THE CANCER LETTER

Jan. 9, 2015 • www.cancerletter.com • Vol. 41 No. 1

Internal Emails Raise New Questions

Duke Officials Silenced Med Student Who Reported Trouble in Anil Potti's Lab

By Paul Goldberg

Duke University would have avoided embarrassment, a misconduct investigation and a lawsuit, had its top administrators paid closer attention to a thoughtful report by a medical student who saw problems in the lab of the disgraced scientist Anil Potti.

Documents obtained by The Cancer Letter show that Duke's deans were warned about Potti's misconduct in late March and early April 2008, at the time when clinical trials of the now discredited Duke genomic technology were getting started.

The three-page document was penned by Bradford Perez, then a third-year medical student and a Howard Hughes Medical Institute scholar.

Instead of rewarding the student's brilliance with a plaque and a potted plant, Potti's collaborator and protector, Joseph Nevins—aided by a phalanx of Duke deans—pressured the young man to refrain from making a final complaint and reporting the matter to HHMI.

(Continued to page 2)

The Med Student's Memo

Research Concerns

I want to address my concerns about how my research year has been in the lab of Dr. Anil Potti. As a student working in this laboratory, I have raised my serious issues with Dr. Potti and also with Dr. Nevins in order to clarify how I might be mistaken. So far, no sincere effort to address these concerns has been made and my concerns have been labeled a "difference of opinion." I respectfully disagree. In raising these concerns, I have nothing to gain and much to lose.

(Continued to page 11)

Perez Memo Contradicts Duke's "No Whistleblowers" Claim

(Continued from page 1)

The Perez memo and internal emails that are being published here for the first time directly contradict the claims made by Duke officials that they had received no whistleblower reports.

Duke officials said they were blindsided by the events that reached a crescendo in 2010, more than two years after the Perez memo, following The Cancer Letter's reporting that Potti had misrepresented his credentials, claiming, among other things, to have been a Rhodes Scholar (The Cancer Letter, July 16, 2010).

The medical student's memo, titled Research Concerns, is a key element in a lawsuit filed on behalf of the patients who were enrolled in the three Duke clinical trials testing the discoveries from the program run by Nevins and Potti. Altogether, 117 patients were enrolled in the trials.

In addition to claiming harm, the patients' lawsuit alleges that Duke officials engaged in a civil conspiracy. The case is expected to go to trial at the Durham County Superior Court on Jan. 26.

Perez's Research Concerns memo is published on page 1.

Whatever its legal significance, the memo and the flurry of emails it touched off provide new insight into Duke's handling of the Potti controversy:

• The memo shows that, by ignoring the content of the Perez memo, Duke's deans allowed Nevins to investigate his protégé himself.

• Responding to Perez' memo, Nevins and Potti promised to conduct a review of the data in April 2008. A thorough, unbiased review of this sort would have produced evidence of fraud, statisticians say.

• Emails demonstrate, step-by-step, how Duke officials convinced Perez to present his principled stance as a difference of opinion between him and two senior scientists.

The Duke case triggered an examination of genomic and proteomic sciences. A committee of the Institute of Medicine was asked to recommend procedures for testing proposed -omic interventions before they are taken to the clinic.

Though crucial to understanding what actually happened at Duke, the Perez memo wasn't among the documents made public as part of the IOM investigation.

When it was convened in December 2010, the IOM committee was instructed by the IOM president at the time, Harvey Fineberg, to seek lessons from in-depth examination of the problems at Duke. No police-style or legal misconduct investigation was to be undertaken, however, since such investigations are the responsibility of the researchers' institution. The scope of the IOM investigation evolved further to include an examination of the administrative structures governing research at Duke.

Now, internal Duke emails show that top Duke officials were aware of the Perez matter, and that their subsequent claims to the IOM that no whistleblower had come forward in the genomics scandal were false.

Insiders say the Perez memo and supporting materials published here would have been relevant to the efforts of the IOM committee not because of what they say about the behavior of a specific person, but because they provide important insights about the institutional oversight process at Duke.

A detailed timeline of the Duke genomics scandal, which shows how the Perez incident alters what was previously known, appears on page 15.

Perez, who is currently a resident at Duke, said the controversy he triggered had caused him to repeat his third year of medical school.

"In the course of my work in the Potti lab, I discovered what I perceived to be problems in the predictor models that made it difficult for me to continue working in that environment," he said in an email to The Cancer Letter. "I raised my concerns with my laboratory peers, laboratory supervisors and medical school administrators and left it to them to determine how best to proceed. I chose to take an additional year to complete medical school in order to have a more successful research experience. My decision to stay at Duke was based on it being the best opportunity both personally and professionally."

Duke officials admitted that mistakes were made,

Editor & Publisher: Paul Goldberg
Associate Editor: Conor Hale
Reporter: Matthew Bin Han Ong

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

Subscription $405 per year worldwide. ISSN 0096-3917. Published 46 times a year by The Cancer Letter Inc.

but didn't respond to specific questions.

"Duke supported Dr. Perez as he raised his concerns during 2008 and thereafter," Duke Medicine officials said. "He continues to be a successful, valued and respected member of the Duke Medicine community.

"With regard to the scientific controversy: Duke acknowledged years ago there are many aspects of this situation that would have been handled differently had there been more complete information at the time decisions were made."

Thomas Henson, an attorney who represents the patients who are suing Duke, declined to comment.

"The medical student was very brave," said Arthur Caplan, director of the Division of Medical Ethics at the NYU Langone Medical Center, who was asked to review the materials cited in this story. "That was quite an act of courage.

"I have a feeling his lowly status made him someone that they would be able to hope would just go away," Caplan said. "There was a little bit of don't-let-the-door-hit-you-on-the-way-out.

"Perez can look at himself in the mirror. Every day. But he paid the price."

Brooding on a Beautiful Weekend

At the time he joined the Potti lab, Perez surely considered himself fortunate.

In 2006, Potti et al. had published a revolutionary paper in Nature Medicine, proposing using genomic signatures to guide the use of chemotherapeutics.

Another Potti paper, published in the New England Journal of Medicine, proposed using genomics to assign early-stage lung cancer patients to treatment regimens.

In both cases, the reported scales of improvements were dramatic.

However, MD Anderson biostatisticians Keith Baggerly, Kevin Coombes and Jing Wang wrote a letter to Nature Medicine in November 2007, stating that they were unable to reproduce the results the Duke group claimed. Responding in Nature Medicine, Nevins and Potti partly acknowledged the criticism, but argued that their findings still stand.

Perez's examination of the Potti lab was triggered by questions he received from editors on a paper he had submitted to the Journal of Clinical Oncology. Alerted by the correspondence in Nature Medicine, the reviewers had specific questions about a paper on which Perez was the first author.

Perez was in better position than Baggerly, Coombes and Wang to assess what was going on. As an insider, he could simply go to the lab and check. What he found appears to have shaken him to the core.

The trail of correspondence obtained by The Cancer Letter begins on March 2, 2008. It's a beautiful day in Durham; a Sunday.

Perez is indoors. A few weeks earlier, he came to the realization that the methods used by his research group aren't validated—and yet they are being used to assign patients to clinical trials.

A choice of therapy made based on faulty criteria can do harm.

Perez makes several cautious attempts to discuss methodological flaws with Potti, but Duke's star researcher isn't open to hearing the message, saying that he takes such criticism personally.

Now, on this gorgeous Sunday, Perez sees a clear choice: (a) he can challenge powerful political forces at Duke or (b) he can allow his good name to figure on papers he knows to be shoddy or worse.

This dilemma has to be resolved pronto.

Reviewers at the JCO are asking questions, and Potti is pressuring Perez to resubmit the paper. Alternatively, Potti says he would submit the paper to a less persnickety journal.

In an email to Katherine Garman, at the time a fellow at Duke, who appears to be playing a role in his training or advising him informally, Perez bemoans his inability to validate the predictors used in his paper.

Because predictions made on data used to build a model are overly optimistic, many groups use the "cross validation" technique, where the model is built using only part of the data, and then used to predict the status of the remaining (unused) samples.

Here, however, validation techniques the Potti lab uses amount to "erasing the samples that don't fit the cross validation from the figure and then reporting the cross validation as meaningful and justification for a good predictor," Perez writes to Garman.

If genes are selected for a model by applying t-tests to all of the genes and choosing the best ones for subsequent cross validation, the chance that these genes will be significant in both subsets of the data—model building and validation—is high. Doing cross validation properly means running the t-tests using just the data available for building the model and seeing if these same genes stand out in the data held out for predictions.

It's a circle. Your model will work only with the dataset you used to construct it. It will never work with any other data.

"When I asked Anil a few months ago about the use of a t-test to develop a predictor and whether this was biased, he mentioned that even though it was it

didn't matter as long as you had strong validation," Perez writes to Garman. "Then when I mentioned at a more recent time that some of the predictors recently developed using t-tests had never been validated he said since the method was validated this was ok. This is really problematic."

Perez senses that a reckoning is close.

"I've tried to [mention concerns one at a time] at times before but it's never been clear to me before, and he said he takes it as a personal insult if people don't believe in what he is doing," Perez writes.

As a final, desperate effort to stay in the lab, Perez proposes bringing in a biostatistician, William Barry, to meet with Potti and him in order to acquaint Potti with the ABCs of methodology.

Perez recognizes that he doesn't have the option to pretend that all is well at the lab. Doing so would ultimately hurt his scientific career and his good name.

"I talked to my dean about my concerns recently because I am nervous that things are coming to a head," Perez writes to Garman. "He mentioned that he knew that papers which were dragged through the mud in the academic press could be problematic later in my career. I think that by publishing all the methods and knowing all these weaknesses in the predictor, I am setting myself up for that.

"How do you think it would be best to proceed? What will happen if Anil says someone else will publish the paper for me?"

Garman responds with a few lines.

Yes, it would be possible to get the biostatistician Barry to sit in on the meeting, she writes. But there could be no assurance that Barry could find the time immediately.

