



## ORI-Potti Deal Doesn't Address Role Played by Deans at Duke

(Continued from page 1)

"We are pleased with the finding of research misconduct by the federal Office of Research Integrity related to work done by Dr. Potti," Duke officials said in a statement to the media. "We trust this will serve to fully absolve the clinicians and researchers who were unwittingly associated with his actions, and bring closure to others who were affected."

The Cancer Letter invited Keith Baggerly, a biostatistician at MD Anderson Cancer Center, and CK Gunsalus, an expert in scientific misconduct at the University of Illinois at Urbana-Champaign, to analyze the ORI action.

"This case is about as serious as one can imagine at the individual level. At the institutional level, it is beyond disappointing at every turn: in handing an internal whistleblower, in responding to credible, serious and repeated external scientific queries, in managing the multiple conflicts of interest in the situation, in limiting the information available to an interim scientific review, in how its leaders testified to an IOM review committee, in its legal responses," Baggerly and Gunsalus wrote.

"A case with millions of taxpayer dollars misused, totally fabricated research, damage to hundreds of patients recruited for treatment with 'the holy grail' of cancer treatment, and a pathetic institutional response is being closed with a five-year funding ban for one investigator, individually and alone."

Their guest editorial appears on p. 1.

Joyce Shoffner, a breast cancer survivor who was treated in one of the Duke trials that enrolled 117

patients, described the settlement as a "travesty."

"The results are a slap in the face to patients who died and for the two patients that are still living the horror of those clinical trials," Shoffner said to The Cancer Letter. "No slap in the face or even a tap on the wrist for Potti."

Kevin Coombes, visiting professor at The Ohio State University College of Medicine Department of Biomedical Informatics, said he is disappointed by the conclusion of the case.

"ORI accepted a voluntary settlement agreement from Dr. Potti in which he 'neither admits nor denies ORI's findings of research misconduct,'" said Coombes, Baggerly's collaborator in examining the papers published by the Duke genomics researchers.

"The data didn't falsify itself; someone must have manipulated it. That becomes particularly clear when you recognize that the changes always involved altering the records of which patients responded to treatment in a way that made their predictions look better than they really were," Coombes said to The Cancer Letter.

"I feel badly for the patients, and their families, who participated in the clinical trials that Duke University ran based on bogus research and falsified data.

"The ORI investigation has now ended with no admission of wrongdoing by Dr. Potti. The malpractice lawsuit against Dr. Potti, [his mentor, Joseph] Nevins, and Duke University was settled out of court, with no admission of guilt by anyone involved," Coombes said. "Apparently, mistakes were made, but no one was responsible for them. That doesn't really feel as though justice has been served."

### Words of Praise from Potti's New Boss

Potti is practicing at the Cancer Center of North Dakota in Grand Forks. William Noyes, the lead oncologist at the center, praised Potti's clinical skills and said that continuing attention appears to have racial undertones.

"I have followed the genomic research at Duke University for some time. The facts are that the Institute of Medicine independently reviewed all of the research data and concluded that there were systematic lapses at many levels at Duke and now the ORI has reviewed the case and concluded that Dr. Potti made mistakes but can continue to do research, if he chooses to do so. There were really no punitive damages applied to Dr. Potti," Noyes said in response to an inquiry from The Cancer Letter.

"I have personally interacted with Dr. Potti for the past three-plus years and can say with utmost confidence

**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

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that Dr Potti has always had a reputation of providing the highest quality of clinical care for his patients. His patients have always responded with the highest of recommendations per patient surveys. One patient even asked him to be an honorary pallbearer—a privilege that is rare amongst physicians.

“Hopefully, this brings closure to this issue as the persistent sensationalism seems to me to suggest an element of racial discrimination. If you are truly ‘fair and balanced,’ you will share what IOM reported that there were no signs of data manipulation, there were obvious errors made by many who were involved and that these were systems errors. Consequently, they made recommendation for all in genomic studies to follow in the future.

“ORI concluded Dr. Potti made some errors, but have concluded he should be allowed to participate in scientific studies if he so chooses.”

In May, Duke settled the suits brought by patients who were enrolled in clinical trials that were testing the technology developed by Anil Potti and his mentor Joseph Nevins, thereby avoiding having to confront embarrassing revelations about how much the university’s deans knew about the problems in the genomic research organization (The Cancer Letter, [May 8](#)). The settlement [was first reported](#) by Retraction Watch.

*The text of the Federal Register notice follows:*

Notice is hereby given that the Office of Research Integrity (ORI) has taken final action in the following case:

*Anil Potti, M.D., Duke University School of Medicine:* Based on the reports of investigations conducted by Duke University School of Medicine (Duke) and additional analysis conducted by ORI in its oversight review, ORI found that Dr. Anil Potti, former Associate Professor of Medicine, Duke, engaged in research misconduct in research supported by National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health (NIH), grant R01 HL072208 and National Cancer Institute (NCI), NIH, grants R01 CA136530, R01 CA131049, K12 CA100639, R01 CA106520, and U54 CA112952.

ORI found that Respondent engaged in research misconduct by including false research data in the following published papers, submitted manuscript, grant application, and the research record as specified in 1-3 below. Specifically, ORI found that:

1. Respondent stated in grant application 1 R01 CA136530-01A1 that 6 out of 33 patients responded positively to dasatinib when only 4 patients were enrolled and none responded and that the 4 CT scans

presented in Figure 14 were from the lung cancer study when they were not.

2. Respondent altered data sets to improve the accuracy of predictors for response to treatments in a submitted paper and in the research record by:

- Reversing the responder status of 24 out of 133 subjects for the adriamycin predictor in a manuscript submitted to *Clinical Cancer Research*

- switching the cancer recurrence phenotype for 46 out of 89 samples to validate the LMS predictor in a file provided to a colleague in 2008

- changing IC-50 and R-code values for the cisplatin predictor in a data set provided to NCI in 2010

3. Respondent reported predictors and/or their validation by disregarding accepted scientific methodology so that false data were reported in the following:

- *Blood* 107:1391-1396, 2006: Describing a predictor for thrombotic phenotypes

- *New England Journal of Medicine* 355:570-580, 2006: Describing a predictor of lung cancer relapse

- *Nature Medicine* 12:1294-1300, 2006: Describing a predictor for the response to the chemotherapeutic drugs topectan and docetaxol

- *Journal of Clinical Oncology* 25:4350-4357, 2007: Describing a predictor for the response to the chemotherapeutic drug cisplatin

- *Lancet Oncology* 8:1071-1078, 2007: Describing a predictor for the response to the combination of the chemotherapeutic drugs flurouracil, epirubicin, and cyclophosphamide or docetaxol, epirubicin, and docetaxol

- *Journal of the American Medical Association* 299:1574-1587, 2008: Describing a predictor for breast cancer relapse

- *Public Library Science One* 3:e1908, 2008: Describing a predictor for the response to the chemotherapeutic drugs paclitaxel, 5-fluouracil, adriamycin, and cyclophosphamide

- *Proceedings of the National Academy of Sciences* 105:19432-19437, 2008: Describing a predictor of colon cancer recurrence

- *Clinical Cancer Research* 15:7553-7561, 2009: Describing a predictor for the response to the chemotherapeutic drug cisplatin

As a result of Duke’s investigation, the published papers listed above were retracted.

Respondent has entered into a Voluntary Settlement Agreement with ORI. Respondent neither admits nor denies ORI’s findings of research misconduct; the settlement is not an admission of liability on the part of

the Respondent. The parties entered into the Agreement to conclude this matter without further expenditure of time, finances, or other resources. Respondent has not applied for or engaged in U.S. Public Health Service (PHS)-supported research since 2010. Respondent stated that he has no intention of applying for or engaging in PHS-supported research or otherwise working with PHS. However, the Respondent voluntarily agreed:

(1) That if the respondent obtains employment in a research position in which he receives or applies for PHS support within five years of the effective date of the Agreement (September 23, 2015), he shall have his research supervised for a period of five years;

(2) that prior to the submission of an application for PHS support for a research project on which the Respondent's participation is proposed and prior to Respondent's participation in any capacity on PHS-supported research, Respondent shall ensure that a plan for supervision of Respondent's duties is submitted to ORI for approval; the supervision plan must be designed to ensure the scientific integrity of Respondent's research contribution; Respondent agreed that he shall not participate in any PHS-supported research until such a supervision plan is submitted to and approved by ORI; Respondent agreed to maintain responsibility for compliance with the agreed upon supervision plan;

(3) that any institution employing him shall submit, in conjunction with each application for PHS funds, or report, manuscript, or abstract involving PHS-supported research in which Respondent is involved, a certification to ORI that the data provided by Respondent are based on actual experiments or are otherwise legitimately derived and that the data, procedures, and methodology are accurately reported in the application, report, manuscript, or abstract; and

(4) to exclude himself voluntarily from serving in any advisory capacity to PHS including, but not limited to, service on any PHS advisory committee, board, and/or peer review committee, or as a consultant for period of five years beginning on September 23, 2015.

