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COMMENTARY

Institutional Responsibility and the Flawed Genomic Biomarkers at Duke University: A Missed Opportunity for Transparency and Accountability

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Abstract When there have been substantial failures by institutional leadership in their oversight responsibility to protect research integrity, the public should demand that these be recognized and addressed by the institution itself, or the funding bodies. This commentary discusses a case of research failures in developing genomic predictors for cancer risk assessment and treatment at a leading university. In its review of this case, the Office of Research Integrity, an agency within the US Department of Health and Human Services, focused their report entirely on one individual faculty member and made no comment on the institution's responsibility and its failure to provide adequate oversight and investigation. These actions missed an important opportunity to emphasize the institution's critical responsibilities in oversight of research integrity and the importance of institutional transparency and accountability.

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When there are substantive failures in an institution's procedures for oversight of research integrity in biomedical research, it is important that these be recognized and effectively addressed. This is especially important when the same institutional leaders will be responsible for safeguarding the integrity of future research. Institutional transparency and accountability are essential to maintain public trust in the biomedical research enterprise (Yarborough et al. 2009; Geller et al. 2010).

For these reasons, we—members of the subcommittee that examined institutional oversight as part of activities of the Institute of Medicine (IOM) Committee on the Review of Omics-Based Tests For Predicting Patient Outcomes in Clinical Trials (Institute of Medicine (IOM) 2012)—are disappointed by the findings of the Office of Research Integrity (ORI) regarding the flawed development of genomic biomarkers at the Duke University Medical School (Office of Research Integrity in Office of the Secretary 2015). These findings, published in the Federal Register on 11/09/2015, focused only on research misconduct by Anil Potti, former associate professor at Duke University Medical School, rather than including a broader consideration of institutional failures.

After external challenges were made about the scientific validity of genomic marker research conducted in the Nevins-Potti lab at Duke University (Goldberg 2009; Baggerly and Coombes 2009), Duke had commissioned an investigation in the fall of 2009 to assess whether the markers were sufficiently reliable to drive the selection of therapies in three clinical trials in oncology patients. In July 2010 the National Cancer Institute called into question the reliability of the biomarkers, and of Duke's 2009 investigation. In part because of that failed university investigation, the NCI (National Cancer Institute) and Duke asked the IOM (institute of Medicine) to investigate the research process in the Nevins-Potti lab, to identify flaws that may have led to the external challenges, and to make recommendations about how to avoid such mistakes in the future (Institute of Medicine (IOM) 2012; Goldberg 2010, 2011a).

The main goal of our IOM Committee was to define the best practices for discovery and translation of omics-based tests into a clinical trial and ultimately clinical practice (Institute of Medicine (IOM) 2012). The IOM Committee Report highlighted in its recommendations the responsibilities not only of investigators, but of co-investigators, supervising or senior investigators, research institutions in which investigators work, the journals in which such research is published, sponsors who provide funding for such research, and the Food and Drug Administration (FDA) who must review genomic tests before their use in clinical practice according to Investigational Device Exemption (IDE) regulations.

The IOM Committee Report outlined specific aspects of institutional responsibility. First, institutions are responsible for establishing, supporting, and overseeing the infrastructure and research processes for omics-based test development and evaluation. Second, institutional leaders should provide oversight and promote a

culture of integrity and transparency by designating officials responsible for: (1) IDE and Investigative New Drug requirements (IND), (2) management of financial and non-financial conflicts of interest (both individual and institutional), (3) a system for preventing, reporting, adjudicating lapses in integrity and (4) establishing clear procedures for responding to inquiries regarding the integrity of research conducted at their institution or by their faculty. Third, institutions should ensure that individuals who collaborate on omics research and test development, including biostatisticians and bioinformaticians: (1) be treated as equal co-investigators and full collaborators, (2) be represented on relevant review and oversight bodies and (3) function in an intellectually independent manner. An important component of the approach to address these IOM recommendations is the training of all investigators, including senior investigators, and staff in the responsible conduct of research (RCR) that includes the ethics of human and animal research.

The recommendations in the IOM report (Institute of Medicine (IOM) 2012) were enlightened by the IOM Committee's identification of significant flaws in the research process in the Nevins-Potti lab at Duke, and failures of the institution to provide appropriate oversight and investigation. Prior to, during and following the work of the IOM Committee, the Cancer Letter also revealed many details surrounding events that took place in the Nevins-Potti lab and failures in institutional oversight. In particular, after the IOM report was released, the Cancer Letter discovered a letter from a medical student working in the Nevins-Potti lab who detailed the problems in the lab with the development of their genomic predictors. Senior institutional leaders were aware of the letter yet, as described below, they responded inappropriately.

After 5 years of investigation, the ORI concluded that Anil Potti engaged in research misconduct by including not only flawed, but "false" research data in published papers, submitted manuscripts, and grant applications (Office of Research Integrity in Office of the Secretary 2015). The ORI had access to the IOM report, supported by extensive files assembled for the IOM Panel's review (Institute of Medicine (IOM) 2012), as well as to the series of articles in the Cancer Letter (Goldberg 2011b, c, d, 2015a, b, c, d, e, f; Baggerly and Gunsalus 2015), many of which emerged later only through subpoena in patient lawsuits, and to a detailed statistical analysis of the Nevins-Potti data (Goldberg 2009; Baggerly and Coombes 2009). Nevertheless, the ORI did not, in its report or in any other public documents, address the substantial institutional failings that had been detailed by these previous sources, sources that had included specific insights about the following important institutional issues:

- In 2008, Bradford Perez, a Duke medical student working in the Nevins-Potti research group, wrote a detailed letter revealing major flaws in data quality and reproducibility that undermined the validity of the genomic tests, yet his lab chief and some among the health sciences Deans and the Chancellor for Health Affairs office dismissed or may even have suppressed his concerns; arrangements were made to transfer him to another research laboratory (Goldberg 2015a, b).