"Do you have an idea of what you are going to tell Anil since he wants to submit tomorrow," Garman writes. "You could also contact Bill [Barry] to review some of your specific concerns. See you tomorrow.

"And it was a beautiful weekend—we spent lots of time outside."

Repeating the Third Year?

As March 2008 drags on, Perez is unable to resolve his problems.

In addition to pressure from Potti, he has to deal with an upcoming poster presentation to HHMI in May. If Perez is to walk away from the Potti lab, how would he assure HHMI that he has been doing actual work rather than, say, catching Frisbees at the campus's Sarah P. Duke Gardens?

His goal is to get residency in radiation oncology the following year, but with his third year of med school producing no publications, his case for getting residency would be weak.

And, in view of the circumstances, Perez hoped that HHMI would give him another fellowship to repeat his third year, making it possible for him to work at another lab.

On the evening of March 27, Perez has a conversation with Caroline Haynes, director of student affairs and associate dean for medical education at Duke.

The following day, Haynes brings in Phil Goodman, associate dean for medical education, who proposes that Perez bring his concerns to Nevins, director of a center within the Duke Institute for Genome Sciences and Policy.

"I believe that your best course of action is to set an appointment with Dr. Nevins to discuss your concerns," Goodman writes. "He would certainly want to know if there is some research misconduct going on in his labs. If you are unsure about seeing him on your own, then Dr. Haynes said she would be happy to accompany you. (I would, too, but Joe Nevins is a personal friend and I wouldn't see me being there as constructive.)"

Goodman's use of the word "misconduct" in an email to a medical student is worth noting. At that time, critics of the Duke group would not have even whispered such accusations. Rather, they claimed only that Nevins and Potti were making spectacularly crude errors. The word "misconduct" wouldn't be uttered until after Potti's enhancement of his credentials caught up with him.

Perez responds late that afternoon.

He proposes a course of action that one would expect for a person of his generation: write Nevins an email.

"If I go through Dr. Potti it will likely be very difficult for me to get a word in edgewise during a meeting between the 3 of us," Perez writes to Goodman. "I suspect that it would develop into Dr. Potti asking me difficult questions that are unrelated to my concerns in order to avoid dealing with the issues at hand.

"Finally, I could just send Dr. Nevins an email detailing my concerns. This seems like a cowardly way to go about raising my concerns and frankly I am not sure what would happen after that but it would avoid the issue of sitting down and having a meeting where it is possible that I am not able to articulate all my concerns."

No, don't send an email, Goodman responds later that day.

"I think you should set up a meeting with Dr. Nevins," he writes. "If you are unsure that a personal meeting with him may leave you speechless or unable to get your points across, then prepare a letter with those

thoughts, bring it, apologize to him, and then read it to him. This at least would set up points for discussion. You should do this ASAP since you might be able to salvage the year with 5 months to go. Dr. Haynes could come with you for moral support if you like.

"I wouldn't worry about Dr. Potti at this point. You've brought the issue to him already."

Perez appears to have taken Goodman's advice and writes out a single-spaced, three page summary of his concerns, providing a robust picture of what was allowed to go wrong at the Potti lab.

Research Concerns

"As a student working in this laboratory, I have raised my serious issues with Dr. Potti and also with Dr. Nevins in order to clarify how I might be mistaken," Perez writes in his Research Concerns memo. "So far, no sincere effort to address these concerns has been made and my concerns have been labeled a 'difference of opinion.'

"I respectfully disagree. In raising these concerns, I have nothing to gain and much to lose. In fact, in raising these concerns, I have given up the opportunity to be included as an author on at least four manuscripts. I have also given up a Merit Award for a poster presentation at this year's annual ASCO meeting. I have also sacrificed seven months of my own hard work and relationships that would likely have helped to further my career.

"Making this decision will make it more difficult for me to gain a residency position in radiation oncology. As a third-year medical student, these are all very important things that I have given up. As a result of these circumstances, I am spending another year of my life pursuing a more meaningful research project.

"The reason that I have made the decision to leave the lab and make these concerns known is because it is important that the work be done right for the sake of our patients and for the field of genomic medicine."

After presenting a thorough critique of problems with the work of the Duke team, Perez proposes this course of action:

"At this point, I believe the situation is serious enough that all further analysis should be stopped to evaluate what is known about each predictor and it should be reconsidered which are appropriate to continue using and under what circumstances.

"By continuing to work in this manner, we are going a great disservice to ourselves, to the field of genomic medicine and to our patients. I would argue that at this point nothing should be taken for granted. All claims of predictor validations should be independently and blindly performed. Unfortunately, since validation databases on the supplementary website have been shown to be misrepresented in multiple situations, those datasets should be obtained from their respective sources through channels that bypass the researchers."

"Brad Perez is a Hero"

Had this been a test, Perez would have nailed it.

According to top-tier biostatisticians who were asked to review these documents, his understanding of biostatistics was extraordinary for a med student—or even for someone with specialized training.

"Brad Perez is a hero," said Donald Berry, a biostatistician at MD Anderson. "To recognize rot is one thing. To challenge and to try to correct one's supervisors and recognized world authorities takes chutzpah. And conviction. And integrity.

"As he said in his refreshingly erudite 'Research Concerns,' he had much to lose, and he had already lost a lot.

"At a President's Council of Advisors on Science and Technology panel in January 2014 dealing with reproducibility in science, someone suggested that young scientists should learn about the scientific method from their mentors.

"I responded: 'Commenting on education, the problem is really who are the educators. The senior scientists are the problem. They are not the solution. And...young statisticians are just as clueless as the senior scientists.'

"A great example is this wonderful story about Perez teaching Potti and Nevins about science and his older, but not wiser students being too entrapped by their hypotheses—or too ignorant about science—to understand.

"There is more to this story than the heroic and principled actions of an erudite young man and the shame that has befallen a great university in blindly and selfishly defending its own. It is indicative of a lack of understanding of the scientific method among many scientists.

"The Duke scandal is extreme, to be sure. But irreproducibility in academic research is common. And the reward structure and complacency of universities is to blame. In the same PCAST panel I suggested that 'the utility is so different for senior scientists. They get a paper in Nature. That's wonderful. If they have to do a correction they get another paper. It's all in the utility structure.'"

Perez's memo had the look of a document that deserves to be taken seriously, statisticians say.

"Perez seems to bring up four criticisms," said Gary Rosner, director of the Division of Biostatistics and

Bioinformatics at the Johns Hopkins University Sidney Kimmel Comprehensive Cancer Center.

"1) The development of the genomic signature is flawed, because they chose to remove data elements that made things look bad.

"2) Potti and Nevins never really tried their signatures in a truly independent dataset.

"3) The software they used (BinReg, presumably) was not stable, leading to substantially different results across versions.

"4) Despite repeatedly raising questions and concerns, Perez was effectively stonewalled by his mentor (Potti), and the project was taken away from him. Essentially, Perez is saying that the response to his questions was that this is more complicated than he can understand.

"It sounds to me like he is saying that they stacked the deck in favor of reproducing the results from the 'training' dataset when they applied the model in the 'validation' data.

"I looked at the exchange between Coombes & Baggerly and Nevins & Potti in Nature Medicine. One of the concerns Coombes and Baggerly raised was the use of all data (training and validation datasets) when generating the metagenes. Nevins & Potti dismiss this concern, arguing incorrectly, that Baggerly & Coombes reproduce the results when developing the model using just the training data.

"Perhaps Perez's concern relates to this same flaw.

"In terms of Nevins & Potti removing data that were not consistent with their model, there's not much we can say. If the data were not made available, then no one would have been able to determine this. Don Berry talks about investigators preprocessing the data prior to giving the dataset to the statistician as a form of multiplicity.

"On the other hand, this practice may explain why no one could reproduce the Nevins & Potti results when they had all of the data."

Perez Meets With Nevins

Perez takes Goodman's advice, and later on March 28, he shoots an email to Nevins.

"I've been having a difficult time, and it was suggested that since you are one of my mentors for this research year that I try to set up a time to meet with you," Perez writes.

Nevins responds two days later, on March 30.

"I am very sorry we haven't kept in touch prior to now," he writes. "I frankly have just let it slip and shouldn't have."

Sent just after midnight on March 31, the Perez response outlines the issues he wants to discuss.

"I am not sure if you are aware that I asked Dr. Potti to remove my name from all publications recently submitted or accepted for publication," Perez writes. "I also decided it was best to avoid resubmitting my own first author publication to JCO. I also received an ASCO Merit Award for this year's meeting, but I don't feel comfortable giving this presentation because it involved applying predictors I was ultimately not comfortable with."

Perez works in an artful backhanded compliment to Potti:

"I have learned a lot and I think that's a testament to Anil and others willingness to spend time teaching me about how we do genomic analysis," he writes. "Some of what I have learned however, is disappointing and I think what's more disappointing is that I have raised these concerns with Dr. Potti before and nothing has changed."

Perez wants to make Nevins aware of his reasons for seeking another year of funding from HHMI.

"I don't expect a letter of endorsement for this application, but feel like it's best to share it with you before I submit," he writes.

Nevins quickly agrees to the meeting.

"You raise some serious issues here and I think we should talk about it sooner rather than later," he writes. "Are you available this afternoon? I could meet around 4 p.m."

The meeting takes place in Nevins's office.

In a deposition, which is cited in part in court documents, Perez describes an exchange with Nevins where the scientist implored him not to send the letter describing his doubts about the science at the foundation of the Duke clinical trials that had already started to accrue patients.

According to the deposition, Nevins said that by sending a letter, Perez would harm his own career as he would not get additional HHMI support for conducting

a different research project at another lab.

Nevins also says that the letter, if sent, would start an internal investigation at Duke. And he pledges to look into Perez's allegations.

An excerpt from the plaintiffs' court filing, which draws on the plaintiff attorneys' deposition with Perez, follows:

In March and April of 2008, Brad Perez pointed out problems with the validation data sets and suggested that there had been "misrepresentations" by Dr. Potti and/or Dr. Nevins regarding the data and the predictors did not work.