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### Were Patients Harmed?

Duke argued that patients who entered these clinical studies were not harmed. The patients were, for the most part, in late stages of disease, and the predictor models were used to assign them to existing therapies.

The plaintiffs' attorneys argued that Duke had ample opportunities to recognize that the technology tested in the three trials was fraudulent. Instead, in the spring of 2008, Duke officials [silenced a whistleblower](#), [frustrated an NCI inquiry](#), and, in the fall of 2009, set up [a flawed internal review of the three trials](#), plaintiffs alleged.

The deans who were directly involved in silencing the whistleblower later told an Institute of Medicine committee that no whistleblower had come forward from Potti's lab.

The consent forms signed by the patients extolled the potential of Duke's technology:

"This genomic predictor looks at hundreds of genes (pieces of DNA—a short form of deoxyribonucleic acid that contains information needed to construct and operate the human body) in your tumor. In initial studies, the genomic predictor seemed to determine which drug would be effective in a given patient with an accuracy of approximately 80%. The genomic predictor is still being tested in research studies and is therefore considered investigational."

The whistleblower—Bradford Perez, a third-year medical student working in Potti's lab—did more than just sound alarm.

Perez submitted a well-argued critique of flaws in the Duke genomics operation. Documents published by The Cancer Letter also show that concerns were brought to the attention of the deans in March 2008 (The Cancer Letter, [Jan. 9](#)).

Instead of a thank-you, Perez faced a full-court press led by Potti's co-author and protector Joseph Nevins, and an all-star team of Duke officials—which included Deans Sally Kornbluth and Nancy Andrews.

Perez was assured that Nevins and Potti would go through their datasets to make sure that there were no "errors" present. 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.

### Disappearing the Whistleblower

The Perez case is not noted in the IOM report.

According to the 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 [then] 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.

Both Kornbluth and Andrews have since been promoted, and Duke officials haven’t apologized for their institution’s testimony to IOM.

An 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 Victor Dzau, the Duke Chancellor for Health Affairs, 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.”

### Other Documents

In another document obtained by The Cancer Letter, Holly Dressman, a top member of the Nevins and Potti operation, expressed hope that NCI officials wouldn’t request the raw data on which Potti’s predictor model for ovarian cancer was based (The Cancer Letter, [Jan. 16](#)).

Had NCI’s statisticians been able to get the code and the data they sought, they would have been able to perform basic forensic bioinformatics that would have enabled them to spot unsubstantiated claims, and worse.

In an email dated May 6, 2008, Holly Dressman, a co-author on the Duke group’s key papers, shot an email to team captain Joseph Nevins, mentor and protector of its star scientist Anil Potti.

Dressman’s email, now cited in a lawsuit against Duke, may cause a double-take:

“I am working on the [topotecan] signature in OVC and it’s a big mess. NCI wants us to resubmit the revisions again and now asking for correct Topo info... and they may want the data for their stat folks to try out like what was done with plat stuff... I am beginning to wonder if the Topo signature is real. I guess for the review, I can just hope they don’t ask for original data and just report what is in the NatMed paper.”

Here, a government-funded researcher—who, despite losing faith in the predictor used to decide which treatment an ovarian cancer patient would receive, expresses hope that NCI would relent before getting the “original” data and would settle for data published in one of the world’s premier scientific journals.

In the litigation, the plaintiffs were seeking release of thousands additional documents that Duke had previously failed to release.

A timeline of the Duke genomics scandal [is available here](#).

*Matthew Bin Han Ong contributed to this story.*

## *Guest Editorial*

# Potti's Penalty Too Light, Duke Not Held Responsible

(Continued from page 1)

This week, ORI released a notice of “[final action](#)” in the case of Anil Potti, M.D. The ORI found that Dr. Potti engaged in several instances of research misconduct and banned him from receiving federal funding for five years.

The principles involved are important and the facts complicated. This was not just a matter of research integrity. This was also a case involving direct patient care and millions of dollars in federal and other funding. The duration and extent of deception were extreme. The case catalyzed an Institute of Medicine review of genomics in clinical trials and attracted national media attention.

If there are no further conclusions coming from ORI and if there are no other investigations under way—despite the importance of the issues involved and the five years that have elapsed since research misconduct investigation began, we do not know—a strong argument can be made that neither justice nor the research community have been served by this outcome.

As background, in a 2014 case involving over \$13 million in grant funding for falsified AIDS vaccine research (but no patient trials), [ORI's penalty](#) was a three-year ban on grant funding for the offender, Dong-Pyou Han. After Sen. Charles Grassley expressed concerns, saying “This seems like a very light penalty for a doctor who purposely tampered with a research trial and directly caused millions of taxpayer dollars to be wasted on fraudulent studies,” the U.S. Attorney's office in Iowa pressed charges, eventually resulting in a jail sentence of 57 months and a fine of \$7 million assessed against Han.

The Potti case—also involving a doctor who purposefully tampered with a research trial—is far worse.

In the Han case, research funds had been misallocated based on falsified data. We understand that his university discovered and reported his fraud. In the Potti case, not only were millions in funds misallocated, but terminally ill cancer patients were enrolled in clinical trials based on completely bogus research. His university rebuffed serious questions about the integrity of the research from multiple sources over an extended period.

Let's examine both Potti's direct actions, which ORI considered in taking their administrative action, and the sufficiency of the institutional response to the misconduct which, at least as far as ORI's announcement goes, seems not to have been assessed.

## **Potti's Actions and the Consequences**

According to the ORI findings, Potti altered datasets resulting in false data being reported in many high-impact papers, in journals such as the New England Journal of Medicine and Nature Medicine, going back at least to 2005 and 2006.

This means Potti, a physician, knew that the underlying data were wrong in 2006 when he and his collaborators proposed a large clinical trial in early-stage lung cancer (CALGB 30506, aka [NCT00863512](#), opened in 2009, with an initial target of 1525 patients), in which their Lung Metagene Score algorithm would be used to guide patient therapy.

At minimum, he knew the informed consents provided by these vulnerable patients were invalid; this remained true even when the National Cancer Institute constrained use of the LMS to evaluation only, not therapy guidance.

This also means Potti knew, as a physician, that the underlying data were wrong *when they started* three other Duke trials in which his genomic signatures were being used to determine therapy (listed in descending order of target enrollments):

- in breast cancer ([NCT00636441](#), 2008, initial target 270 patients),
- in early-stage lung cancer ([NCT00545948](#), 2007, initial target 117 patients),
- in late-stage lung cancer ([NCT00509366](#), 2007, initial target 100 patients).

Potti knew the consents for these trials were invalid. Further, for at least one of them (late-stage lung cancer), Potti was initially the trial's principal investigator, and yet enrolled his own patients in a trial for which he knew the data had been fabricated.

Potti knew, as a physician, that the underlying data were wrong for another proposed clinical trial:

- in late-stage lung cancer (CALGB 30702, initial target 144 patients), when he submitted the protocol to the NCI in 2009. (This trial was not approved and never conducted).

The patients enrolled in these clinical trials [were lied to](#), given false hope, exposed to unnecessary invasive procedures to obtain tissue to prescribe or monitor therapy, and exposed to additional risks which could never result in improvements in their care or in patient care in general. These risks were real; filings in civil lawsuits—settled for undisclosed amounts in April 2015—note, [for example](#), that “Juliet Jacobs underwent an unnecessary second biopsy [that was required for participation in the fraudulent clinical trials] that caused her great injury.”

