 608 Sylatron-treated patients. The most common (>60%) grade 1-4 adverse reactions experienced by Sylatron-treated patients were fatigue, increased ALT, increased AST, pyrexia, headache, anorexia, myalgia, nausea, chills, and injection site reactions. The most common serious adverse reactions occurring in Sylatron-treated patients were fatigue, increased ALT, increased AST, and pyrexia.

Thirty-three percent of patients recieving Sylatron discontinued treatment due to adverse reactions.

The most common adverse reactions present at the time of treatment discontinuation were fatigue, depression, anorexia, increased ALT, increased AST, myalgia, nausea, headache, and pyrexia.

Five deaths were reported within 30 days of the last Sylatron dose.

Two were attributed to recurrent disease, two to cardiovascular disease possibly related to Sylatron, and one to an accident.

The recommended dose and schedule for Sylatron is 6 mcg/kg/week, subcutaneously for 8 doses, followed by 3 mcg/kg/week subcutaneously. The maximum treatment period is five years.

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AMGEN said it submitted a request to the European Medicines Agency for a re-examination of the negative opinion for the use of **Vectibix** in combination with chemotherapy for wild-type KRAS metastatic colorectal cancer.

The Committee For Medicinal Products for Human Use issued the opinion in March.

Data from studies 20050203 (PRIME) and 20050181 ('181') showed that adding Vectibix to FOLFOX and FOLFIRI chemotherapy, improved progression-free survival versus chemotherapy alone in patients with wild-type KRAS mCRC, the company said.

The response rate to Vectibix plus chemotherapy was higher than chemotherapy alone, the company said. The improvement in median overall survival did not achieve statistical significance in the Vectibix arm of either trial.

Vectibix-related grade 3-4 infusion reactions were reported in less than one percent of patients. In patients with mutant KRAS tumors, outcomes were inferior for those receiving Vectibix plus FOLFOX versus FOLFOX alone.

In the U.S., Vectibix received accelerated approval in September 2006 as a monotherapy for the treatment of patients with EGFR-expressing mCRC after disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

Use of Vectibix is not recommended in patients whose tumors have KRAS mutations in codon 12 or 13. Vectibix is approved in more than 30 countries as a monotherapy treatment for wild-type KRAS mCRC, when standard chemotherapy is no longer effective.

In the Cancer Centers:

Emory Plans $200 Million Proton Treatment Center

EMORY HEALTHCARE signed a letter of intent with Advanced Particle Therapy, LLC, opening the door to a final exploratory phase for development of **the Georgia Proton Treatment Center**.

The closest proton therapy facility is the University of Florida Proton Therapy Institute in Jacksonville. Since that facility opened in 2006, approximately 1,500 patients have been treated there. Currently there are nine proton therapy centers in the U.S.

The 100,000-square-foot facility is expected to cost approximately $200 million, which will be funded by GPTC. The proton system will be provided Varian Medical Systems.

MICHAEL NEUSS was named chief medical officer at **Vanderbilt-Ingram Cancer Center**.

Neuss starts at the new position July 1. He will also hold a faculty position as professor in the Department of Medicine's Division of Hematology/Oncology.

A practicing oncologist since 1986, Neuss was vice president of the largest oncology practice in the Cincinnati area.

Neuss has been involved in several quality initiatives of the American Society of Clinical Oncology as well as an American Board of Medical Specialties project to define oncology episodes and a national panel defining quality oncology services for payers.

MATTHEW CALLISTER was appointed radiation oncology section chief for the **Banner MD Anderson Cancer Center**. This is the first of seven appointments for the center, scheduled to open in September of this year.

Callister is an assistant professor of radiation oncology at Mayo Clinic, Scottsdale. He will begin his new role in April. Callister graduated from Duke University School of Medicine, and completed his residency in radiation oncology at The University of Texas MD Anderson Cancer Center in Houston. His clinical practice focus has been in the treatment of gastrointestinal, skin, head and neck cancers, and lymphoma. He has served as local study chair or co-investigator for several clinical trials.

When Banner MD Anderson opens, cancer patients will be cared for in a new three-story, 133,000 square-foot outpatient center, supported by 76 beds on two floors inside Banner Gateway Medical Center. The outpatient center will house physician clinics, medical imaging, radiation oncology, infusion therapy and many support services.

CYNTHIA THOMSON, a researcher at the Arizona Cancer Center, received a $3 million grant from the **National Institutes of Health** to study whether a compound found in broccoli can enhance the health-promoting effects of the breast cancer drug tamoxifen in women at risk of developing breast cancer or those previously treated for early-stage breast cancer.

Thomson, an associate professor of nutritional sciences at the University of Arizona, notes that data from diet studies of people who have a higher intake of cruciferous vegetables – cauliflower, Brussels sprouts, kohlrabi and broccoli – suggest that may reduce the risk of certain cancers, including breast, colorectal, bladder and possibly prostate.