In a letter sent to Dr. Potti and Nevins, Brad Perez wrote:

"In looking back at previous publications that claim to validate some of the predictors being used today, most validation data is either unavailable, missing clinical data or methodological methods so that validation cannot be performed, or even misrepresented. If the validation sets are not accurate, then they should not be used to make predictors…"

Brad Perez said that in a meeting Dr. Nevins validated many of Brad Perez's concerns by referring to the serious issues raised regarding Dr. Potti's lab as "being somewhere along the spectrum between sloppy research and a difference of opinion to research fraud," and that Dr. Nevins confirmed that he would "go back through each and every dataset that we have posted in relation to various publications to ensure that there are no errors."

Dr. Nevins did not, however, want Brad Perez to send the letter because he did not want Duke or any other entity looking closely at the data underlying the clinical trials.

Q: And then you say he [Nevins] asked me not to send the letter because he felt that my additional year would not get funded anyway and he thought that by sending a letter I would essentially be initiating an internal Duke investigation. I think he wants to avoid that. Is that what you said in your email?

A: Yes.

Brad Perez had access to the underlying data and methodology and he could not reproduce the results that Dr. Potti and Dr. Nevins claimed. He was convinced by Dr. Nevins to not send the full letter that would expose Dr. Nevins and Dr. Potti.

Brad Perez, to his own personal and professional detriment "made the decision to leave the lab and make these concerns known because it is important that the work be done right for the sake of our patients and for the field of genomic medicine."

Nevins Acknowledges Gravity of the Situation

Internal Duke emails obtained by The Cancer Letter confirm this version of events.

In an email to Goodman late on March 31, Perez describes his meeting with Nevins.

"[Nevins] seemed very tense which I think is a clear sign that there are serious issues to be dealt with," Perez wrote. "He referred to the situation as being somewhere along the spectrum between sloppy research and a difference of opinion to research fraud," Perez writes.

"He asked me not to send the letter to HHMI because he felt that my additional year would not get funded anyway and he thought that by sending that letter I would essentially be initiating an internal Duke investigation. I think he wants to avoid that.

"He wants to meet on Friday to start discussing my concerns that I outlined on the application since we basically spoke in generalities during our meeting today.

"He recognizes that he has a serious conflict of interest in this matter but wanted the chance to deal with the situation in a non-partisan way himself. That seems fair. It's my assumption that for his own benefit he wants to be in the driver's seat so that if an investigation needs to be done he can be the one to initiate that.

Here, "out of respect for Dr. Nevins and Duke as an institution," Perez agrees to not submit the account of problems at the lab to HHMI, leaving it to Duke to support his application for another year of funding.

Nevins's acknowledgment that Potti may have committed "research fraud" merits attention. At a time when no outside critic is suggesting anything more sinister than carelessness and ignorance, Perez has heard Goodman speak of "misconduct" and now he hears Nevins mention "research fraud."

In subsequent communications with Perez, Goodman appears to play the role of peacemaker.

"Sounds like Anil is genuinely sorry about your year," Goodman writes in an April 1 email to Perez. "A lunch meeting would probably not be bad. Avoid the circumstances that led to your departure and enjoy conversing about other things. There is no doubt that if you let HHMI know of your concerns that the proper way to deal with it would be to let someone internally know first."

Then Goodman dangles the possibility of Nevins securing another job for Perez:

"I thought that Dr. Nevins was going to try to find you another lab to finish out the year. Am I wrong about that? Again HHMI funds the investigator and the lab, not the student. They will probably feel that this is an institutional matter and may not feel loyalty to you."

"For My Own Health…"

Intensive wrangling and uncertainty about his future appear to take a toll on Perez. He wants this torture to end.

"For my own health, I need to remove myself from this situation entirely," he writes to Goodman on April 1. "I largely made the decision to do another third year so that would be possible. I am happy to go to a final luncheon and I am happy to meet with Dr. Nevins (as many times as necessary) to discuss concerns with him so that he can take the appropriate steps to correct the research. I don't want to find myself working in his lab or any affiliated lab for the next 5 months to finish out this fellowship term. While I do feel that me leaving is a necessary step, I don't feel that a formal investigation is necessary at this time. Dr. Nevins may do a very good job of making sure that all appropriate measures are taken."

Documents show that at that time controversy around Potti reaches the medical school's top leadership.

In an email April 10, 2008, Sally Kornbluth, vice dean for research, writes to Nancy Andrews, dean of the Duke University School of Medicine and vice chancellor for academic affairs, and Edward Buckley, interim vice dean for medical education:

"Nancy (and Ed):

"Ed Buckley spoke to me briefly (and confidentially of course) about Anil Potti to see if we had any background on this. I have no first-hand knowledge, but remembered seeing the correspondence in Nature Medicine that is described in the link below. This link (which I came upon through google in my attempt to remember in which journal I had seen the original correspondence) seems to be a follow-up and contains the link to the original Nature Medicine correspondence—though I of course don't know if the current issue pertains to this. Sally."

Another official, Wesley Byerly, associate dean for research support services, is brought in, and the group decides to meet and discuss the matter in the next few days.

On April 16, Nevins and Potti respond to Perez's Research Concerns memo.

"We have now decided to go back through each and every dataset that we have posted in relation to various publications to ensure that there are no errors," Nevins and Potti wrote. "As you might imagine, this is a laborious process that requites quite a lot of checking of data to ensure that what is reported is accurate. But we do believe this is important and in the end will be in everyone's best interests."

Had this been done, fraud would have become evident more than two years earlier—in 2008 instead of 2010—and Duke's clinical trials of the predictor model would have stopped months after they began.

"The response from Potti and Nevins seems quite similar in tone and substance to the responses they sent to Baggerly and Coombes," said Johns Hopkins biostatistician Rosner. "While they seem to acknowledge some problems, history does not indicate they ever rectified their practice."

"An Unusual Situation"

With Perez planning to report irregularities in the Potti lab to HHMI, Duke now faces the prospect of the controversy spilling out into the outside world.

On April 22, in a package of letters to HHMI, Buckley, the interim vice dean for medical education, presents the matter as an honest difference of opinion between a medical student and the two world-famous researchers.

"Enclosed please find two letters explaining an unusual situation which has resulted from Brad Perez's HHMI Fellowship experience here at Duke under the supervision of Dr. Anil Potti and Dr. Joseph Nevins," Buckley writes. "As outlined in the letters, there appears to be an issue with regards to the methodology used for the research activities that Mr. Perez has been performing in the Potti lab. Because of this situation Mr. Perez feels uncomfortable in pursuing continued research activities in the lab. He has requested and been granted permission to seek out a new research experience in a different lab.

"This is with the full support of his current mentors and the institution. It is important to note that there have been no allegations of scientific misconduct. The mentors and Mr. Perez have reached this decision amicably. The Duke University Medicine administration has looked into this situation and also supports this recommendation.

"It is hoped that the Howard Hughes Medical Institute will continue to support Mr. Perez in his efforts to obtain a meaningful and productive medical research experience. It is our belief that even though his current activities have been abbreviated that he has benefited greatly by his experience."

The Perez letter is brief.

He says that the work in the Potti lab wasn't done in accordance with his standards of quality in genomic research, that he no longer feels comfortable working at the lab, and that he wishes to have his name removed from all the manuscripts published by the lab.

"I have made my concerns known to the appropriate individuals within Duke University and steps are being taken to evaluate those concerns internally," he writes. Stripped of erudite discussion and astute analysis, this version of the letter makes him sound like an overly confident young man.

Nevins and Potti portray the situation as a difference of opinion.

"We recognize that everyone has their own opinions about standards and level of proof and we respect his position on these issues," they write. "Given our differences on these matters, Brad has determined that his best course would be to find another research opportunity at Duke. While we do regret his decision, we also believe it is likely the appropriate choice and we will do whatever we can to support him in his future endeavors."

New Perspective on Nevins and Potti

Eighteen months after Perez bows out, in October 2009, MD Anderson statisticians Baggerly and Coombes publish a paper claiming there is potential for patient harm in the Duke trials.

Nevins and Potti have to defend themselves from the unusual continuing examination. After publication, Duke suspends the trials.

After a paper by Baggerly and Coombes claims that the Duke trials are potentially putting patients at risk, Nevins and Potti agreed to speak with this reporter.

The pair mounted an energetic defense of their work. With Potti on the conference call, Nevins says that a paper previously published in Lancet Oncology in December 2007 constitutes a blinded validation of the Duke group's methodology.

Says Nevins:

"Data was made available to us, blinded. All we got was the gene expression data. "We ran the predictions and sent it back to the EORTC investigators, including the statisticians in the EORTC group. They took the results, analyzed it in the context of the clinical responses in that study, and did further analyses with respect to evaluating developing combined probability measures." (The Cancer Letter, Oct. 2, 2009).

Nevins and Potti made similar claims in published correspondence with Nature Medicine.

In reality, the Lancet Oncology paper—which was ultimately retracted—didn't contain the words "blinded validation."

In a matter of days, the European researchers register disagreement with this statement. The validation wasn't blinded, they said. They provided the data in question (The Cancer Letter, Oct. 23, 2009)

Indeed, the dataset Potti used to "validate" the predictor model contained disease characteristics and it contained outcomes. As an author, Nevins would have been ordinarily expected to know this.

This occurred 18 months after the Perez memo—after Nevins sought to convince Perez not to send his letter and pledged that he would review the data and validity of predictors.

An audio recording of the conversation with Nevins and Potti is posted here.

During Duke's internal investigation of concerns raised in the Baggerly and Coombes, Nevins had the authority to decide which criticisms and documents should be shared with the two external reviewers.

Allowing Nevins to play a role in handling controversies coming from the genomics operations he directed is consistent with the maneuvers that resulted in the silencing of Brad Perez.

The decision to give Nevins this power was made at the highest levels of Duke Medicine.

The three trials were restarted in January 2010, following a brief internal investigation.

