

Article Review: Will Genetics Revolutionalize Medicine?

Holtzman NA and TM Marteau. 2000.
New England Journal of Medicine. 343:141-144.

Background

- New England Journal of Medicine:
“Sounding Board articles are opinion essays. They are similar to editorials but are not tied to a particular article. They often present opinions on health policy issues and are normally unsolicited. The text is limited to 2000 words.”
- This article is 7.5 years old, so some specifics may be outdated

Background

- Neil A. Holtzman, M.D., M.P.H., is professor of pediatrics at the Johns Hopkins University School of Medicine. He holds joint appointments in Health Policy and Epidemiology at the Johns Hopkins School of Hygiene and Public Health and is director of Genetics and Public Policy Studies at the Johns Hopkins Medical Institutions.
http://www.press.jhu.edu/books/title_pages/2203.html
- Theresa Marteau, Professor of Health Psychology, Psychology and Genetics Research Group, King's College London
<http://www.medschl.cam.ac.uk/gppcru/Collaborators.htm>

Prior Claim

- “Within the next decade genetic testing will be used widely for predictive testing in healthy people and for diagnosis and management of patients...The excitement in the field has shifted to the elucidation of the genetic basis of the common disease.”
(John Bell, 1998)

Assertions from Authors

- “Mapping and sequencing the human genome will lead to the identification of more genes causing mendelian disorders and to the development of diagnostic and predictive tests for them.”
- “The development of safe and effective treatments will usually lag behind...”
- “The new genetics will not revolutionize the way in which common diseases are identified or prevented.”
- “Most people will have little interest in learning their genotypes...”

Penetrance

- Most genotypes for common disease are less penetrant (low correlation between genotype and phenotype)
- Frequently occurring genotypes ($\geq 1\%$) unlikely to have high penetrance for diseases that reduce reproductive fitness (unless heterozygosity counterbalances)
- Possible gene-gene interactions and gene-environment interactions may cause challenges for statistical analysis

Treatment

- If a single locus causes susceptibility to a disease, gene-therapy treatments may be feasible (but success has been limited)
- What if 2, 3, or more loci work together to cause susceptibility?
- Prophylactic treatments and monitoring
- Personalized drug treatments based on genotypes holds promise; however, low penetrance presents challenges

Magnitude of Risks

- Positive predictive value will be high only for rare genotypes that confer a high relative risk
- Rare genotypes—even with high relative risk—account for a small proportion of overall disease risk
- Common genotypes with high relative risks may account for a large proportion of disease risk; however, PPV will be low
- Tests should be used sparingly

Public Interest

- Interest in genetic testing may be low if sensitivity and/or PPV are low or when no treatment is available
- Potential for false sense of security
- Potential for apathy or despair when behavior thought to be irrelevant
- Modifying social structure, lifestyle, and environment may have greater impact on public health

Current Status

- Genetic tests are commonly available for BRCA1/BRCA2 (breast cancer) and mismatch-repair genes (hereditary non-polyposis colon cancer)
- New breast-cancer genes identified in 2007 (common but low relative risk)
- GeneTests.org references testing for 1219 diseases (for clinical purposes)
- Personal genetic tests are now offered to consumers

Current Status

“At this stage, it is unlikely that these SNPs will be appropriate for predictive genetic testing, either alone or in combination with each other. However, as further susceptibility alleles are identified, a combination of such alleles together with other breast cancer risk factors may become sufficiently predictive to be important clinically.”

Relevance to Informatics

- Disease-gene mapping is an Informatics discipline (at Utah)
- Clinical testing for susceptibility to genetic diseases requires Informatics tools to analyze large amounts of data (*translational informatics?*)
- Informatics tools could help consumers and physicians track disease susceptibility as research advances

Relevance to My Research

- If my goal is to use an individual's genetic profile to predict disease risk, I would prefer my solutions apply to common, complex diseases (to help as many people as possible)
- If current approaches are not adequate, an exciting research area is to find better ways to do this

Questions / Discussion

- What do you think of the article / assertions / conclusions?
- Is the emperor wearing clothes?
- Which obstacles, if any, have already been overcome?
- Which obstacles still exist, and how might they be overcome?
- Under what circumstances would you pay \$1000 for genetic testing?