Based on the proposed enrollments, Potti was prepared to expose over 2,000 cancer patients to these risks. Potti owed his patients a duty of care that he abused by misleading them. He repeatedly enticed cancer sufferers into trials and medical treatment, knowing that the protocols for their treatments were not based on performed research but on manipulated data.

None of this was fully discussed when Potti's medical license was being reviewed by the North Carolina medical board in 2010-2011; many details only came out over the course of the IOM review (which lasted until 2012) and in the process of discovery in the civil lawsuits.

Every time there was an unnecessary test or procedure there was direct physical injury, loss, or damage—i.e., truly an adverse event.

Falsifying data is a dereliction of professional duty.

Subjecting human subjects to trials one knows to be useless goes against the Nuremberg Code and inflicts dignitary harm.

There was no later sign of remorse or repentance; when Potti and colleagues were challenged at various points with respect to the accuracy of their data, he lied:

- to those reviewing CALGB 30506,
- to other investigators (including one of the authors of this paper) who raised questions about the Nature Medicine paper in 2006-2007,
- to Duke's Institutional Review Board-equivalent charged with overseeing patient safety in genomics-driven trials,
- to external reviewers convened by Duke to review the science of "chemosensitivity prediction" when NCI echoed concerns we raised in 2009, leading to a temporary suspension of trial enrollments, and
- to those reviewing CALGB 30702, a new lung cancer study Potti *et al.* proposed repeatedly before being disapproved by NCI in 2009.

Potti put patients at risk in 2005, 2006, 2007, 2008, 2009, and 2010. Every time a new trial was proposed that would use these approaches to guide patient care, he made the choice again.

These various observations show Potti's behavior was egregious and warrants more severe punishment than just a five-year ban on NIH funding. It's not that ORI doesn't have the ability to impose more stringent penalties. [ORI's website](#) explains: "Which administrative actions, the number of administrative actions, and the length of the administrative actions depends on the seriousness of the misconduct, the impact of the misconduct, and whether the misconduct demonstrates a pattern of behavior. Administrative

actions are usually imposed for three years, but have ranged from one year to a lifetime."

Further, the [regulatory authority](#) for ORI provides, in Section V, that "If the funding agency believes that criminal or civil fraud violations may have occurred, the agency shall promptly refer the matter to the Department of Justice, the Inspector General for the agency, or other appropriate investigative body." In other words, ORI can refer extreme cases for criminal prosecution, rather than stopping at funding bans.

We do not know whether ORI has referred Potti's case for criminal prosecution, but their characterization of the ban as their "final action" suggests it did not. We do not have access to their reasoning. Was it because they ceded this option as part of securing a negotiated settlement?

What messages does this send? To the research community? To research institutions? To taxpayers who fund public research? And what about the patients?

As Joyce Shoffner, a patient in one of the trials, [says](#), "If you steal a TV you're going to be a whole lot worse off...I think this is pretty dreadful. Five years, what is five years? I'm absolutely disgusted."

### **The Institutional Response**

Even more worrisome than the extensive and persistent behavior of one investigator, is the institutional oversight of the research and patient treatment. In our current approach to research integrity funded by the government, universities—which receive the funds, are the employers of researchers, and the fiduciary agent for all research funding—are full partners with the government, charged with creating and maintaining research environments, evaluating allegations and conducting investigations.

To receive federal funding, universities pledge that they will fulfill these responsibilities. The federal role in the partnership is to evaluate proposals and award funds, develop and apply regulations (funding, protection of subjects of research, research compliance, etc.) and to oversee the research integrity process.

This case raises significant questions about how well Duke University fulfilled its institutional obligations. Some of the actions taken by its administrators could even be characterized as having the appearance of trying to thwart effective oversight. ORI—whose job it is to oversee the overseers (the university) when HHS funds are involved—did not comment on Duke's performance in its statement. We, as outsiders, are very curious about how ORI assessed that aspect of this complex matter, what they concluded about the efficacy of Duke's role,

whether they consider that parts of the oversight system failed in places, and if so, how to fix it. These should be pressing questions for all of us.

For context, we provide a brief chronology of some major events here.

- 2007: [Baggerly and Coombes](#) first publicly reported problems with the data. We do not know of any action on Duke's part at the time.

- 2008: [Brad Perez](#), a member of Potti's lab, investigated the predictors internally and was so disturbed by what he found that he repeated a year of his program, pulled his name from submitted papers and wrote a detailed letter of concerns about the conduct of the research, which he discussed with Duke administrators.

Those administrators referred Perez back to Joseph Nevins (Potti's mentor), an individual with profound personal and professional conflicts of interest in the situation. Nevins and Potti downplayed the critique.

- 2009: [Baggerly and Coombes](#) reported (and The Cancer Letter [publicized](#)) more extensive problems with the data (September-October).

In response to an unprecedented expression of concern on the part of the NCI to Duke's Institutional Review Board about patient safety concerns, Duke organized a review in late 2009 (before the misconduct investigation began). At the urging of Nevins, Duke administrators withheld the full extent of external critiques of the research from the reviewers, so this review lacked depth. It concluded that the data being challenged, later found to be false, were strong enough to warrant re-starting patient trials using the questioned genomic predictors.

- 2010: [Revelation of a falsified CV](#); Potti suspended; misconduct investigation begins.

- 2011: In testimony to the IOM review committee, Duke administrators acknowledged that Nevins had been allowed to effectively control what data were examined as part of the 2009 review, but said they were not aware of problems with the data: "Some members of the laboratory did ultimately come forward with concerns about the research, but only after the University began an investigation." The Perez report was not mentioned.

- September 2011: [Civil lawsuits](#) by injured patients filed.

- 2015: Perez's Letter of Research Concerns, which surfaced in the process of discovery as part of the civil lawsuits, was made public by The Cancer Letter in January 2015.

Let's review Duke's role in this matter:

Duke University was the fiduciary for the research funding.

Duke signed the federal assurances that it would maintain an environment of research integrity and respond promptly to allegations.

Duke owns and operates a hospital that recruited and treated patients in the clinical trials. It extended practice privileges to Dr. Potti.

Duke created and disseminated [video](#) and print campaigns highlighting the research.

Duke had an interest in intellectual property in the "personalized" cancer treatment that the research promised and had licensed the technology to at least one company working to commercialize it.

Duke's administrators and Dr. Nevins had an obligation to funders, colleagues, the research literature and patients to conduct research with integrity, yet they disregarded repeated internal and external signals that something was seriously amiss with the research underlying the clinical trials.

That last point is worth repeating: there is extensive [documentation](#) that multiple Duke administrators received credible information about serious problems in the Nevins/Potti lab as much as two years before they finally acted in 2010.

The repeated serious concerns directly expressed to them about the integrity of research and patient care conducted under their auspices did not lead to any apparent action. Their first action against Anil Potti immediately followed the revelation by The Cancer Letter that his CV contained false information.

Some of what we know now about the extensive problems with this research came out in the course of Duke's internal review of the case after the falsified CV revelations, which they described in testimony to the IOM in 2011-12. Other elements have had to emerge over time and from other sources: Duke is a private university and not required to respond to the Freedom of Information Act requests that public universities face.

Information from those other sources now makes it clear that the IOM testimony provided by several Duke administrators was incomplete or inaccurate when they said that they had not received any reports from within Duke until they had already begun their investigation.

Because Duke's review of Potti's papers that might need to be retracted focused only on those with primary research data, the literature still contains commentaries such as a 2010 piece in [Science](#)



[Translational Medicine](#) where Potti *et al.* hold their approach up as a model to be emulated and conclude:

“It could be argued that it is unwise and perhaps unethical to continue the practice of treating large numbers of unselected patients knowing that only a fraction will benefit—and further knowing that there are technologies available that have the potential to match the right drug with the right patient. We owe it to the patients, and to all of us who potentially will be patients, to change this practice if we are to make meaningful gains in implementing effective cancer therapy and winning the war on cancer.”

### Our Questions

Upton Sinclair once said, “It is difficult to get a man to understand something, when his salary depends on his not understanding it.” Social psychology calls this “motivated blindness.”

What do we expect well-funded research institutions to know about this now well-known phenomenon? Do we expect our universities to implement steps to counteract its effects? If we do not hold our most sophisticated research universities accountable for internal oversight of conflicts of interest, can we expect any institution to take them seriously? If not in the face of mounting signals of problems over several years, when?