The three trials were stopped again—this time for good—in July 2010, only because of the publication of Potti's enhancement of his credentials.

A story about the controversy aired on the CBS program 60 Minutes.

More than anything, 60 Minutes loves extracting an on-camera mea culpa, and Nevins gave a good one:

"I regret that some of the issues that were raised along the way I didn't recognize earlier, and that this could have been brought to a halt at an earlier time," Nevins says. "I felt that I had addressed the issues that had been raised."

Nevins says that it was well after The Cancer Letter reported Potti's misrepresentation of his credentials that he started to lose confidence in his colleague. When he did look at the data—which would have had to happen after late 2010—he found manipulation.

"It became clear that there was no explanation other than there was a manipulation of the data, a manipulation of somebody's credentials and manipulation of a lot of people's trust," Nevins says to 60 Minutes four full years after the Perez incident. "It simply couldn't be random, it simply couldn't be inadvertent. It had to have been based on the desire to make something work."

The story does not mention the Perez incident, which is being reported here for the first time.

Limits on IOM Investigation

The Perez story didn't come up in the IOM review of the case, either.

There was no interest in starting a police-style investigation. This is understandable, perhaps, because the committee had no lawyers and no investigators, and wasn't ideally positioned to deal with issues of scientific misconduct.

NCI Director Harold Varmus, for example, said he was interested in high-level lessons that can be learned from the case, and the request for the IOM examination came from both NCI and Duke.

In July 2011, in a Q&A with The Cancer Letter, this reporter asked Varmus to explain how high-level lessons can be learned without a shoe-leather investigation: "As a former police beat reporter, I'm wondering to what extent it's futile to try to derive a high-level lesson from something that's pretty low level."

"I think you are seeing it the wrong way," Varmus replied. "There is a falsified CV. That's of no interest to me. That's someone else's problem… It was crucial to the case only because it helped people pay more attention to the underlying issue." (The Cancer Letter, July 22, 2011).

At the first meeting of the IOM committee Dec. 20, 2010, Gilbert Omenn, the panel chairman and director of the University of Michigan Center for Computational Medicine and Biology, outlined the focus of the investigation.

"A committee of the Institute of Medicine will refrain from launching a police-style investigation of the Duke scandal," he said. "We are not an investigative body."

"I think we are heading into a morass—to try to figure out what really happened at Duke and who should bear responsibility and who should be held accountable." (The Cancer Letter Jan. 7, 2011).

As the committee delved deeper into the problems of omics, Omenn and his committee members recognized that the problems at Duke needed to be examined. In the end, the Duke sections added up to 100 pages of the 338-page report.

Though the Perez incident would have been of interest to the committee, it was never mentioned.

Robert Califf, Duke's vice chancellor of clinical and translational research, director of the Duke Translational Medicine Institute and professor of medicine in the Division of Cardiology, is quoted saying that none of Potti's co-authors had expressed misgivings about his science.

In the report, Califf says that Duke had surveyed 162 investigators involved in 40 papers coauthored by Potti.

"Two-thirds of these papers, he testified, will be partially or fully retracted, with others pending evaluation," the report says. "Yet in no instance did anyone make any inquiries or call for retractions until contacted by Duke. This experience suggests the need for co-authors to have more shared responsibility for the integrity of the published research."

Califf doesn't figure in any of correspondence related to the Perez case and he had no oversight authority over the trials of the Nevins and Potti technology.

Califf's statement is technically correct. His survey of Potti's co-authors wouldn't have included Perez, who had taken his name off the Potti papers.

Statements by Kornbluth, who was recently named Duke provost, cannot be reconciled with emails obtained by The Cancer Letter.

According to the IOM report, "there was discontinuity in the statistical team, which may have contributed to the research team's failure to follow proper data management practices (Kornbluth and Dzau, 2011). Junior investigators on the team either did not recognize what was wrong or did not feel comfortable expressing their concerns even though whistle-blowing systems were in place. Some members of the laboratory did ultimately come forward with concerns about the research, but only after the University began an investigation (Kornbluth, 2011)."

Elsewhere in the report, Duke officials are quoted describing the university's "just culture," which encourages anyone at any level to criticize the scientific methods of a study without fear.

The report continues:

"However, the problems with the three clinical trials were not brought to the attention of the appropriate individuals within the university leadership through

any of these whistleblowing channels. According to Vice Dean for Research Sally Kornbluth, a number of people came forward after the university undertook its investigation and said they 'were glad [the university was] reviewing things carefully' (Kornbluth, 2011).

"Why no one came forward earlier, or perhaps any such concern was not forwarded appropriately, is not known, but the fact that these problems were not brought forward earlier may be an indication of the discomfort or lack of confidence that faculty and staff may have with these systems."

The report was vetted by Duke officials, which presumably means that they reviewed it and didn't see reasons to correct it.

Did Kornbluth know about the Perez case? Did Victor Dzau, who was then Duke Chancellor?

The answers are yes and yes.

Kornbluth's name figures in the 2008 exchange of emails in preparation for a meeting about "Anil Potti" at the time Perez was circulating communicating his research concerns to HHMI. It is not publicly known whether the meeting actually took place.

Another exchange of emails obtained by The Cancer Letter shows that Kornbluth was aware of the Perez controversy on Oct. 5, 2010, three months before the IOM committee held its first meeting and six months before the committee first met publicly with Duke officials.

At that time, Duke's top administrators were deciding the best way to handle the Perez incident in the context of the scientific misconduct investigation. Should the Perez documents be presented to an internal Duke committee that was deciding on the scope of the misconduct investigation.

At first, Kornbluth decides that charges would be appropriate. Then she changes her mind, choosing to present the Perez materials to the standing committee, leaving it up to the group whether charges are justified.

The email is addressed to Dzau, who has since been named IOM president:

"Victor,

"My two cents: I've had a change on heart about this. I've talked to Wesley [Byerly, associate dean for research support services] at length and I think his thoughts to let the Perez stuff go in with the existing allegations (and not draft another charge) is right. I think Joe [Nevins] is going to the committee to debrief and I think the committee can then decide if they really think there is any merit in charging Joe with anything. I am feeling more and more that we may have jumped the gun with that and the answer is probably 'no.' Happy to discuss if you want. Sally."

It's not publicly known what was actually done. More than four years after its launch, the Duke misconduct investigation remains a work in progress.

It's not a crime to give deceptive testimony to IOM. "They are a private club," said NYU's Caplan, who is an IOM member. "You can lie to them all you want. It's like lying to The Cancer Letter. It's probably bad form, but you are not going to go to jail."

Matthew Bin Han Ong contributed to this story.

Research Concerns

Perez's Memo, Printed in Full

(Continued from page 1)

In fact, in raising these concerns, I have given up the opportunity to be included as an author on at least 4 manuscripts. I have also given up a Merit Award for a poster presentation at this year's annual ASCO meeting. I have also sacrificed 7 months of my own hard work and relationships that would likely have helped to further my career. Making this decision will make it more difficult for me to gain a residency position in radiation oncology. As a third year medical student, these are all very important things that I have given up. As a result of these circumstances, I am spending another year of my life pursuing a more meaningful research project. The reason that I have made the decision to leave the lab and make these concerns known is because it is Important that the work be done right for the sake of our patients and for field of genomic medicine.

I joined the Potti lab in late August of last year and I cannot tell you how excited I was to have the opportunity to work in a lab that was making so much progress in oncology. The work in laboratory uses computer models to make predictions of individual cancer patient's prognosis and sensitivity to currently available chemotherapies. It also works to better understand tumor biology by predicting likelihood of cancer pathway deregulation. Over the course of the last 7 months, I have worked with feverish effort to learn as much as possible regarding the application of genomic technology to clinical decision making in oncology. As soon as I joined the lab, we started laying the ground work for my own first author publication submitted to the Journal of Clinical Oncology and I found myself (as most students do) often having questions about the best way to proceed. The publication involved applying previously developed predictors to a large number

of lung tumor samples from which RNA had been extracted and analyzed to measure gene expression. Our analysis for this project was centered on looking at differences in characteristics of tumor biology and chemosensitivity between males and females with lung cancer. I felt lucky to have a mentor who was there in the lab with me to teach me how to replicate previous success. I believed the daily advice on how to proceed was a blessing and it was helping me to move forward in my work at an amazingly fast rate. As we were finishing up the publication and began writing the manuscript, I discovered the lack of interest in including the details of our analysis. I wondered why it was so important not to include exactly how we performed our analysis. I trusted my mentor because I was constantly reminded that he had done this before and I didn't know how things worked. We submitted our manuscript with a short, edited methods section and lack of any real description for how we performed our analysis. I felt relieved to be done with the project, but I found myself concerned regarding why there had been such a pushback to include the details of how we performed our analysis. An updated look at previous papers published before I joined the lab showed me that others were also concerned with the methods of our lab's previous analyses. This in conjunction with my mentor's desire to not include the details of our analysis was very concerning. I received my own paper back with comments from the editor and 4 reviewers. These reviewers shared some criticisms regarding our findings and were concerned about the lack of even the option to reproduce our findings since we had included none of the predictors, software, or instructions regarding how we performed this analysis. The implication in the paper was that the study was reproducible using publicly available datasets and previously published predictors even though this was not the case. While I still maintained respect for my mentor's experience, I felt strongly that we needed to include all the details. Ultimately, I decided that I was not comfortable resubmitting the manuscript even with a completely transparent methods section because I believe that we have no way of knowing whether the predictors I was applying were meaningful. In addition to the red flags with regard to lack of transparency that I mentioned already, I would like to share some of the reasons that I find myself very uncomfortable with the work being done in the lab.