Alison Stopeck, a co-investigator in the study and the director of the Clinical Breast Cancer Program at the Arizona Cancer Center, sees this research as a unique opportunity to determine the potential of non-invasive imaging to be a reliable biomarker for breast cancer risk. Women in the 18-month study will have periodic MRIs to measure breast characteristics.

SAIKRISHNA YENDAMURI received a $555,000 grant from the **U.S. Army** to develop a method of establishing which post-surgery lung cancer patients have the highest risk of recurrence. Yendamuri is an assistant professor in the departments of surgical oncology and thoracic oncology at **Roswell Park Cancer Institute**.

Yendamuri plans to study the use of microRNA to establish biomarkers for non-small-cell lung cancer. By profiling their expression in the epithelial and stromal cells of the tumor separately—by using novel laser-capture dissection, instead of using whole-tumor tissue—he intends to develop a marker that can be used to predict recurrence.

The UNIVERSITY OF KANSAS Cancer Center and the **Kansas City Cancer Center** said they will combine their operations, creating a new organization for outpatient care.

Kansas City Cancer Center facilities and non-physician staff will become part of the University of Kansas Hospital. The center's physicians will become faculty of the university's medical center, specifically in the departments of Internal Medicine, Radiation Oncology, and Pathology and Laboratory Medicine. Previously, in 2007, they combined their blood and

marrow transplant program into the university's cancer center.

DANIEL VON HOFF was presented this month with the **Scripps Genomic Medicine Award** for his "pioneering efforts" in sequencing the DNA of patients with rare cancers.

Von Hoff's research and clinical work advances the art of using the fully sequenced genomes of cancer patients, spelling out all 3 billion letters of their DNA, to help determine the best course of treatment.

Von Hoff holds the titles of Physician-in-Chief and Distinguished Professor at the Translational Genomics Research Institute; professor of medicine at Mayo Clinic and at the University of Arizona College of Medicine; and chief scientific officer at the Virginia G. Piper Cancer Center at Scottsdale Healthcare and at US Oncology.

Professional Societies:

Thomas Beck Wins ACCC Clinical Scientist Award

THOMAS BECK received the Association of Community Cancer Centers' David King Community Clinical Scientist Award for his outstanding service, leadership and commitment to the oncology community.

Beck is medical director at the **St. Luke's Mountain States Tumor Institute** in Boise, Idaho. The award was presented at the association's annual meeting March 26 in Washington, D.C. Beck was chief and principal investigator for original studies of Ondansetron, a drug that helps patients deal with nausea and vomiting caused by chemotherapy. He was also instrumental in the original trials of Rituxan and Herceptin.

Beck served as co-principal investigator for the Prostate, Lung, Colon, and Ovarian Cancer Screening Trial. Also, he served as co-principal investigator for the National Lung Screening Trial. More than 3,000 individuals were enrolled in these screening trials in the Boise region.

In the 1980s, Beck was instrumental in creating the Mountain States Tumor and Medical Research Institute, which continues to be the only medical research institute in the state. He orchestrated relationships with the institute and the local veterans affairs hospital and four local universities to expand the research into bench science. Currently he is working on a joint basic science research center on the VA campus that will include the only tissue bank in the state.

The Cancer Letter Duke Series Wins Health Journalism Prize

The Cancer Letter won an Award for Excellence in Health Care Journalism from the Association of Health Care Journalists.

This publication's coverage of genomic research at Duke University won the third place award in the Trade Publications/Newsletter category. The series of stories, by editor and publisher Paul Goldberg, was titled "The Duke Debacle: Misadventures in Personalized Medicine."

The newsletter reported that a Duke researcher had misrepresented his credentials, claiming falsely to have won a Rhodes scholarship and a number of lesser awards. These falsified credentials helped the researcher in question—Anil Potti—obtain millions of dollars in grants from NCI and the American Cancer Society.

Other researchers were relying on his work and cancer patients were being treated based on his technology.

The AHCJ judges' comments follow:

"An extremely thorough and dogged accomplishment of reporting with a remarkable outcome—the downfall of a well-established and regarded researcher, as well as the retraction of his major research. It also raised significant questions about the integrity among top brass at Duke University. It's clear the reporter's knowledge base and access to sources were critical in the success of this investigation."

The coverage has led to retractions of papers in The New England Journal of Medicine, Nature Medicine, The Lancet Oncology, and The Journal of Clinical Oncology.

FDA has conducted an audit that was apparently focused on three clinical trials based on the technology invented by the university's genomic scientists, and the Institute of Medicine has formed a committee to determine what went wrong and when clinical trials of such technologies can be conducted appropriately.

First place in the category went to "The Cost of Living," by Kathy LaTour of the CURE Media Group.

Second place went to "Closing the Distance: Native Americans and Epilepsy," by Aliyah Baruchin of EpilepsyUSA.