This week, Duke characterized the ORI finding focused on Potti as vindication for his associates, implicitly separating the witting and unwitting: “We trust this will serve to fully absolve the clinicians and researchers who were unwittingly associated with his actions, and bring closure to others who were affected.”

We are willing to provide the benefit of the doubt to the unwitting. We are less willing, however, to extend such benefit to those who were knowingly blind to a fraud so blatant that, once finally examined, there is testimony that it took “[about an hour](#)” to find “[abundantly clear](#)” manipulations of the data. This is especially so, given the relationship of the data to patient care.

It’s hard to tell how those around Potti—cast here as a sole and only bad apple—have been “absolved.” Who, exactly, is on that roster? Who were the witting? What steps are being taken internally to do better? What information are they sharing with the community from which we could all learn?

Leaving aside the implausibility of this massive fraud being perpetuated over years by one bad actor, what is reasonable to expect when things go wrong in research? Not every case of inappropriate choices

or actions in research should be treated as research misconduct. Not every case of research misconduct warrants severe penalties. Not every case reported to a funding agency should become a federal case. Not every case should bear the most serious penalties.

How could this case not be one deserving the most serious penalties?

And as for the institution that received the funding, employed the researchers, treated the patients, responded to regulators, and stood to gain enormously if the research had been valid? What of the discharge of their duties in this situation?

No one expects universities to prevent misconduct. It seems de minimus to ask them to respond responsibly to credible questions about the validity of research, and to be forthcoming and share lessons learned after a tragic case in which the institutional response was repeatedly so deficient.

This case is about as serious as one can imagine at the individual level. At the institutional level, it is beyond disappointing at every turn: in handing an internal whistleblower, in responding to credible, serious and repeated external scientific queries, in managing the multiple conflicts of interest in the situation, in limiting the information available to an interim scientific review, in how its leaders testified to an IOM review committee, in its legal responses.

A case with millions of taxpayer dollars misused, totally fabricated research, damage to hundreds of patients recruited for treatment with “the holy grail” of cancer treatment, and a pathetic institutional response is being closed with a five-year funding ban for one investigator, individually and alone.

This outcome has apparently been judged a full, complete, measured response.

Are we alone in thinking something is very wrong with this picture?

*Baggerly is a biostatistician at MD Anderson Cancer Center. Gunsalus is the director of the [National Center for Professional and Research Ethics](#), research professor at Coordinated Science Laboratory, and professor emerita of the College of Business at the University of Illinois at Urbana-Champaign. She runs [a consulting company](#) and is the author of *The Young Professional’s Survival Guide* (Harvard University Press, 2012) and *The College Administrator’s Survival Guide* (Harvard University Press, 2006).*

## Rep.: Brigham Retaliated Against My Constituents

(Continued from page 1)

Noorchashm had to submit to being tailed by a security guard while his wife was undergoing an urgent cancer surgery Nov. 2.

“As Dr. Reed’s and Dr. Noorchashm’s Representative in Congress, I am deeply concerned about what appears to be an effort to retaliate against their advocacy and silence their First Amendment Rights,” Fitzpatrick (R-Pa.) wrote in a letter Nov. 5 to Ron Walls, executive vice president and chief operating officer at Brigham.

“Dr. Reed’s husband was put under surveillance, targeted for enhanced security, and told if he did not submit to the terms ordered by Brigham that he would not be permitted to be by his wife’s side during her surgery to remove a third reoccurrence of her leiomyosarcoma,” Fitzpatrick wrote.

Fitzpatrick’s letter to Walls is posted on page 11.

The day after Reed’s surgery, a Boston Superior Court judge ordered Brigham to lift the security restrictions, finding that Reed and Noorchashm will “suffer irreparable harm.” (The Cancer Letter, [Nov. 3.](#))

Brigham officials acknowledge that they knew that Reed and Noorchashm were preparing to file a malpractice lawsuit at the time Walls decided to subject them to enhanced security measures.

However, hospital officials say the couple’s stated intentions to sue “absolutely” didn’t figure into Walls’s decision.

“Dr. Walls was aware that an intention to sue had been expressed in 2014,” a hospital spokesperson said to The Cancer Letter. “Threat of legal action does not supersede the hospital’s responsibility to provide a safe and secure work environment for our employees.”

Responding to Fitzpatrick’s letter, Walls said he stands by his original decision, stating that the security measures were reasonable, because of Noorchashm’s “disturbing and threatening” emails to hospital faculty and staff.

“It was not feasible to provide personal protection to all for the duration of his visit, so I put discreet security measures in place that would both ensure the protection of and alleviate the anxiety of our faculty and staff while allowing Dr. Noorchashm to be with his wife during her stay,” Walls wrote to Fitzpatrick Nov. 10. “I undertook these precautions with full knowledge that he would use them to distort the truth and once again publically criticize the hospital.

“Responding to the safety and security needs of our faculty, staff, our patients and their families is far more important to me than the impact of Dr. Noorchashm’s campaign of distortions.” Walls’s response to Fitzpatrick is posted on page 12.

Reed, formerly an anesthesiologist at Beth Israel Deaconess Medical Center, and Noorchashm, formerly a cardiothoracic surgeon at Brigham, have been vocal critics of the leadership of the Harvard-affiliated hospital. The couple led a national campaign to stop power morcellation, a surgical procedure routinely used by gynecologists, after Reed’s undetected sarcoma was spread by the procedure, performed at Brigham in October 2013 (The Cancer Letter, [July 4, 2014](#)).

Reed and Noorchashm’s attorney, Tom Greene, called Walls’s allegations “baseless.”

“Nowhere in Walls’s letter does he identify the faculty or staff who he claimed experienced ‘fear and anxiety.’ Nor does he identify any staff who found my client’s emails to be ‘threatening,’” Greene said to The Cancer Letter. “These same baseless allegations were made to the court by BWH’s counsel at the hearing on Nov. 3.

“[Boston Superior Court] Judge Elizabeth Fahey asked BWH’s counsel to produce an affidavit signed by the person who felt threatened. BWH counsel told the court he would produce an affidavit the following day at 9 a.m. After the hearing, BWH counsel informed me that BWH would not be producing the affidavit or returning to court the following day.

“Walls claims that the BWH was not retaliating or trying to silence my client’s expression of his opinions, arguments BWH counsel made to Judge Fahey, but these arguments were rejected by the court. Judge Fahey found that the BWH’s conduct damaged my client’s reputation and was in retaliation for his outspoken criticism.”

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## **Reed Alleges Retaliation; Brigham Says “Absolutely Not”**

After the power morcellation procedure spread her undetected tumor in 2013, Reed continued to return to Brigham for some of her cancer therapy.

“I find it inconsistent that despite dozens of visits to BWH, my husband’s letters to the administration, that are indeed numerous spread over two years, were suddenly deemed threatening to the point of requiring security measures two days after we filed a lawsuit against BWH?” Reed wrote in a letter to Walls Nov. 13.

Reed’s letter is posted on page 12.

The couple’s attorney Greene said that on Dec. 11, 2014, Brigham officials were informed via letter about the couple’s intent to file a medical malpractice suit.

The suit was filed on Oct. 27, but Brigham officials weren’t immediately served.

On Oct. 29, Walls informed Reed and Noorchashm about his decision to institute the security measures. Greene said that a day later, he informed Brigham attorney Bob Hamel that the malpractice suit had been filed.

“Attorney Greene mentioned the filing of the suit in an off-hand comment to a hospital attorney on Monday, Nov. 2, 2015, during a telephone call in which they were discussing the potential filing of an injunction relating to the security precautions we had put in place,” Brigham officials said to The Cancer Letter.

“Service of the summons and complaint was not made until the afternoon of Nov. 9. Dr. Walls was informed sometime thereafter.”

Brigham officials declined to comment on the pending litigation, citing hospital policy.

In the days following the security imbroglio, Noorchashm organized a letter-writing campaign against Brigham. Close to 300 supporters flooded Walls’s inbox, carbon-copying the press, Fitzpatrick, FDA and Congressional investigators.

“Many of us have met Drs. Noorchashm and Reed, seen them speak, or read their writings,” stated the majority of the letters, which contained similar language. “We do not see them as citizens capable of being a physical threat to anyone, rather, it is corporate misbehavior like yours that is a clear and present danger to the lives of ordinary citizens across the nation.”