When I returned from the holidays after submitting my manuscript, I started work on a new project to develop a radiation sensitivity predictor using methods similar to those previously developed. I realized for the first time how hard it was to actually meet with success in developing my own prediction model. No preplanned method of separation into distinct phenotypes worked very well. After two weeks of fruitless efforts, my mentor encouraged me to turn things over to someone else in the lab and let them develop the predictor for me. I was gladly ready to hand off my frustration with the project but later learned methods of predictor development to be flawed. Fifty-nine cell line samples with mRNA expression data from NCI-60 with associated radiation sensitivity were split in half to designate sensitive and resistant phenotypes. Then in developing the model, only those samples which fit the model best in cross validation were included. Over half of the original samples were removed. It is very possible that using these methods two samples with very little if any difference in radiation sensitivity could be in separate phenotypic categories. This was an incredibly biased approach which does little more than give the appearance of a successful cross validation. While this predictor has not been published yet, it was another red flag to me that inappropriate methods of predictor development were being implemented.

After this troubling experience, I looked to other predictors which have been developed to learn if in any other circumstances samples were removed for no other reason than that they did not fit the model in cross validation. Other predictors of chemosensitivity were developed by removing samples which did not fit the cross validation results. At times, almost half of the original samples intended to be used in the model are removed. Once again, this is an incredibly biased approach which does little more than give the appearance of a successful cross validation. These predictors are then applied to unknown samples and statements are made about those unknowns despite the fact that in some cases no independent validation at all has been performed.

A closer look at some of the other methods used m the development of the predictors is also concerning. Applying prior multiple T-tests to specifically filter data being used to develop a predictor is an inappropriate use of the technology as it biases the cross validation to be extremely successful when the T-tests are performed only once before development begins. This bias is so great, that accuracy exceeding 90% can be achieved with random samples. I learned this to be true some months ago and raised concerns at that time to my mentor but was once again pressured to

understand that this was not inappropriate as long as 'robust' independent validation of the model's accuracy .exists. So far, no 'robust' independent validation bas been performed on any of these predictors and no independent validation at all has been performed on many of these predictors despite the fact that they are being used in descriptive studies.

My efforts in the lab have led me to have concerns about the robustness of these prediction models in different situations. Over time, different versions of software which apply these predictors have been developed. In using some of the different versions of software, I found that my results were drastically different despite the fact that I bad been previously told that the different versions of the classifier code yielded almost exactly the same results. The results from the different versions are so drastically different that it is impossible for all versions to be accurate. Publications using different versions have been published and predictions are claimed to be accurate in all circumstances. If a predictor is being applied in a descriptive study or in a clinical for any reason, it should be confined that the version of software that is being used to apply that predictor yields accurate predictions in independent validation.

A number of other predictors of chemosensitivity were developed and published before I came to join the lab. I applied the previously developed and published Affymetrix U95 based predictors for sensitivity (Potti et al, Nature Medicine, 2006) and found that in some situations there was extremely poor correlation between that predictor and a newly developed predictor for the same chemotherapeutic agent on the UI33A platform (Salter et al. PLOSOne, 2008). This kind of complete disconnect in two predictors that should be predicting the same thing is concerning and yet our lab considers them both to be valid.

Some other predictors which have been developed in the lab claim to predict likelihood of tumor biology deregulation. The publication which reports the development of these predictors was recently accepted for publication in JAMA. The cancer biology predictors were developed by taking gene lists from prominent papers in the literature and using them to generate signatures of tumor biology/microenvironment deregulation. The problem is in the methods used to generate those predictors. A dataset consisting of a conglomerate of cancer cell lines (which we refer to as IJC) was used for each predictor's development An in-house program, Filemerger, was used to bring the gene list of the IJC down to include only the relevant genes for a given predictor. At that point, samples were sorted using hierarchical clustering and then removed one by one and reclustered at each step until two distinct clusters of expression were shown. This step in and of itself biases the model to work successfully in cross validation although an argument could be made that this is acceptable because the gene list is already known to be relevant. The decision regarding how to identify one group of samples as properly regulated and the other as deregulated is where the methods become unclear. There is no way to know if the phenotypes were assigned appropriately, backwards, or if the two groups accurately represent the two phenotypes in question at all.

Since I have been in the lab, I have worked for countless hours to apply what I believed to be valid models to predict chemosensitivity, oncogenic pathway deregulation, and tumor biology. In looking back at previous publications which claim to validate some of these predictors being used today, most validation data is either unavailable, missing clinical data or methodological methods so that validation cannot be performed, or even misrepresented. If the validation sets are not accurate on the version of the software being used today, then they should not be used to make predictions of unknown samples.

After an earlier publication which claimed to make extremely accurate predictions of chemosensitivity (Potti et al, Nature Medicine, 2006), I think that it was assumed that It was easy to generate predictors. More recent events have shown that the methods were more complicated and perhaps different than first described. Given the number of errors that have already been found and the contradicting methods for this paper that have been reported, I think it would be worthwhile to attempt to replicate all the findings of that paper (including methods for development AND claimed validations) in an independent manner. More recently, when we've met with trouble in predictor development we've resorted to applying prior multiple t tests or simply removing multiple samples from the initial set of phenotypes as we find that they don't fit the cross validation model. These methods which bias the accuracy of the cross validation are not clearly (if at all) reported in publications and in most situations the accuracy of the cross validation is being used as at least one measure of the validity of a given model. Also concerning is that models are being applied to describe unknown samples in situations where we are not sure that the models accurately predict what is claimed. Finally, the lack of transparency in making validation

sets and methods available so that others can confirm the work is concerning.

At this point, I believe that the situation is serious enough that all further analysis should be stopped to evaluate what is known about each predictor and it should be reconsidered which are appropriate to continue using and wonder what circumstances. By continuing to work in this manner, we are doing a great disservice ourselves, to the field of genomic medicine, and to our patients. I would argue that at this point nothing that should be taken for granted. All claims of predictor validations should be independently and blindly performed. Unfortunately, since validation datasets on the supplementary website have been shown to be misrepresented in multiple situations, those datasets should be obtained from their respective sources through channels that bypass the researchers.

I have had concerns for a while; however I waited to be absolutely certain that they were grounded before bringing them forward. As I learn more and more about how analysis is performed in our lab, the stress of knowing these problems exist is overwhelming. Once again, I have nothing to gain by raising these concerns. In fact, I have already lost. As a student, I do not claim to understand the best way to go about performing this analysis; however to this point no one has shared with me why my concerns are inappropriate. I believe that a truly independent third party intimately familiar with methods of genomic predictor development and application would agree that my concerns are worth considering.

Research Concerns

Nevins and Potti Respond To Perez's Questions and Worries

Dear Brad,

We regret the fact that you have decided to terminate your fellowship in the group here and that your research experience did not tum out in a way that you found to be positive. We also appreciate your concerns about the nature of the work and the approaches taken to the problems. While we disagree with some of the measures you suggest should be taken to address the issues raised, we do recognize that there are some areas of the work that were less than perfect and need to be rectified. We thought it would perhaps be best to summarize our view and also steps we have decided to take in relation to several of the problems you cite.

1. Concerning the use of various forms of the BinReg algorithm and the fact that validations have not always been adequately performed when switching from one version to the next.

As we think you know, we have struggled with the use of BinReg and what works best in various settings. This reflects not so much the nature of the program but rather the reality of doing these studies in an imperfect world—datasets with different characteristics being predicted with training sets of varying characteristics. While we would very much like for all of the samples that we use to be perfectly compatible, this is virtually never the case and necessitates measures to adjust and accommodate the differences. As we think you know, the two versions of BinReg try to accomplish these goals in different ways and we are frankly still evaluating what might be optimal in different circumstances. That said, we have tried to be careful in presenting analyses with a different version of the program to be sure that the results are valid. I suspect that we likely disagree with what constitutes validation.

2. Concerning the methods for developing a predictor that involve feature selection.

We recognize that you are concerned about some of the methods used to develop predictors. As we have discussed, the reality is that there are often challenges in generating a predictor that necessitates trying various methods to explore the potential. Clearly, some instances arc very straightforward such as the pathway predictors since we have complete control of the characteristics of the training samples. But, other instances are not so clear and require various approaches to explore the potential of creating a useful signature including in some cases using information from initial cross validations to select samples. If that was all that was done in each instance, there is certainly a danger of overfitting and getting overly optimistic prediction results. We have tried in all instances to make use of independent samples for validation of which then puts the predictor to a real test. This has been done in most such cases but we do recognize that there are a few instances where there was no such opportunity. It was our judgment that since the methods used were essentially the same as in other cases that were validated, that it was then reasonable move forward. You clearly disagree and we respect that view but we do believe that our approach is reasonable as a method of investigation.

3. Concerning discrepancies in datasets that have been used for validation and that were posted on our web pages.

In one instance, you made note of the fact that

an adriamycin response dataset contained a number of duplications or triplications of samples. It turns out that upon discussion with the individuals at St. Jude who provided this data to us that the duplications and triplications were generated by them when they assembled the data to provide to us. This was unfortunate and clearly something that we wish was recognized prior to this time. In retrospect, it might have been a good idea to do a data quality check upon first receiving this data that might have then uncovered the fact that there were duplicated or triplicated samples. Unfortunately, this was not done and we only recognized the issue you have pointed it out. We are grateful to you for identifying this issue and we are in the process of correcting the dataset on the web page along with a notation to users of the site to alert them to this change. We have also examined the consequence of this error on the predictive accuracy of adriamycin response. The original accuracy reported in the paper was 81%·when we eliminate the repeated samples, the accuracy is 76%. As such, the conclusion that the signature developed to predict adriamycin sensitivity does predict clinical response is still valid.

You also make note of a second instance of data duplication in one of our datasets—this involves data from the thrombosis study reported in Blood in 2006. You noted that there were several samples that were clearly duplicated in the database. We have also now reviewed this data and realize that indeed there were several samples that received different names in the process of generated the final data. This did not involve using the same samples multiple times in the assays reported in the paper but rather represents duplicate entries of the samples when the final table was assembled. Thus, this has no effect on the results reported in the paper. We have now corrected this database on the web page and again, we appreciate the fact that you have made note of the error.

