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Penalty Too Light

A Guest Editorial by Keith Baggerly and C.K. Gunsalus

What does it say about our national commitment to research integrity that the Department of Health and Human Services' Office of Research Integrity has concluded that a five-year ban on federal research funding for one individual researcher is a sufficient response to a case involving millions of taxpayer dollars, completely fabricated data, and hundreds to thousands of patients in invasive clinical trials?

This week, ORI released a notice of “final action (<https://s3.amazonaws.com/public-inspection.federalregister.gov/2015-28437.pdf>)” 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 (http://www.nature.com/polopoly_fs/1.17660!/menu/main/topColumns/topLeftColumn/pdf/nature.2015.17660.pdf) 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 (<https://clinicaltrials.gov/ct2/show/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 (<https://clinicaltrials.gov/ct2/show/NCT00636441>), 2008, initial target 270 patients),
- in early-stage lung cancer (NCT00545948 (<https://clinicaltrials.gov/ct2/show/NCT00545948>), 2007, initial target 117 patients),
- in late-stage lung cancer (NCT00509366 (<https://clinicaltrials.gov/ct2/show/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 (<http://www.cbsnews.com/news/deception-at-duke-fraud-in-cancer-care/3/>), 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 (http://www.cancerletter.com/downloads/20150123_1/download), 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 (<https://ori.hhs.gov/administrative-actions>) 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 (<http://www.gpo.gov/fdsys/pkg/FR-2000-12-06/html/00-30852.htm>) 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 (<http://www.newsobserver.com/news/local/education/article43885173.html>), “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 (<http://www.nature.com/nm/journal/v13/n11/full/nm1107-1276b.html>) first publicly reported problems with the data. We do not know of any action on Duke’s part at the time.

- 2008: Brad Perez (http://www.cancerletter.com/articles/20150109_1), 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 (<https://projecteuclid.org/euclid.aos/1267453942>) reported (and The Cancer Letter publicized (http://www.cancerletter.com/articles/20101201_5)) 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

(http://www.cancerletter.com/downloads/20100803_9); 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 (<http://www.wral.com/news/local/story/10104999/>) 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 (<https://vimeo.com/128633555>) 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

(http://www.cancerletter.com/articles/20150109_8) 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* (<http://stm.sciencemag.org/content/2/28/28cm13>) 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 (http://www.cancerletter.com/articles/20150116_1)” to find “abundantly clear (<http://www.cbsnews.com/news/deception-at-duke-fraud-in-cancer-care/>)” 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 handling 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 (<http://www.nationalethicscenter.org/>), 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 (<http://www.gunsalus.net/>) and is the author of *The Young Professional's Survival Guide* (<http://www.cabfaresmoral snares.com/>) (Harvard University Press, 2012) and *The College Administrator's Survival Guide* (<http://www.marchingventures.com/college-administrators-guide/>) (Harvard University Press, 2006).*

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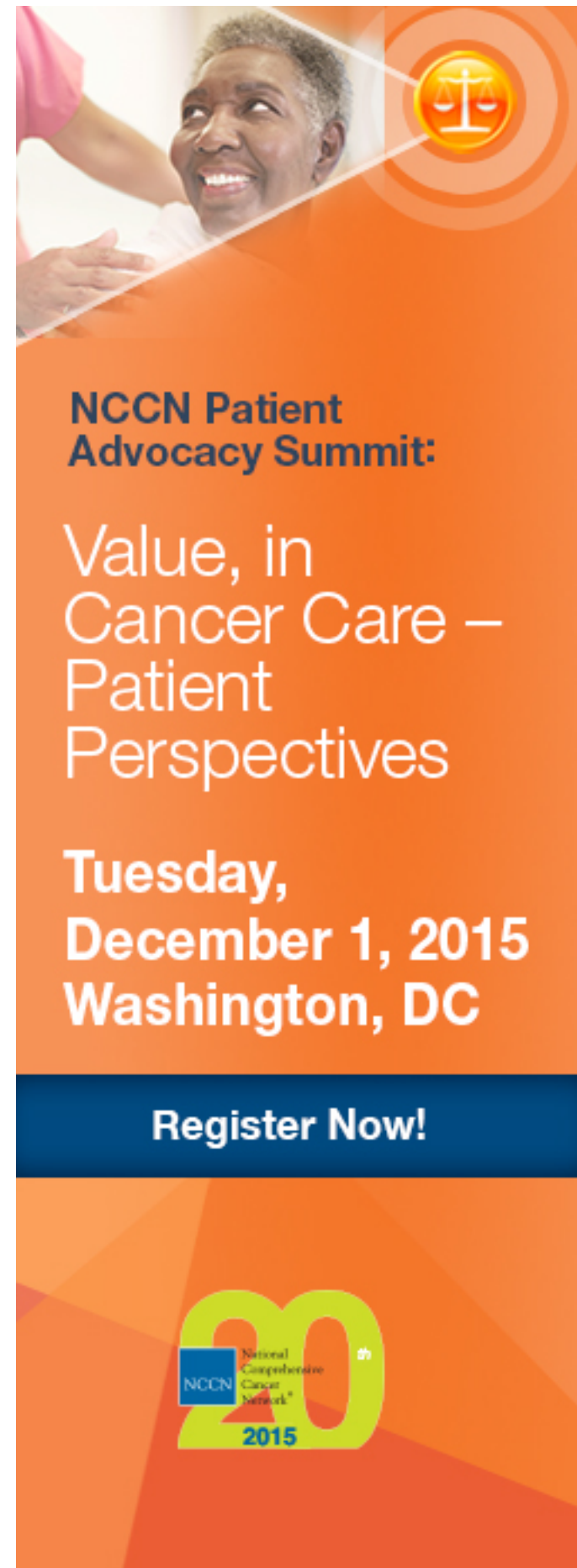
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