Several letters demanded Walls’s resignation. Noorchashm contends that these demands are reasonable.

“First, Brigham didn’t act on a previous patient who was harmed, second, they failed to report adverse

outcomes as required by federal law, and third, they violated our First Amendment rights by retaliating, as determined by a judge,” Noorchashm said to The Cancer Letter. “That’s not leadership behavior.”

Noorchashm’s response to Walls’s letter to Fitzpatrick is posted on page 13.

Over the past two years, the couple’s advocacy led to FDA restrictions on the use of power morcellators and largely ended insurance coverage of the procedure.

The Government Accountability Office and FBI are looking into claims of violation of federal law—specifically Title 21, Section 803 of the Code of Federal Regulations—by neglecting to report adverse events.

## **Fitzpatrick: Brigham Retaliated Against My Constituents**

*The text of Rep. Mike Fitzpatrick’s Nov. 5 letter to Ron Walls, executive vice president and chief operating officer at Brigham & Women’s Hospital, follows:*

Dr. Walls,

As you may be aware, my constituent Dr. Amy Reed has been courageously battling an aggressive leiomyosarcoma that was spread throughout her body by a dangerous medical device known as a laparoscopic power morcellator.

This device has taken the lives of hundreds, if not thousands, of women since it was allowed on the market by the Food and Drug Administration. This tragic reality hangs over this mother of six’s head every single day.

And because of this, Dr. Reed and her husband, Dr. Hooman Noorchashm, have passionately advocated for improved medical device safety to ensure no other family has to endure the same pain and heartbreak they and other have experienced.

But I write today because of a different concern raised in a Nov. 4, 2015 Boston Globe report. This report details how Dr. Reed’s husband was put under surveillance, targeted for enhanced security, and told if he did not submit to the terms ordered by Brigham that he would not be permitted to be by his wife’s side during her surgery to remove a third reoccurrence of her leiomyosarcoma.

As Dr. Reed’s and Dr. Noorchashm’s Representative in Congress, I am deeply concerned about what appears to be an effort to retaliate against their advocacy and silence their First Amendment Rights.

Dr. Reed chose Brigham because of its world-class surgery division. She knew the doctors at your hospital provided the best chance to take her one step

closer to claiming victory in her battle to slay the aggressive leiomyosarcoma that is ravaging her body.

I hope the outcome of Dr. Reed's surgery will prove to be successful, and I hope that she never has to be admitted as a patient to Brigham, or any other hospital for that matter, ever again to treat this cancer. But if she does, I hope that she and her husband are treated with dignity and respect—just as should any other family who are facing some of the darkest days in their lifetime.

Sincerely,  
Mike Fitzpatrick  
Congressman

**Walls: Noorchashm's "Campaign of Distortions"**

*The text of Ron Walls's Nov. 10 response to Rep. Mike Fitzpatrick's (R-Pa.) letter follows. Walls is executive vice president and chief operating officer at Brigham & Women's Hospital.*

Dear Congressman Fitzpatrick:

I am in receipt of your letter dated November 5.

I appreciate your interest in this matter, but want to be very clear that the security measures taken during Dr. Noorchashm's visit were the direct result of the fear and anxiety expressed by faculty and staff on learning that Dr. Noorchashm would be returning to the hospital.

Since December 2013, Dr. Noorchashm has sent thousands of emails to faculty and staff at Brigham and Women's Hospital, many of which contained language that recipients found disturbing and threatening.

It is my responsibility to provide a safe and secure work environment for our 18,000 employees. A number of our employees expressed concern about the presence of Dr. Noorchashm within the hospital, given his previous and on-going correspondence and behavior.

It was not feasible to provide personal protection to all for the duration of his visit, so I put discreet security measures in place that would both ensure the protection of and alleviate the anxiety of our faculty and staff while allowing Dr. Noorchashm to be with his wife during her stay.

I undertook these precautions with full knowledge that he would use them to distort the truth and once again publically criticize the hospital. Responding to the safety and security needs of our faculty, staff, our patients and their families is far more important to me than the impact of Dr. Noorchashm's campaign of distortions.

I also want to assure you that neither I, nor any representative of Brigham and Women's Hospital, have or would ever retaliate against or try to silence Dr. Noorchashm for expressing his opinions. He has every right to do so. However, when his speech instills fear in our faculty and staff—people who dedicate their lives to caring for our patients and their families—thus impacting their ability to provide that care, then I will do what I must to ensure their safety.

Sincerely,  
Ron M. Walls, MD  
Executive Vice President  
Chief Operating Officer

**Reed: Please Stop This Craziiness, Dr. Walls**

*The text of Amy Reed's Nov. 13 letter to Ron Walls, executive vice president and chief operating officer at Brigham & Women's Hospital, follows. Reed is an assistant professor of anesthesia and critical care medicine at the Hospital of the University of Pennsylvania.*

Dear Dr. Walls,

Hello. My name is Amy Reed. Last week I had surgery at BWH by an excellent surgeon who works at your hospital. The surgery, as I'm sure you know, went very well and we were able to return home to our family mid-week.

Your hospital has some of the best doctors in their fields. Between visits to my oncologist, who we have a wonderful relationship with, specialists and subspecialists, including surgeons, who have now operated on me twice, I can't begin to count the number of times we have pulled up Francis Street to the front of BWH.

So, I was all the more distressed by the letter we received the week before my surgery, stating that there were concerns regarding my husband's presence in BWH and that there were to be searches, a security escort, and most concerning of all, a reminder that the hospital was private property, and should these demands not be satisfied by my husband that he would be forced to leave the hospital.

My husband has been nothing but a patient advocate, albeit a very vocal one, since my diagnosis in 2013. Cancer made worse by physicians in BWH, by a practice, that we brought to the attention of BWH administration in December of 2013.

At the meeting we were told that my husband "should take a break from working for awhile" and that the morcellation that spread my cancer (as another

woman lay dying from her cancer spread the same exact way in BWH) “was not up for discussion.”

I find it inconsistent that despite dozens of visits to BWH, my husband’s letters to the administration, that are indeed numerous spread over two years, were suddenly deemed threatening to the point of requiring security measures two days after we filed a lawsuit against BWH?

It’s also not unnoticed that not a single one of our caring physicians, including the psychologist who works with the newly diagnosed cancer patients, were consulted in regards to such a threat?

Finally, there were the haphazard searches, half-hearted security escort and lack of notification of the people who actually would have been in harms way, had a security threat actually existed. I would actually be concerned at the lack of protection that you offered to your staff, if indeed that was the objective, instead of intimidation, which I think it is.

I have sarcoma. It’s a bad cancer, and your hospital made it worse, even after your doctors spread it in another woman before me and she lay dying as I had my surgery. The administration’s handling of the morcellator situation was tragic, retaliatory, and basically was recapitulated in the same corporate bullying that we were subjected to last week.

And the Suffolk County Court judge who heard this case last Tuesday agreed with us.

So please stop this craziness. There have never been threats made against anyone at BWH. Ever. But perhaps there have been things said that you haven’t liked to hear, things that make people feel badly because they are being told they are not doing the right things.

That does not make threatening. Rather, threatening is an academic hospital using its name and legal power to intimidate patients and their families.

Do you know what it’s like to have a hospital administration threaten your health care proxy with being forced out of the hospital, when you are six hours from home and family, and could potentially be left without anyone to speak for you in person, because of some arbitrary hospital rules that have been made up and apply only to them?

Threatening? Yes. Terrifying. You should be ashamed of yourselves for penalizing patients and their families for speaking up. For saying something’s wrong. For saying that there was a real patient safety issue, and when no one listened, called them on it.

And if my husband hadn’t spoken up again, got legal counsel, wrote more letters, we would not have had respite against the injustices we were faced with.

But he did, unlike so many other patients who, at the very least, would have been dealing with a major surgery in their loved one, most likely would have said nothing, stressed out all the more. How many patients and families have you subjected to this threatening treatment in the past?

Shame on you Dr. Walls. My husband should receive accolades from BWH, not threats.

Regards,

Amy J. Reed MD PhD

Morcellated uLMS 2013

**Noorchashm: Nice Try, Professor Walls**

*The text of Hooman Noorchashm’s Nov. 13 letter to the editor of The Cancer Letter follows. Noorchashm is an assistant professor and cardiac surgeon at Thomas Jefferson University Hospital.*

Dear Editor,

Thank you for forwarding Dr. Walls’ letter of Nov. 10, 2015, in response to Pennsylvania Congressman Mike Fitzpatrick, to me.