Given these two instances, we have now decided to go back through each and every dataset that we have posted in relation to various publications to ensure that there are no errors. As you might imagine, this is a laborious process that requires quite a lot of checking of data to ensure that what is reported is accurate. But, we do believe this is important and in the end will be in everyone's best interest. The reality is that these errors do occur, and no degree of quality control will likely complete [sic] eliminate the problem. In most instances they are corrected as a result of someone trying to use the data. As maybe was the case for you, and in the course or doing so notices problems of this sort and then points them out to us. We then respond by making the corrections. But, we're sure that there are likely other cases that people have problems, get frustrated, but then give up without contacting us and that would be unfortunate. So, in the end we believe trying to make these sources of information as accurate as possible is in everyone's best interest, including ours. We appreciate that you have pointed out these mistakes to us. We do wish to emphasize, however, that we have never misrepresented data or methods in the web page material as you seem to suggest in the initial draft statement to HHMI. We may have neglected to include necessary information or, as described above, we may have inadvertently introduced mistakes into some of the data, but this was in no way intentional. When problems or errors or the need for additional information has been reported to us by other investigators, we have always responded promptly and made the changes or provided the information. This happens continually and is part of the normal scientific process.

We recognize that these responses are likely only partially satisfactory to you and that in some instances, such as the nature of the validations that are appropriate for use of a signature, you remain in disagreement. We understand that position and respect it—in no way, would we want to force you into a circumstance that was inappropriate in your mind. But, at the same time, we believe it is important to recognize that many of these cases are judgment calls and that others might have a different point of view or standard for the science from your own. We don't ask you to condone an approach that you disagree with but do hope that you can understand that others might have a different point of view that is not necessarily wrong.

Finally, we would like to once again say that we regret this circumstance. We wish that this would have worked out differently but at this point, it is important to move forward.

Sincerely yours,
Joseph Nevins
Anil Potti

How the Perez Case Fits Into the Duke Scandal Timeline

2000

Joseph Nevins, Mike West founds Computational and Applied Genomics Program (CAGP) at Duke University.

2003

Duke Institute for Genome Sciences and Policy is created. CAGP becomes the new IGSP Center for Applied Genomics and Technology (CAGT).

2003

Anil Potti begins fellowship at Duke. He joins Nevins's laboratory in 2004.

2006

CAGT hires Potti to establish an independent lab focused on gene expression–based research.

October 2006

Nature Medicine publishes Potti et al. paper, "Genomic signatures to guide the use of chemotherapeutics."

November 2006

MD Anderson biostatisticians, Keith Baggerly, Kevin Coombes and colleagues, begin correspondence with Potti and colleagues about the Nature Medicine paper and subsequent publications.

2007

Duke establishes Clinical Genomics Studies Unit.

June 2007

A Phase II trial (NCT00509366) using cisplatin chemosensitivity test to direct therapy for advanced-stage lung cancer patients, began enrolling patients.

July 2007

Cancer and Leukemia Group B submits "Study Using a Genomic Predictor of Platinum Resistance to Guide Therapy in Stage IIIB/IV Non-Small Cell Lung Cancer" to ClinicalTrials.gov

October 2007

"Adjuvant Cisplatin With Either Genomic-Guided Vinorelbine or Pemetrexed for Early Stage Non -Small Cell Lung Cancer" (NCT00545948) is entered on ClinicalTrials.gov.

October 2007

Journal of Clinical Oncology publishes "Pharmacogenomic strategies provide a rational approach to the treatment of cisplatin-resistant patients with advanced cancer" by Hsu et al.

November 2007

Nature Medicine publishes Coombes et al. letter critiquing the Potti et al. paper, together with a rebuttal.

December 2007

Lancet Oncology publishes "Validation of gene signatures that predict the response of breast cancer to neoadjuvant chemotherapy: A substudy of the EORTC 10994/BIG 00-01 clinical trial."

March 2008

"Trial to Evaluate Genomic Expression Profiles to Direct Preoperative Chemotherapy in Early Stage Breast Cancer" (NCT00636441) entered on ClinicalTrials.gov.

April 2008

Bradford Perez, a third-year medical student working in Potti's lab, resigns, withdraws his name from publications, and writes a memorandum titled "Research Concerns." Duke officials convince Perez to not make a detailed report to the Howard Hughes Medical Institute, which is funding his research through Duke.

April 2008

Potti and Nevins promise to fix errors in studies.

October 2008

Duke academic administrators meet to discuss Potti. The meeting appears to have been triggered by Perez's memo.

June 2009

Baggerly and Coombes learn that the three Duke clinical trials are underway.

July 2009

CALGB submits revised protocol (Genome-Guided Chemotherapy for Untreated and Treated Advanced Stage Non-Small Cell Lung Cancer: A Limited Institution, Randomized Phase II Study). Current Oncology Reports publishes "Translating genomics into clinical practice: Applications in lung cancer."

September 2009

Annals of Applied Statistics publishes "Deriving chemosensitivity from cell lines: Forensic bioinformatics and reproducible research in high-throughput biology" by Baggerly and Coombes. NCI contacts Duke to ask that the university carefully consider the validity of the work and its extrapolation to the clinic.

October 2009

The Cancer Letter first covers the story; Nevins asserts that the approach has been shown to work in a blinded validation by Bonnefoi et al. (2007). Enrollment in the three Duke trials is suspended. Patients already enrolled in the trials are informed of the controversy and reconsented. The Cancer Letter reports statements from coauthors of the Lancet Oncology study that the validation was never blinded.

Nov. 9, 2009

Baggerly sends a report highlighting problems with data posted on a webpage on the cisplatin and pemetrexed tests to Kornbluth at Duke. This report was shared with Nevins, who asked that it be withheld from the external reviewers; Duke leadership decided to honor Nevins' request.

Nov. 9, 2009

Claudio Dansky Ullmann of NCI submits the review of revised CALGB-30702 protocol (Genome-Guided Chemotherapy for Untreated and Treated Advanced Stage Non-Small Cell Lung Cancer: A Limited Institution, Randomized Phase II Study) to NCI's Cancer Therapy Evaluation Program (CTEP) Protocol and Information Office and forwards the review and disapproval letter to CALGB.

Nov. 16, 2009

Lisa McShane and Jeffrey Abrams of NCI contact CALGB requesting re-evaluation of the Lung Metagene Score test for CALGB-30506.

December 2009

External reviewers find that, "In summary, we believe the predictors are scientifically valid and with a few additions can be fully responsive to the comments of Baggerly and Coombes."

January 2010

Duke restarts the three trials (NCT00545948, NCT00509366, and NCT00636441).

February 2010

NCI completes reevaluation of supporting data for the CALGB-30506 trial.

March 2010

Nevins et al. send a letter to McShane in response to some of her concerns about the LMS used in CALGB-30506. McShane and Abrams reply with the conclusions of their analysis of the LMS in the clinical trial: The test should not remain as a stratification factor, and the coprimary aim to evaluate its performance should be removed from the study.

April 2010

The Cancer Letter obtains a copy of Duke University's external review report from NCI via a Freedom of Information Act request and publishes the document.

June 2010

NCI completes reevaluation of the cisplatin chemosensitivity test. NCI hosts Duke researchers to discuss the gene expression–based tests developed at Duke. NCI states that it is not satisfied, and directs Potti and Nevins to conduct a search of their labs to supply the data and code reproducing the results in Hsu et al. (2007) and justifying the trials under way.

July 16, 2010

The Cancer Letter reports that Anil Potti incorrectly stated his credentials. Duke places Potti on administrative leave while the University investigates allegations of inaccuracies in his CV and in the research.

July 19, 2010

Thirty-one biostatisticians and bioinformatics experts from around the world send a letter, "Concerns about prediction models used in Duke clinical trials," to NCI director Harold Varmus.

July 23, 2010

Lancet Oncology issues an expression of concern for "Validation of gene signatures that predict the response of breast cancer to neoadjuvant chemotherapy." Duke suspends trials for a second time.

July 30, 2010

NCI and Duke request assistance from the Institute of Medicine in assessing the scientific foundation of the three clinical trials and identifying appropriate evaluation criteria for future tests based on omics technologies.

Aug. 27, 2010

Duke completes its review of Potti's credentials; identifies issues of substantial concern resulting in corresponding sanctions. Potti remains on administrative leave.

Oct. 5, 2010

Duke administrators—Victor Dzau, Wesley Byerly, Sally Kornbluth, Nancy Andrews and Ed Buckley—discuss the Perez matter in the context of the misconduct investigation.

Oct. 22, 2010

Duke officials inform NCI that they have determined that several datasets reported to have been used to validate the cisplatin test were found to be flawed. The Hsu et al. (2007) paper would be retracted. Investigation into other datasets was ongoing.

November 2010

NCT00545948, NCT00509366, and NCT00636441 trials terminated in ClinicalTrials.gov.

Nov. 16, 2010

Journal of Clinical Oncology retracts "Pharmacogenomic strategies provide a rational approach to the treatment of cisplatin- resistant patients with advanced cancer."

Nov. 19, 2010

Anil Potti resigns from his position at Duke, later taking a position as an oncologist in South Carolina with strong endorsement from some Duke faculty members.

December 2010

McShane describes to the IOM committee the NCI interactions with the Duke investigators pertaining to the gene expression–based tests, and supplies documentation to the committee. She reveals that NCI had discovered that it had been providing partial funding to the trial NCT00509366 through an R01 grant awarded to Anil Potti. She describes her unsuccessful attempts to reproduce the results reported in the Hsu et al. (2007) paper for the cisplatin test and how that eventually led to discovery of several corrupted datasets.

January 2011

Potti et al. Nature Medicine paper retracted. IGSP Center for Applied Genomics and Technology is dissolved. FDA conducts an inspection at Duke University to detemine the rationale for the IRB's initial non-significant risk decision regarding an investigational device exemption.

February 2011

Lancet Oncology retraction (Bonnefoi et al., 2011).

March 2011

NEJM retraction (Potti et al., 2011b). Draft document, A framework for the quality of translational medicine with a focus on human genomic studies: Principles from the Duke Medicine Translational Medicine Quality Framework committee, released. Final draft is released in May 2011.