- Duke leadership did not respond adequately when Keith Baggerly and Kevin Coombs, statisticians at the M.D. Anderson Cancer Center (Goldberg 2009; Baggerly and Coombes 2009), and Lisa McShane, a statistician at the National Cancer Institute (Goldberg 2011a), provided significant evidence challenging the validity of the genomic tests the Nevins-Potti research group developed.
- Senior leadership in the Duke University Health System failed to challenge Joseph Nevins, an established senior investigator.
- Duke senior leadership permitted trials to be launched and continued for a period of time in the face of serious external challenges to their scientific underpinnings.
- Genomic trials were conducted at Duke in an Institute of Genome Sciences and Policy, which was organizationally outside the Duke Cancer Center and the School of Medicine and lacked experience in clinical trials as well as adequate infrastructure and oversight.
- The Duke Institutional Review Board (IRB), which must approve any research protocols on human subjects, did not recognize that an algorithm such as a genomic test is a medical device and must follow FDA requirements, including obtaining an Investigational Device Exemption (IDE) to allow investigators to conduct research on medical devices involving human subjects.
- Arguably, the most telling of the failures in institutional responsibility were statements by Duke senior leadership, during discussions with the IOM Committee in 2011, that "no one came forward" at Duke to express concerns about data, even though the substantive concerns detailed by Perez in 2008 had, as documented in emails later discovered by subpoena, already reached senior Duke leaders (Institute of Medicine (IOM) 2012; Goldberg 2015a, b).
- Two-thirds of the 40 articles presenting related work by researchers in the Nevins-Potti lab that had been published in leading scientific journals were ultimately retracted by the Duke leadership (Institute of Medicine (IOM) 2012).

In response to the ORI's reported findings, the leadership at Duke apparently interpreted the ORI's narrow public statement about Potti as the "one bad apple" theory that provides "exoneration" of the institution. A Duke University spokesperson, commenting about the ORI Report in a Washington Post story (Barbash 2015), indicated "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 absence of the admission of important failures in administrative oversight is glaring, as recognized by others (Goldberg 2015f; Baggerly and Gunsalus 2015; Barbash 2015; Duke University Student Newspaper 2016; Hinkes-Jones 2015). Even the student newspaper at Duke has written that the Duke administration has never explained its role: "We believe the reputation of the Duke's School of Medicine demands public statements from the Duke administration to clear the haze around their handling of Potti's case…." (2015).

We are disappointed that the ORI has taken such a narrow view in this case, focusing only on Potti's actions as the "bad apple" (Redman 2013), and failing to address the activities of the senior leadership at Duke (Master 2015). The Division of Investigative Oversight (DIO), a part of the ORI, is charged to (Yarborough et al.

2009) review and monitor research misconduct investigations conducted by the awardee institution and (Geller et al. 2010) evaluate investigations and investigatory findings of awardee institutions and recommend to the ORI Director findings of research misconduct and propose administrative actions (The Office of Research Integrity 2016; The Office of Research Integrity: Policies-Mission 2016). The criteria to be used are not spelled out in detail but the ORI guidelines for whistle blowers outlines that institutions have a duty to provide objective and fair procedures for examining complaints, and to follow procedures that are not tainted by institutional conflicts of interest (The Office of Research Integrity: Whistle-blowers 2016).

We understand from their web site (The Office of Research Integrity: Policies-Mission 2016) that the ORI generally defers to institutions to undertake their own review. However, when the internal institutional review has failed dramatically, as has been documented in this case (Institute of Medicine (IOM) 2012), we believe that the ORI's stated responsibility for "oversight of research misconduct inquiries and investigations" (The Office of Research Integrity 2016) should lead to independent assessments and recommendations from the ORI. When the institution has failed to adequately review itself, the ORI needs to fill a gap of oversight. The Office of Human Research Protection can shut off federal research funding for institutional violations of Institutional Review Board (IRB) procedures. As Redman (2013) suggests, the ORI should have similar powers when institutions fail to provide proper research oversight in the face of misconduct or fraud and should require corrections be made to implement proper responsible research training. Random or for cause audits may also need to be implemented.

The narrowness of the reported findings by the ORI and the public statement by the Duke leadership send a message that co-investigators, senior investigators, university leaders and administrators will not be held accountable for their failures to oversee research integrity. The narrowness of findings represents a missed opportunity for investigators, universities, and the public to learn why systems of oversight may fail, and how to prevent such failure in the future, whether at Duke or elsewhere (Colliton 1983, Knox 1983, Resnik 2003). This leaves vulnerabilities in the systems that are needed to protect the integrity of research and the human research subjects from indignities or other harms. While the primary responsibility for research integrity begins with the principal investigator and extends to the investigating team, those in positions of institutional leadership also share significant responsibility. Institutional leaders should ensure there is an environment that enhances research integrity and should provide proper oversight. When there are indications of violations of research integrity, whether these arise in an inadvertent manner or through misconduct, the institutional leadership must respond quickly and appropriately. In settings where there have been substantial failures in oversight by institutional leadership, as in this case at Duke University Health System and the School of Medicine, the ORI should ensure that there is an investigative process that is transparent and that will ensure accountability not only for the individuals involved in the research but also for those in institutional leadership positions who have oversight responsibilities surrounding the case.

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