I assure you that the BWH corporate leadership requires public exposure—because this leadership is ethically corrupted and protectionist in a way unbecoming of trusted physicians at one of the most powerful hospitals in our nation.

Mike Fitzpatrick’s letter of Nov. 5, 2015 to the BWH administration stemmed from his surprise by the BWH action against us. Specifically, because of the close interactions we’ve had with the congressman and his staff since January 2015.

Dr. Reed, myself and our entire family recognize, as should the BWH administration, that if this congressman believed that I represented a threat to public safety, he would not have written this letter to Professor Walls. In fact, one of Mr. Fitzpatrick’s legislative hallmarks is public safety and national security—in which he is tough, well recognized and highly effective.

The relationship between our family and Rep. Fitzpatrick’s is one of mutual respect for the work we are accomplishing together in defense of public health and patient safety.

Rep. Fitzpatrick is moving quite powerfully to bring legislative cogency and government oversight to the FDA’s medical device regulatory paradigm and to women’s health in the U.S.—specifically, by aiming to eliminate power morcellators and the Essure sterilization coils in women’s health, so that no other

women are ever harmed by these dangerous medical devices in America again.

My overall response to Dr. Walls's crude reaction to the Fitzpatrick letter, frankly, is "Nice try, professor!" It would've been better for the BWH leadership to comply with the mandates of federal law (Section 803, Title 21 in the Code of Federal Regulations) and medical ethics—as delineated in the Code of Federal Regulations and the AMA's Code of Medical Ethics.

Notwithstanding, based on the BWH corporate leadership's continued unintelligible actions, such as the present letter to Mr. Fitzpatrick, I feel compelled to respond in some detail to Dr. Walls's letter of November 10.

What follows is a complete response to Dr. Walls and the BWH leadership, and their most recent illegal and unethical behavior towards my wife and I—while we were patients at the Brigham on Nov. 2 to Nov. 4 this year.

We ask that you publish this detailed letter for the public record and for the history of the Brigham and Women's Hospital and Harvard Medical School to remember:

First and foremost, on Nov. 3, a senior Suffolk County judge heard our case against Dr. Walls and the BWH leadership and granted a TRO (temporary restraining order), finding irreparable harm based on the potential for even more damage to our reputations.

Our attorney argued that BWH imposed the restrictions in retaliation of my criticism and was retaliating based on my outspoken criticism, which violated my First Amendment right to free speech. Of course, these leaders arrogantly seem to believe that the court system is in the wrong—as they have stated to the media on several occasions.

Let me be clear: this case went to court in Suffolk County, Mass., it was argued by skilled lawyers on both side, and it was vetted by an experienced judge who ruled that the BWH behavior was retaliatory and in violation of my constitutional rights.

The fact that these folks in current BWH corporate leadership wish to continue retaliating and creating further bad publicity for themselves is really quite foolish and short-sighted of them. Particularly, because there is no possible way that myself or anyone in my family could pose a physical threat to anyone, ever!

This retaliatory behavior is certain to create both legal and public relations problems for this leadership in the near future. Dr. Reed and I are both fully committed to demonstrating this leadership's weakness and ethical corruption, which led to American lives

being compromised at BWH and elsewhere. Such negligent behavior is unworthy of Harvard leadership or of the city of Boston—as Dr. Reed and I have stated repeatedly.

Second, what I originally took to the BWH surgical leadership's attention (i.e., Drs. Stan Ashley, Robert Barbieri and Michael Zinner) in October 2013, after my wife's complication, was a severe nationwide public health hazard in the care of women.

Since December 2013, this hazard has been vetted and demonstrated to be factual, repeatedly, by the FDA and other scientific bodies—that morcellation is an avoidable, oncologically hazardous and potentially deadly practice, is no longer a matter of controversy.

In fact, a majority of hospitals and doctors in the U.S. have abandoned power morcellation as a result of our public health campaign. Tragically, the BWH leadership in GYN and the BWH's upper management had prior knowledge of and had suppressed the information since before 2011, by vacillating on it or fully ignoring it—hemming and hawing without action, and even denying that a hazard exists.

They didn't even bother informing their patients of the hazard until we came to them with a promise of introducing the BWH failure to the Wall Street Journal reporters. You see, when innocent and unsuspecting lives are in harm's way, it is unbecoming of their leadership station as doctors at the most powerful medical establishment in the world to not have acted to protect women's health.

These men and women behaved as they did, because their corporate and liability interests were being threatened and they found themselves unable to act as leading physicians ought to. These were risk-managers at work, not doctors.

Third, my several thousand emails to the BWH management starting October 2013 were calls to moral leadership as physicians. By December 2013, I had fully recognized that they would be incapable of standing strongly in defense of women's health nationwide from their Harvard perch—as such, Dr. Reed and I were left with no choice but to go public and to vocally call for their resignation.

And I have done so vigorously and non-stop for nearly two years now, because I am certain that the current corporate leadership of the BWH is ethically corrupted and in violation of federal regulation. Engaging in this fight with the BWH corporate leadership was a grave and difficult personal decision for me, because for many years I had aspired to and respected the station Harvard professors hold in the

American medical establishment and history.

I did, in fact, call their actions unforgivable and I stand by this characterization—the accusations were and remain very pointed. And I continue to maintain that the BWH corporate behavior in not terminating power morcellation at BWH has been criminal. I am sure that hearing such loud objections was rattling to all corporate staff and GYN leaders.

I also suspect that it is unprecedented for these men and women to be spoken to so bluntly given their high sense of self-importance as Harvard professors and leaders. But for these corporate leaders to make the jump from my verbal critique of their awful leadership to any threat of physical violence in order to retaliate against me is absurd, protectionist and mafia-like behavior.

Very certainly, hiring a witch-hunter to smear my name and publicly allege that I am capable of violent action against colleagues, many of whom are my dear friends, is terribly corrupt and very weak.

Fourth, Dr. Reed and I have visited BWH and DFCI at least ten times since her complication and no safety issues were raised. None of our physicians, as they have stated in court records ever felt unsafe in our presence. Now, suddenly, on Nov. 2, 2015 I am returning my wife to undergo life-saving treatment from her physicians, who are truly the best in the nation, and this administration chooses to retaliate and exercise unlawful protectionism?

Incredibly, this retaliatory action coincided with our lawyer filing a suit against the GYN faculty for medical negligence leading to irreversible harm to my wife and family. Of course, the amazing reality is that even the BWH security guards, who were assigned to our detail on Nov. 2 to Nov. 3, thought the whole thing was a joke—especially as our friends and colleagues at BWH surrounded us warmly. The guards routinely left me alone in the presence of my former colleagues, friends and other staff members and on the inpatient floor: a security threat, indeed!

Finally, I find the BWH's persistent and thoughtless response to us and our campaign against morcellation and against their leadership to be elementary and amateur from a public relations and risk management standpoint—as demonstrated in their latest letter to Mr. Fitzpatrick.

I think the best they could do at this juncture in time is to issue a sincere, heartfelt and public apology to my entire family, call for a total abandonment of morcellation in gynecology at Partners Health hospitals (and nationwide), and then step down from

the Brigham's leadership—to allow a strong breed of leading doctors and surgeons to take the helm at BWH.

Of course, my experience with these folks has demonstrated that there is simply too much of what some have called “Harvard Hubris” guiding their actions for them to see the correct and logical course of action—or perhaps it is the ineptitude of their legal advisors.

Dr. Reed and I are committed to relying on public outcry and the court system to vet out these weak men and women—because Harvard Medical School appears unable to eliminate weakness and ethical corruption well enough.

If and when necessary again, our attorney, Mr. Tom Greene, will move to bring the full force of legal protections, the United States constitution and the pertinent law enforcement agencies against the BWH for any further illegal and unethical behavior—should they continue to persist in their retaliatory behavior, in any further attempts at defaming myself and my family, or attempt to prevent my wife to receive the care of her outstanding BWH/DFCI physicians.

I assure you that in the aftermath of falling to what is now confirmed to be a disaster in women's health because of a BWH leadership negligence, Dr. Amy Reed and I have risen, as a son and daughter of the medical establishment in the United States, in vocal defense of public health, patient safety and medical ethics.