March 30, 2011

Nevins presents at IOM, acknowledges "nonrandom data corruption" in research.

July 2011

Duke sends the IOM committee a list of identified problems, missed signals, and proposed solutions based on the work of the TMQF committee.

August 2011

Duke representatives meet with the IOM committee: Robert Califf, Sally Kornbluth, Michael Cuffe, Ross McKinney, John Falletta, Geoff Ginsburg, Michael Kelley, and William Barry. **Dzau does not attend the session, citing prior commitments. Duke representatives do not turn over Perez memo and emails to IOM. Officials stated that Duke has a "culture of openness" and that there were no whistleblowers.**

January 2012

FDA posts documents on its website indicating that it informed Duke in 2009 that an IDE should have been obtained for the three trials. Journal of Clinical Oncology retracts "An integrated genomic-based approach to individualized treatment of patients with advanced-stage ovarian cancer."

February 2012

CBS's 60 Minutes airs "Deception at Duke: Fraud in cancer care?"

March 2012

IOM issues report, "Evolution of Translation Omics: Lessons Learned and the Path Forward."

This timeline is adapted from The Cancer Letter archives and the 2012 Institute of Medicine report, "Evolution of Translational Omics: Lessons Learned and the Path Forward."

An Appreciation

Joseph McLaughlin, 66, Cancer Epidemiologist

By William J. Blot

Joseph McLaughlin, an internationally recognized epidemiologist who made numerous contributions towards increasing understanding of the causes of cancer, died unexpectedly Dec. 10, 2014.

He directed key research in the United States and abroad clarifying the roles of tobacco, obesity, diet, occupation and other factors in the etiology of several cancers, especially kidney cancer, for which he was considered among the world's experts. He led some of the largest studies exploring the etiology of renal cell and renal pelvis cancers, quantifying levels of risk associated with multiple lifestyle and environmental factors.

Joe's interests were broad, however, and he became an expert in, and passionate about, multiple scientific and intellectual pursuits, including economics, soviet espionage, evolutionary psychology, Hollywood films and the philosophy of science.

He was a member and committee leader of the Cosmos Club of Washington, D.C., and comfortable discussing science, history and various au currant topics in its elegant halls. His office, his home office, and any other space with spare shelves available were filled with his books—between work and home, he had more than 4,000 books. And not only did he read these, but he loved discussing these interests with the people around him.

Joe was an adherent of the strict application of the scientific method in epidemiologic research and felt that the field at times had lost its bearings. He noted the common occurrence of false positive associations in medical research, citing as one prominent example the declarations of some that use of cell phones likely caused brain cancer when the bulk of the evidence tended to rule this out.

He was critical of what he viewed as an increasingly common lack of skepticism, noting that science is always tentative, with hypotheses subject to refutation as well as confirmation, and cautioning that scientists who become unwavering advocates of their findings risk losing objectivity.

In an article in JNCI he called for "epistemological modesty" when interpreting results from non-experimental, observational studies, the type of research design characteristic of most epidemiologic investigations.

He was at times brash, bold, stubborn, tough, yet also generous, considerate and intellectually honest, all traits that made him a fascinating character and one who was frequently sought for his advice and guidance on the practice of epidemiology.

McLaughlin received his doctoral degree in epidemiology in 1981 from the University of Minnesota, spent two years on the faculty of the Johns Hopkins School of Hygiene and Public Health in the early 1980s, later returning as an adjunct professor, but continually serving in planning the Hopkins' graduate summer institute sessions in epidemiology, a program he helped establish.

He then joined the National Cancer Institute where he carried out research in kidney and other cancers as well as in the development of epidemiologic methods.

He co-founded the International Epidemiology Institute in 1994, where he served as President and led epidemiologic studies addressing multiple topical health concerns, including the potential for adverse health effects among women with breast implants (demonstrating local complications and increased suicide risk, but not cancer or other systemic abnormalities), aircraft manufacturers building stealth airplanes, and workers in the semi-conductor industry.

He is survived by his wife of 30 years, Jeanne Rosenthal, and daughter Alison.

The author is CEO of the International Epidemiology Institute and professor in the Department of Medicine of Vanderbilt University Medical Center.

Obituary

Anthony Murgo, of the FDA Office of Hematology and Oncology Products

Anthony (Tony) J. Murgo, died Dec. 17, 2014 after a courageous year-long battle with cancer. He was a passionate research physician with a kind bedside manner.

Murgo was a dedicated federal employee for 25 years, serving in multiple capacities at FDA and NCI. As the associate director of regulatory science of the FDA's Office of Hematology and Oncology Products, Murgo was the liaison between that office and NCI's Cancer Therapy Evaluation Program. Within OHOP, Murgo also served as a medical reviewer, a team leader and a division director for Division of Oncology Products 1.

"Tony has served as a mentor to many of the oncologists and hematologists throughout the FDA

and the NCI," said OHOP Director Richard Pazdur. "We will deeply miss his kind, friendly nature and his extensive knowledge and expertise."

Murgo received his medical degree from the State University of New York Downstate Medical Center College of Medicine, and practiced for 39 years. Beyond his work, Murgo loved reading, traveling and spending time with his family. He loved taking long walks with his previous Irish Setters, Rossini and Puccini.

He was preceded in death by his mother, Angelina Murgo; father, Joseph Murgo; and friend and brother-in-law, Philip Scollo. He is survived by his beloved wife of 49 years, Barbara; daughter Lisa Zeff and husband Ron; son, Joseph Murgo and wife Mara; sister, Maria Scollo; brother Joseph Murgo and wife Patricia; and grandchildren Jessica and Warren Zeff and Kristen and Rebecca Murgo.

Drugs and Targets

Accelerated Approval Granted To Opdivo in Metastatic Melanoma

FDA approved Opdivo (nivolumab) injection for the treatment of patients with unresectable or metastatic melanoma and disease progression following Yervoy (ipilimumab) and, if BRAF V600 mutation positive, a BRAF inhibitor.

This indication was granted under an accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. Opdivo is sponsored by Bristol-Myers Squibb Company.

The efficacy of Opdivo was evaluated based on a single-arm, non-comparative planned interim analysis of the first 120 patients who received Opdivo with a minimum of six months follow-up in the phase III CheckMate-037 trial.

Opdivo achieved a 32 percent response rate (95% CI: 23, 41) with a dosing strength and frequency of 3 mg/kg intravenously over 60 minutes every two weeks. Three percent of patients achieved a complete response, and 28 percent achieved a partial response. Of 38 patients with responses, 33 patients had ongoing responses with durability of response ranging from 2.6+ to 10+ months, which included 13 patients with ongoing responses of six months or longer. Responses to Opdivo were demonstrated in both patients with and without BRAF mutation.

FDA approved a supplemental biologics license application for Gazyva (obinutuzumab) in combination with chlorambucil chemotherapy in people with previously untreated chronic lymphocytic leukemia.

The sBLA adds to the label data from Stage 2 of the phase III CLL11 study showing significant improvements with Gazyva plus chlorambucil across multiple clinical endpoints when compared head-to-head with Rituxan (rituximab) plus chlorambucil.

The approval includes complete response and minimal residual disease data from the study. Additionally, overall survival data was added from Stage 1 of the study comparing Gazyva plus chlorambucil to chlorambucil alone. Gazyva is sponsored by Genentech, a member of the Roche Group.

The sBLA approval updated the Gazyva prescribing information with the following data: Gazyva plus chlorambucil helped people with previously untreated CLL live nearly a year longer without their disease worsening or death than Rituxan plus chlorambucil (median PFS: 26.7 months vs. 14.9 months, respectively. HR=0.42, 95 percent CI 0.33-0.54, $p<0.0001$); and that Gazyva plus chlorambucil nearly tripled the number of people showing no evidence of disease compared to Rituxan plus chlorambucil (26.1 percent vs. 8.8 percent, respectively).

FDA approved an updated version of MarginProbe, a medical device that enables real-time detection of cancer at the surface of excised tissue specimens during breast-conserving cancer surgery. MarginProbe is developed by Dune Medical Devices.

Surgeon feedback, design ideas and miniaturization engineering were the driving forces behind the development of MarginProbe 1.2, according to Dune. The new version uses the same diagnostic technology as version 1.1, improving functionality, portability and overall ease of use, including a smaller size and a brighter screen.

FDA granted Fast Track designation to SGX301 (synthetic hypericin) for the first-line treatment of cutaneous T-cell lymphoma.

The designation is designed to facilitate the development and expedite the review of new drugs. Soligenix Inc., the drug's sponsor, will be eligible to submit a new drug application for SGX301 on a rolling basis, permitting the FDA to review sections of the NDA prior to receiving the complete submission.

Additionally, NDAs for fast track development programs ordinarily will be eligible for priority review, which imparts an abbreviated review time of approximately six months. SGX301 has already received orphan drug designation from the FDA.

SGX301 is a first-in-class photodynamic therapy utilizing visible light for activation. The active ingredient in SGX301 is synthetic hypericin, a potent photosensitizer which is topically applied to skin lesions and then activated by fluorescent light 16 to 24 hours later. In a phase II study in CTCL, patients experienced a statistically significant ($p < 0.04$) improvement with topical hypericin treatment whereas the placebo was ineffective: 58.3 percent compared to 8.3 percent, respectively.

Polaris Group's lead product candidate, ADI-PEG 20 (pegylated arginine deiminase), received orphan drug designations for the treatment of malignant pleural mesothelioma in the U.S. and the European Union.

Having completed a successful randomized phase II trial in argininosuccinate synthetase -deficient MPM patients with ADI-PEG 20 as monotherapy, Polaris is currently conducting a phase 1 trial of ADI-PEG 20 in combination with pemetrexed and cisplatin, the approved first-line treatment for MPM, for the treatment of MPM and non-squamous non-small cell lung carcinoma.

Polaris is also conducting clinical trials on ADI-PEG 20 both as monotherapy and in combination with other agents, for the treatment of several other indications including breast cancer, melanomas, ovarian cancer and hepatocellular carcinoma.

