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Genomic signatures to guide the use of chemotherapeutics

Anil Potti1,2, Holly K Dressman1,3, Andrea Bild1,3, Richard F Riedel1,2, Gina Chan4, Robyn Sayer4, Janel Cragun4, Hope Cottrill1, Michael J Kelley2, Rebecca Petersen5, David Harpole5, Jeffrey Marks5, Andrew Berchuck1,6, Geoffrey S Ginsburg1,2, Phillip Febbo1,2,3, Johnathan Lancaster4 & Joseph R Nevins1,2,3

Using in vitro drug sensitivity data coupled with Affymetrix microarray data, we developed gene expression signatures that predict sensitivity to individual chemotherapeutic drugs. Each signature was validated with response data from an independent set of cell line studies. We further show that many of these signatures can accurately predict clinical response in individuals treated with these drugs. Notably, signatures developed to predict response to individual agents, when combined, could also predict response to multidrug regimens. Finally, we integrated the chemotherapy response signatures with signatures of oncogenic pathway deregulation to identify new therapeutic strategies that make use of all available drugs. The development of gene expression profiles that can predict response to
DERIVING CHEMOSENSITIVITY FROM CELL LINES: FORENSIC BIOINFORMATICS AND REPRODUCIBLE RESEARCH IN HIGH-THROUGHPUT BIOLOGY

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High-throughput biological assays such as microarrays let us ask very detailed questions about how diseases operate, and promise to let us personalize therapy. Data processing, however, is often not described well enough to allow for exact reproduction of the results, leading to exercises in “forensic bioinformatics” where aspects of raw data and reported results are used to infer what methods must have been employed. Unfortunately, poor documentation can shift from an inconvenience to an active danger when it obscures not just methods but errors. In this report, we examine several related papers purporting to use microarray-based signatures of drug sensitivity derived from cell lines to predict patient response. Patients in clinical trials are currently being allocated to treatment arms on the basis of these results. However, we show in five case studies that the results incorporate several simple errors that may be putting patients at risk. One theme that emerges is that the most common errors are simple (e.g., row or column offsets); conversely, it is our experience that the most simple errors are common. We then discuss steps we are taking to avoid such errors in our own investigations.

Annals of Applied Statistics

Reference: http://projecteuclid.org/euclid.aoas/1267453942
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Box: How events unfolded

From the article:

**Cancer trial errors revealed**

2006 Anil Potti, a cancer geneticist at Duke University in Durham, North Carolina, and others file patent applications on the idea of using gene-expression data to predict sensitivity to cancer drugs. Potti is first author on a paper in *Nature Medicine*.1

2007 Potti is last author on a paper in the *Journal of Clinical Oncology (JCO)*.2 Duke begins three clinical trials to test Potti’s predictors in patients with breast or lung cancer.

**SEPTEMBER 2009** Keith Baggerly and Kevin Coombes, statisticians at the University of Texas M. D. Anderson Cancer Centre in Houston, publish a paper in *Annals of Applied Statistics*3 stating that they could not replicate Potti’s claims. Duke suspends the trials and asks a review panel to investigate.

**NOVEMBER 2009** Potti places data underlying the *JCO* paper online. Baggerly writes to Sally Kornbluth, Duke vice-dean for research, and Michael Cuffe, Duke vice-president for medical affairs, to point out differences from raw data.

**DECEMBER 2009** An unredacted copy of the report by Duke’s review panel, later obtained by *Nature*, shows that the panel replicated Potti’s claims using his data, but were unaware that those data contained discrepancies.

**JANUARY 2010** Duke restarts clinical trials.

**JULY 2010** The *Cancer Letter* reveals that Potti made false claims about his CV. Trials are suspended and an investigation begins. Harold Varmus, director of the National Cancer Institute in Bethesda, Maryland, asks the Institute of Medicine to review Duke’s trials.

**NOVEMBER 2010** *JCO* paper is retracted. Duke closes the trials permanently. Potti resigns.

**DECEMBER 2010** Institute of Medicine study begins, but will now focus more generally on criteria for genomics predictor.

**JANUARY 2011** *Nature Medicine* paper is retracted.

Second Potti suit filed against Duke

By Julian Spector on September 23, 2011

Two lawsuits have now been filed in Durham Superior Court against Duke University, Duke University Health System and other members of the Duke Medicine community.

Former patients of discredited Duke cancer researcher Anil Potti have filed complaints in early September. The first suit was filed by eight joint plaintiffs Sept. 7. A second suit, was filed the same day by a single plaintiff—breast cancer patient Joyce Shoffner of Wake County.

Lawyer Robert Zaytoun of Raleigh, N.C. filed the 82-page lawsuit on behalf of Shoffner. The suit states that in seeking treatment for breast cancer, Shoffner participated in clinical trials based on the research of Anil Potti.

“There is a lot of common information alleged in the [two] complaints,” Zaytoun said. “The reason for that is there is already a lot of information already out into the public domain about the faulty nature of much of the research at Duke University.”
When is Reproducibility an Ethical Issue? Genomics, Personalized Medicine, and Human Error

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BIRS Workshop, Aug 14, 2013

Reference: http://www.birs.ca/events/2013/5-day-workshops/13w5083/videos/watch/201308141121-Baggerly.mp4
GROWTH IN A TIME OF DEBT

Carmen M. Reinhart
Kenneth S. Rogoff

Working Paper 15639
http://www.nber.org/papers/w15639

http://goo.gl/HP69Rb
Error?

Does High Public Debt Consistently Stifle Economic Growth? A Critique of Reinhart and Rogoff

Thomas Herndon*    Michael Ash    Robert Pollin
April 15, 2013