Biomarkers in the Clinic: A Cautionary Tale

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Biomarker profiling is well established as a powerful research tool. These so-called “omics” tests are based on signatures of molecules, such as nucleic acids, proteins, and metabolites. In recent years, the potential utility of such tests in diagnosis and prognosis has attracted much commercial investment. Consequently, the institutions developing these tests are under increasing pressure to deliver them to the clinic. In some cases, this urgency has led to clinical trials of tests that are unfit for purpose, having been generated from error-ridden data. A notable example of this situation occurred at Duke University, where flawed genomic test profiles were used in cancer trials. The recent article by Kaiser (1), summarized below, discusses the failures that led to the controversy at Duke and reviews the lessons learned to help prevent a recurrence of such actions in the future.

Controversy at Duke

In 2006, a team at Duke University published a groundbreaking article showcasing how gene expression profiles could be used to predict responsiveness to chemotherapy. The University quickly launched a series of clinical trials based on data from the studies; however, cancer researchers called the validity of the data into question after several groups failed to replicate work published by the Duke team. Two biostatisticians, Keith Baggerly and Kevin Coombes from the M.D. Anderson Cancer Center, discovered major errors in the Duke data, which they published in a critique in 2009. Researchers from the National Cancer Institute were also skeptical of the Duke findings. They had planned to use one of the Duke “signature genes” in their own trial but were unable to validate the data. In response, Duke shut down 3 clinical trials pending further review. Multiple investigations into their work

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were subsequently carried out, including those by the National Cancer Institute and the Institute of Medicine.

**Systems Failures**

The fallout from the Duke investigation was considerable: retracted publications, damaged reputations, lawsuits, and compromised patient safety. It also exposed the failure of the institution, funders, journals, and the broader scientific community to identify research irregularities before initiation of clinical trials. In addition, a review conducted by the Institute of Medicine questioned the role of the US Food and Drug Administration. The Duke investigators were able to proceed to clinical trials without complete approval because of ambiguous guidance set out by the agency. The Institute of Medicine report also uncovered a number of financial disparities. They found that several of the investigators possessed patents on the technologies used and had extensive ties to the companies developing the tests.

**Lessons Learned**

The Institute of Medicine has recommended the introduction of more stringent validation of molecular-signature tests. There is consensus of a need for greater awareness of research activities, beginning with the institutions, including identification of conflicts of interest. Data should be readily available to journals, funders, and other institutions for cross-checking and review. The Food and Drug Administration is encouraged to take a stronger stance in enforcing clear guidance for the regulation of tests generated by individual laboratories. Concern is growing that we are observing a “gold rush” of commercial interest in these technologies. Companies aim to bring tests to market as soon as possible, even when the science is largely unproved. In recent times we have witnessed the reckless actions of a poorly regulated financial sector that have contributed to global recession. Similarly, the rapid transition of biomarker testing to the clinic has the potential for large-scale failure, unless it is carried out in a transparent and controlled fashion.

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**Reference**


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