These corporate leaders at BWH, who stand retaliating against us, are standing on the wrong side of medical history, in diametric opposition to the purpose of one of Boston's most esteemed hospitals.

We look forward to demonstrating these fact before a court of law and in the public eye—and we anticipate the departure of these men and women from Harvard leadership, soon.

My sincere thanks to you for the opportunity to provide this detailed rebuttal to an unethical corporate leadership, which is guilty of violating federal law and the fundamentals of human decency. Their days as corporate leaders at BWH are now numbered.

Sincerely,

Hooman Noorchashm, MD, PhD  
Brigham-trained Cardiac Surgeon

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## *Capitol Hill*

# Advocacy Organizations Urge Congress to Consider FDA's Role in Regulating LDTs

A group of 42 organizations sent an open letter to a congressional committee urging them to consider the important role of the FDA in the regulation of laboratory-developed tests.

Ahead of next week's hearing of the House Energy and Commerce Committee, titled "Examining the Regulation of Diagnostic Tests and Laboratory Operations," the letter addressed concerns that agency involvement would impede patient access to LDTs, saying that the FDA has a track record of approving new technologies in a timely manner.

"In 2013 FDA allowed marketing of four next-generation sequencing (NGS) diagnostic devices, the first-ever clearance of its kind," the authors wrote.

"The FDA developed the expertise and tools to conduct a thorough review and used separate approval pathways to reflect the risk associated with each device. The FDA's draft guidance on LDT oversight also reflects a commitment to flexibility, given the proposal's risk-based approach to oversight."

The organizations, which include Friends of Cancer Research, the American Association for Cancer Research, the American Cancer Society Cancer Action Network, and the American Society for Clinical Oncology, noted examples when FDA oversight was necessary to protect patients.

"The discovery of faulty and clinically invalid tests being used in ovarian cancer (OvaSure) and cardiology (KIF6 testing) highlights examples of inadequate oversight," the authors wrote. "Apart from these examples, the general lack of publicly-available information about many LDTs has raised concerns among many that not enough is known about many tests currently in use."

"The FDA can provide the assurance that when tests are performed they lead to the proper use of associated treatments, a step that's necessary to improve the public health."

The full letter [can be read here](#).

The full list of signed organizations includes: Action to Cure Kidney Cancer; Addario Lung Cancer Foundation; Addario Lung Cancer Medical Institute; The ALS Association; Alliance for Aging Research; American Association for Cancer Research; American Autoimmune Related Diseases Association; American

Brain Tumor Association; American Cancer Society Cancer Action Network; American Heart Association; American Medical Student Association; American Society of Clinical Oncology; Annie Appleseed Project; Breast Cancer Action; CancerCare; Cancer Prevention and Treatment Fund; Cancer Support Community; C-Change; Connecticut Center for Patient Safety; Cutaneous Lymphoma Foundation; Fight Colorectal Cancer; Friends of Cancer Research; Kidney Cancer Association; Kids v. Cancer; The Leukemia & Lymphoma Society; Lung Cancer Alliance; LUNGeivity; Lupus and Allied Diseases Association Inc.; Melanoma Research Alliance; MRSA Survivors Network; National Brain Tumor Society; National Coalition for Cancer Survivorship; National Consumers League; National Multiple Sclerosis Society; National Organization for Women; National Patient Advocate Foundation; National Physicians Alliance; Ovarian Cancer National Alliance; Prevent Cancer Foundation; US Pain Foundation; WomenHeart: The National Coalition for Women with Heart Disease; and Woody Matters.

## *In Brief*

# Zinner Named CEO of Miami Cancer Institute

**MICHAEL ZINNER** was named CEO and executive medical director of **Miami Cancer Institute at Baptist Health South Florida**.

Zinner served as clinical director at Dana-Farber/Brigham and Women's Cancer Center, and surgeon-in-chief at the Brigham and Women's Hospital. He is also the Moseley Professor of Surgery at Harvard Medical School and founder of Harvard's Center for Surgery and Public Health. Zinner is also co-founder and co-director of the Gastrointestinal Cancer Center at Dana-Farber Cancer Institute.

From 2008 to 2010, Zinner was the chairman of the Board of Governors of the American College of Surgeons, and is now vice chair of the Board of Regents. Additionally, he is chairman of the organization's Health Policy and Advocacy Committee.

A Miami native, Dr. Zinner received his M.D. degree from the University of Florida and did his surgical residency at Johns Hopkins Hospital.

**STUART ORKIN** received **Boston Children's Hospital's Lifetime Impact Award** at the hospital's third annual Global Pediatric Innovation Summit.

Orkin is associate chief of hematology/oncology



at Boston Children's Hospital and chair of pediatric oncology at Dana-Farber Cancer Institute.

"Dr. Orkin's contributions to the patients, families and staff from both our hospitals have been immeasurable," said Boston Children's Hospital President and CEO Sandra Fenwick. "For all of his dedication to research and care, he has never lost sight of teaching the next generation of researchers and caregivers, and we have all learned so much from him, particularly when it comes to commitment to excellence."

Orkin's laboratory was one of the first to apply molecular biology and DNA sequencing techniques to thalassemia, a blood disorder characterized by defects in genes that provide the instructions for producing hemoglobin. In addition, he has systematically dissected the hematopoietic process, identifying nearly every one of the master genes called transcription factors that regulate the development of every cell type found in the blood.

"Stu has always been in the vanguard when it comes to expanding our understanding of gene regulation, hematopoiesis and how they can go awry to cause blood disorders and leukemias," said David Williams, president of Dana-Farber/Boston Children's Cancer and Blood Disorders Center. "We will continue to see the impact of his work as a scientist, a leader and a mentor for years to come."

In recent years, his laboratory has studied the roles of two molecular switches—gene BCL11A and an enhancer that controls its activity—in controlling production of the adult and fetal forms of hemoglobin. Sickle cell anemia and thalassemia are both caused by mutations in adult hemoglobin. Orkin and his collaborators are attempting to use gene editing technologies such as CRISPR to manipulate BCL11A's enhancer and force red blood cells to dial down adult hemoglobin production in favor of the fetal form.

Orkin also is a member of the National Academy of Sciences, the National Academy of Medicine and the American Academy of Arts and Sciences. He is a fellow of the American Association for the Advancement of Science, an investigator with the Howard Hughes Medical Institute, and the David G. Nathan Professor of Pediatrics at Harvard Medical School.

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**CITY OF HOPE** announced several appointments to its faculty.

**Susanne Warner** was named an assistant clinical professor in the department of surgery. In 2010, Warner completed a research fellowship at Memorial Sloan Kettering Cancer Center. Following residency, Warner completed a clinical fellowship in hepatopancreatobiliary and advanced gastrointestinal surgery at the University of Michigan Medical Center, where she was also a clinical lecturer. Her research interests include clinical applications of oncolytic viral therapies, and humanities research centered on the spiritual, emotional, and physical optimization of the perioperative patient experience.

**Ling Li** joined as an assistant professor in Gehr Family Center for Leukemia Research and Division of Hematopoietic Stem Cell and Leukemia Research. Li's research focuses on studying the aberrantly regulated epigenetics that initiate or maintain acute myeloid leukemia. Li was the first to report aberrant activity of SIRT1 leads to deacetylation and therefore suppression of p53-signaling contributing to survival of leukemia stem cells. His laboratory is currently determining the epigenetic-related resistance mechanisms of LSC to the treatment of tyrosine kinase inhibitors. The primary goal of this effort is to develop novel therapeutics to specifically target LSC and advance these strategies for clinical trials in AML.

**Edwin Manuel** joined the Department of Experimental Therapeutics as an assistant professor. Manuel's current research focuses on approaches to overcome mechanisms of tumor escape, which can compromise the efficacy of immunotherapeutic strategies. One major contributor to tumor escape is the over-expression of tumor-derived proteins that cause significant immune suppression. Manuel has developed a bacterial-based approach that effectively targets a variety of immunosuppressive proteins to rescue anti-tumor responses in preclinical models of melanoma and pancreatic cancer.