ADI-PEG 20 is designed to deplete the external supply of arginine, which causes arginine-dependent cancer cells to die while leaving the patient's normal cells unharmed.

Amgen and Kite Pharma entered into a strategic research collaboration and license agreement to develop and commercialize novel Chimeric Antigen Receptor T cell immunotherapies based on Kite's engineered autologous cell therapy platform and Amgen's array of cancer targets.

Kite will be responsible for conducting all preclinical research and cell manufacturing and processing through Investigational New Drug filing. Each company will then be responsible for clinical development and commercialization of their respective CAR therapeutic candidates, including all related expenses.

Kite will receive from Amgen an upfront payment of $60 million, as well as funding for R&D costs through IND filing. Kite will be eligible to receive up to $525 million in milestone payments per Amgen program based on the successful completion of regulatory and commercialization milestones, plus tiered high single- to double-digit royalties for sales and the license of Kite's intellectual property for CAR T cell products. Amgen is eligible to receive up to $525 million in milestone payments per Kite program, plus tiered single-digit sales royalties. Further terms of the agreement were not disclosed.

Taiho Oncology Inc., a subsidiary of Taiho Pharmaceutical Co. Ltd., completed its rolling New Drug Application submission to FDA for TAS-102 (trifluridine and tipiracil hydrochloride). TAS-102 is an oral combination anticancer drug under investigation for the treatment of refractory metastatic colorectal cancer.

TAS-102 was granted Fast Track designation in September 2014, with the first sections of the rolling submission accepted by the FDA on Oct. 16, 2014. The submission is supported by the results from the phase III RECOURSE trial of TAS-102 in 800 mCRC patients, whose disease had progressed after or who were intolerant to standard therapies.

The trial met the primary efficacy endpoint of statistically significant improvement in overall survival versus placebo ($HR = 0.68$, $p < 0.0001$) and demonstrated a safety profile consistent with that observed in earlier clinical trials.

TAS-102 is an oral combination investigational anticancer drug of trifluridine and tipiracil hydrochloride. FTD is an antineoplastic nucleoside analog, which is incorporated directly into DNA, thereby interfering with the function of DNA. The blood concentration of FTD is maintained via TPI, which is an inhibitor of the FTD-degrading enzyme, thymidine phosphorylase.

In Brief

Donald Trump to Lead Inova Research Institute

DONALD "SKIP" TRUMP was named the first CEO and executive director of the newly created **Inova Cancer Care and Research Institute**, part of the Inova Health System.

In October 2014, Trump stepped down as president and CEO of Roswell Park Cancer Institute, which he led since 2007. He will maintain his appointment there as a professor of oncology.

"Inova is committed to building a destination cancer care and research facility," Trump wrote in an email to his colleagues. "We will be recruiting a number of clinical, administrative and research leaders."

DARIO ALTIERI was named CEO of **The Wistar Institute**, following the announced retirement of President and CEO Russel Kaufman, effective March 2. Altieri will continue to serve as director of the Wistar Cancer Center, and Kaufman will become president emeritus.

Altieri also serves as Wistar's executive vice president, chief scientific officer and the Robert and Penny Fox Distinguished Professor. He joined Wistar in 2010.

Kaufman joined Wistar in 2002 from Duke University School of Medicine where he was vice dean for Education and Academic Affairs as well as chancellor for Academic Affairs for the Duke University Health System.

Kaufman led the institute during its ongoing $35 million capital campaign, which began in 2010. The campaign supported Wistar's first major building project since 1976, the Robert and Penny Fox Tower. According to the institute, Wistar has raised close to $80 million during Kaufman's nearly 13 years.

SHARMILA MAKHIJA was named professor and chair of the Department of Obstetrics & Gynecology and Women's Health at **Albert Einstein College of Medicine** and **Montefiore Health System**, effective April 1.

Previously, Makhija served as chair and professor of obstetrics and gynecology at University of Louisville School Of Medicine.

Makhija has also held faculty positions at the University of Pittsburgh School of Medicine/ Magee-Women's Hospital, the University of Alabama at Birmingham School of Medicine, and Emory University School of Medicine.

She is a fellow of the American College of Obstetrics and Gynecology and a member of the American Medical Association, American Association of Cancer Research, and the American Society of Gynecologic Cancer. She is on the editorial board of the Journal of Oncology Practice and has served on the editorial boards of Women's Oncology Review Journal and the International Journal of Gynecological Cancer.

NIPUN MERCHANT is joining the **Sylvester Comprehensive Cancer Center** as chief surgical officer and director of Surgical Oncology Research Programs.

Merchant will also take on the newly created position of vice chair of Surgical Oncologic Services and Academic Affairs within the Department of Surgery, and will be the chief of Surgical Oncology at University of Miami Hospital as well as chief surgical officer at UMHC/Sylvester. In addition, he will serve as chief of the Division of Surgical Oncology.

He comes to the University of Miami from Vanderbilt University Medical Center, where he has been the director of the Vanderbilt Pancreas Center, chief of GI Surgical Oncology and co-leader of the GI Oncology Program at Vanderbilt-Ingram Comprehensive Cancer Center.

As vice chair, he will lead the clinical and research enterprises of surgical oncology and oversee the educational and academic programs. Merchant's clinical practice is in GI malignancies with a focus on hepatobiliary and pancreatic cancers.

ST. JUDE CHILDREN'S RESEARCH HOSPITAL received a pledge of $2 million over the next 10 years from **InfinityQS International Inc**.

St. Jude has named the Large Auditorium Gathering Space in the Marlo Thomas Center for Global Education and Collaboration in honor of InfinityQS to commemorate the company's support.

InfinityQS received the Cardinal Stritch Donor of the Year Award, which recognizes a donor whose commitment reflects the vision and leadership of St. Jude founder Danny Thomas' spiritual mentor, Samuel Cardinal Stritch, the Catholic archbishop of Chicago. InfinityQS has also sponsored and participated as St. Jude Heroes in three of the hospital's annual St. Jude Memphis Marathon Weekend fundraisers.

NCI DIRECTOR HAROLD VARMUS, in a new year's message to NCI staff and grantees, outlined the NCI's goals and obstacles for 2015 as the institute pursues new trials in precision medicine.

Though Congress has appropriated a slight increase in funding for NCI and NIH for the entirety of the 2015 fiscal year, Varmus pointed out that this small boost—amounting to approximately 0.6 percent—is still less than the rate of inflation.

"We who lead the NCI face a difficult dilemma: how to provide sufficient resources to our grantees to allow them to accomplish their ambitious goals, without reducing the numbers of awards we can make—further attenuating the cancer research community," Varmus wrote.

His full letter follows:

To NCI staff, grantees, and advisors:

Now that the new year has begun in earnest, I am writing to send seasonal greetings and offer my views about the near-term prospects for cancer research.

This year, unlike most recent years, we are in the fortunate position of having received our appropriation for the rest of the fiscal year within the first quarter, helping us to plan and manage use of those funds. Although this year's appropriation ($4.95 B) is slightly larger than last year's (by about 0.6%), the increase is less than the rate of inflation, as has been the case nearly every year since 2003. This signifies further erosion of the NCI's "buying power" at a time when cancer research is becoming more expensive, expanding in new directions, and showing unprecedented promise.

As a result, we who lead the NCI face a difficult dilemma: how to provide sufficient resources to our grantees to allow them to accomplish their ambitious goals, without reducing the numbers of awards we can make—further attenuating the cancer research community. Moreover, the recent, rapid growth in knowledge about cancer—its genetic basis, the signaling pathways that govern cell misbehavior, immune responses to cancer cells—is a spur to the development of new approaches and new programs that are difficult to finance under current circumstances without reducing support for existing worthwhile programs.

Despite these recurrent anxieties, the new calendar year promises to be pivotal and exciting for the NCI. We will be reviewing the first round of applications for the new Outstanding Investigator Award, which is intended to provide more stable funding for some of our best scientists. The newly reorganized National Clinical Trials Network (NCTN), in close collaboration with the reconfigured NCI Community Oncology Research Program (NCORP), will be expanding an array of scientifically informed trials—MATCH, MPACT, ALCHEMIST, and others—that will accelerate the on-going transformation of cancer therapy as a part of the broader movement to "precision medicine." This transformation of oncology will proceed hand-in-hand with improvements in bioinformatics (helped by NCI's new cloud computation pilots and our membership in the Global Alliance for Genomics and Health [GA4GH]); with expanded genomic studies of pediatric and common adult cancers and the creation of a Genomic Data Commons; and with rapidly increasing knowledge about how to manipulate the immune system to treat cancers.

While we celebrate these prospects, the NCI will also remain deeply engaged in confronting the problems created by growth of the scientific community in a time of fiscal constraint. At the forthcoming NCI Leadership Retreat in late January, we will be discussing some potential solutions to these challenges: new mechanisms to accelerate the training of the most promising young investigators; grants to encourage the careers of staff scientists; the merits and liabilities of some of the current grant mechanisms for supporting research; trends in NCI's support of basic science; and various ways to enhance the diversity of the research community.

Throughout the coming year, we also expect to be giving close attention to the funding of NCI-designated cancer centers, a critical resource for the entire cancer research effort; to implementation of recommendations emerging from a recent evaluation of the NIH intramural program; to new ideas for preventing, screening for, and monitoring cancers; to proposals for new initiatives at the Frederick National Laboratory for Cancer Research; and to the evaluation of the Provocative Questions program as it enters its third year of grant-making.

Many of these topics and others are summarized in broad terms in NCI's recently issued budget plan for FY2016 (the so-called "bypass budget proposal"), which can be viewed on line at http://www.cancer.gov/NCIresearchfuture. In all of these domains, we seek the views of those we serve—extra- and intramural scientists, cancer research advocates, the health care community, and the general public—and we welcome your comments at http://www.cancer.gov/global/contact/email-us.

With best wishes for the new year,
Harold Varmus