**Irina Chilian** was named associate clinical professor in the department of medical specialists, specializing in neurology. Chilian joins City of Hope after being in private practice for 13 years, and serving as a consultant to City of Hope since 2012. In 2002, Dr. Chilian completed a clinical neurophysiology fellowship from USC's Keck School of Medicine/VA Medical Center.

**SIDNEY KIMMEL CANCER CENTER** at **Johns Hopkins University** made several personnel changes.

**Kenneth Cohen** was named associate director of integration and strategic relationships for the Department of Oncology. In this role, Cohen will work with faculty members and administration to represent the interests of the department and the Cancer Center in discussions and negotiations with outside entities.

**Charles Drake** was appointed co-director of the Kimmel Cancer Center's Immunology Program. He joins Drew Pardoll in leading the program. In addition to his research responsibilities, Drake is a clinical oncologist specializing in prostate, kidney, bladder and testicular cancers.

**Khinh Ranh Voong** has been appointed instructor in the Department of Radiation Oncology and Molecular Radiation Sciences, where she will be a part of the thoracic oncology team based at Johns Hopkins Bayview Medical Center.

**Syed Ali** was appointed as an instructor in oncology for the Division of Hematologic Malignancies. Ali will focus on novel and immune-based approaches for the treatment of multiple myeloma. He will serve as an attending on the inpatient hematologic malignancy service, supervise fellows' clinic, participate in bone marrow reading and see patients in clinic.

**Nilanjan Chatterjee** has joined the faculty as a Bloomberg Distinguished Professor with a dual appointment in the Department of Oncology's Division of Biostatistics and Bioinformatics and in the Department of Biostatistics at the Bloomberg School of Public Health.

**Doug Smith**, of the Department of Oncology's Division of Hematologic Malignancies, was promoted to professor of oncology.

**ST. JUDE CHILDREN'S RESEARCH HOSPITAL, The Scripps Research Institute** and other institutions launched the Human Dark Proteome Initiative, to focus on the portion of the proteome that does not adopt defined 3D structures.

Recent developments in technology, including advances in nuclear magnetic resonance spectroscopy methods, allow researchers to study intrinsically disordered proteins and intrinsically disordered regions of these molecules.

"Our goal is to raise awareness about the potential societal impacts of a broad-based research infrastructure for these understudied proteins," said Richard Kriwacki, a member of the St. Jude Department of Structural Biology.

**THE AMERICAN COLLEGE OF RADIOLOGY** and several colorectal cancer care advocacy groups urged Congress to pass the **CT Colonography Screening for Colorectal Cancer Act**, which would provide Medicare coverage for seniors who choose those screening exams.

"A third of those who should be screened for colorectal cancer can't have or won't get a colonoscopy. CT colonography increases screening rates where offered. Medicare coverage would provide seniors with insured access to an exam that may appeal to them. This would jump-start screening, catch more cancers early and saves more lives," said Eric Hargis, CEO of Colon Cancer Alliance. Other advocacy groups included the Prevent Cancer Foundation, Chris4Life Colon Cancer Foundation, the Colon Cancer Coalition, and Fight Colorectal Cancer.

Several major insurers cover screening with virtual colonoscopy, and more than 20 states require insurers to cover these exams. However, Medicare does not cover beneficiaries for CT colonography.

In recent draft recommendations, the U.S. Preventive Services Task Force named virtual colonoscopy an alternative screening exam; the task force did not grade specific screening exams. The American Cancer Society strongly supported CT colonography in its comments to the task force on those draft recommendations. The ACR has urged the task force to reclassify CT colonography as a recommended screening exam.

**THE TISCH CANCER INSTITUTE** at the Icahn School of Medicine at Mount Sinai and **CTI BioPharma Corp.** established a \$1.5 million research endowment fund, the CTI BioPharma International Postdoctoral Research Fellowship, for international collaboration in translational research in hematology and immunobiology.

The fellowship and endowment will provide seed funding to young physician researchers. Mount Sinai will receive endowment funding over three years to identify and select research projects from medical researchers currently working at international institutions based outside the U.S.

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## *Drugs and Targets*

# **Osimertinib Tablets Granted Accelerated Approval in NSCLC**

**FDA granted accelerated approval to Tagrisso (osimertinib) tablets** for the treatment of patients with metastatic epidermal growth factor receptor T790M mutation-positive non-small cell lung cancer, as detected by an FDA-approved test, who have progressed on or after EGFR tyrosine kinase inhibitor therapy.

The approval was based on two multicenter, single-arm, open-label clinical trials in patients with metastatic EGFR T790M mutation-positive NSCLC who had progressed on prior systemic therapy, including an EGFR TKI. All patients were required to have EGFR T790M mutation-positive NSCLC as detected by the cobas EGFR mutation test and received osimertinib 80 mg once daily.

The major efficacy outcome measure was objective response rate according to RECIST v1.1 as evaluated by a Blinded Independent Central Review. Duration of response was an additional outcome measure.

The first study (n=201) showed an ORR of 57 percent (95% CI: 50%, 64%). The second study (n=210) demonstrated an ORR of 61 percent (95% CI: 54%, 68%). The majority, 96 percent, of patients in both trials had ongoing responses at the time of primary analysis, and the median DOR had not been reached, with duration of ongoing responses ranging from 1.1 to 5.6 months after a median duration of follow-up of 4.2 months in Study 1 and 4.0 months in Study 2. The dose finding phase of Study 1 (n=63) showed an ORR of 51 percent and median DOR of 12.4 months.

Safety data was evaluated in 411 patients who received osimertinib at a dose of 80 mg daily. The most common adverse events were diarrhea, rash, dry skin, nail toxicity, eye disorders, nausea, decreased appetite, and constipation.

Osimertinib, sponsored by AstraZeneca Pharmaceuticals LP, previously received a Breakthrough Therapy Designation, and the application was granted a Priority Review. The application was approved before the Prescription Drug User Fee Act goal date of Feb. 6, 2016.

**FDA approved Cotellic tablets (cobimetinib) for the treatment of patients with unresectable or metastatic melanoma** with a BRAF V600E or V600K mutation, in combination with vemurafenib. Cobimetinib is not indicated for treatment of patients with wild-type BRAF melanoma.

The approval was based on the demonstration of improved progression-free survival and overall survival in a double-blind, randomized, active-controlled trial conducted in 495 patients with previously untreated, BRAF V600 mutation-positive, unresectable or metastatic melanoma as detected using the cobas 4800 BRAF V600 mutation test. Cobimetinib is sponsored by Genentech.

All patients received vemurafenib 960 mg orally twice daily and were randomized (1:1) to receive cobimetinib 60 mg (n=247) or matching placebo (n=248) orally once daily on days 1-21 of an every 28-day cycle. The median age of the study population was 55 years (range 23 to 88 years), 60 percent had stage M1c disease, 72 percent had a baseline ECOG performance status of 0, 45 percent had an elevated baseline serum lactate dehydrogenase, 10 percent had received prior adjuvant therapy, and less than 1 percent had previously treated brain metastases.

The trial demonstrated a statistically significant improvement in PFS [HR: 0.56 (95% CI: 0.45, 0.70),  $p < 0.001$ ]; the median PFS was 12.3 months (95% CI: 9.5, 13.4) and 7.2 months (95% CI: 5.6, 7.5) on the cobimetinib plus vemurafenib and single-agent vemurafenib arms, respectively.

The trial also demonstrated a statistically significant improvement in OS based on an interim analysis [HR: 0.63 (95% CI: 0.47, 0.85); stratified log-rank  $p$ -value=0.0019]. The median OS was not reached (95% CI: 20.7, NR) and was 17 months (95% CI: 15.0, NR) on the cobimetinib plus vemurafenib and single-agent vemurafenib arms, respectively.

The confirmed objective response rates were 70 percent (95% CI: 64, 75) and 50 percent (95% CI: 44, 56) on the cobimetinib plus vemurafenib and single-agent vemurafenib arms, respectively ( $p < 0.001$ ).

Safety data was evaluated in 247 patients who received at least one dose of cobimetinib. The most common adverse reactions were diarrhea, photosensitivity reaction, nausea, pyrexia, and vomiting. The most serious risks in patients receiving cobimetinib were new primary malignancies, hemorrhage, cardiomyopathy, severe dermatologic reactions, serous retinopathy and retinal vein occlusion, hepatotoxicity, rhabdomyolysis, and severe photosensitivity reactions.