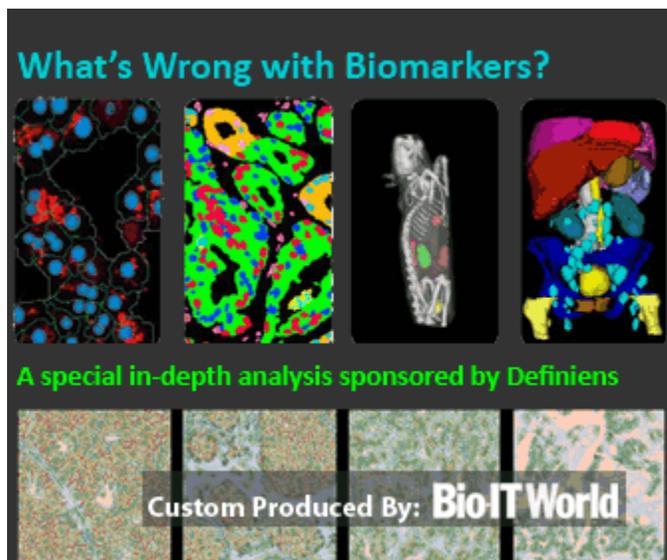


A REVEALing Study on Genetic Testing for Alzheimer's Disease



By Kevin Davies

July 16, 2009 | During a panel discussion at last year's Bio-IT World Expo, the Editor-in-Chief of the *New England Journal of Medicine*, Jeffrey Drazen, an early skeptic of the predictive power of personal genomics, outlined what steps he needed to see from the genetics community. "I'm from Missouri, and you have to show me," Drazen said. "You've got to do the study that shows that making a difference in [genetic] knowledge will make a difference in how people behave."

Drazen added, "We're not there yet... I wish you good luck, and send me your papers when you show that it works!" Sitting in the audience, Boston University neurologist Robert Green gladly seized the opening and informed Drazen he was preparing to submit just such a manuscript.

That paper, presenting the findings of the REVEAL (Risk Evaluation and Education for Alzheimer's Disease) study, is finally published in the *Journal* this week. It represents a milestone in judging the public's attitude to—and ability to cope with—the sometimes adverse results of personal genetic testing.

Green's group set out to examine attitudes of people with a family history of Alzheimer's disease to learning their all-important APOE genotype. The apolipoprotein E (APOE) gene on chromosome 19 is a well-known predictor of Alzheimer's risk. Individuals who inherit one copy of the $\epsilon 4$ allele have a 2-3 fold relative risk of the disease, whereas $\epsilon 4$ homozygotes have around a 15-fold greater risk.

The study was actually performed between 2000 and 2003. Green and his colleagues enrolled 162 adults who had one or both parents diagnosed with AD. All received counseling information before the trial began. 111 were told their APOE genotype, whereas 51 remained as controls in the nondisclosure group. Of the 111 individuals tested, 53 were heterozygous or homozygous for the $\epsilon 4$ allele.

Green and colleagues found few if any differences between the two groups with regard to the individuals' levels of anxiety, depression or distress, even up to one year after the study. "Subjects who learned they were $\epsilon 4$ positive... showed no more anxiety, depression or test-related distress than those who did not learn their genotype," the authors write. (There was a slight short-term but transient increase in anxiety in the $\epsilon 4$ group.) The individuals that showed the most dramatic, or clinically meaningful, changes in psychological profile were spread evenly between the control group and the disclosure group (regardless of $\epsilon 4$ carrier status).

Despite the lengthy genesis of the study, there are inevitably shortcomings. As Green et al. note, "If APOE genotyping had been provided without genetic counseling or to subjects who had no family history of Alzheimer's disease, the results might have been different. In addition, the exclusion of subjects with low neurocognitive scores and high depression scores may have influenced the results."

Some of those caveats are amplified in an accompanying editorial by the University of Minnesota's

Rosalie and Robert Kane. They praise REVEAL as a “rare and welcome trial of a process that might inform ethics guidelines,” but wonder whether more negative outcomes might have been seen if the subjects had been more prone initially to anxiety or depression, or less educated, or if the study had been continued for a longer time. What would be the reaction if a subject forgot a name or saw a close relative succumb to the disease? Kane and Kane see little reason to advocate widespread APOE testing now, but as treatments improve in years to come, “perhaps the social effects of genetic testing will be less worrisome by the time a clinical rationale for the test becomes apparent.”

While advocating more expansive follow-up studies, nevertheless, Green’s team draws satisfaction from the REVEAL findings that disclosing genotyping information to individuals who test negative is beneficial, and causes only transient, modest distress to those who end up testing positive. “These data support the psychological safety of disclosing data regarding genetic-counseling protocols” to Alzheimer’s family members, “despite the frightening nature of the disease and the fact that the disclosure has no clear medical benefit.”

One of the most dramatic results Green and colleagues have observed was not included in the published study. As he reported last year at the American Society of Human Genetics conference, people who learned they were ε4 positive were several times more likely to purchase long-term care insurance. Not surprisingly, this does not sit well with many in the insurance industry, who “are thinking very hard about whether they can offer this product without requiring ε4 testing.”

*Green, R.C. et al. “Disclosure of APOE genotype for risk of Alzheimer’s disease.” New England Journal of Medicine 361, 245-254; July 16 2009.

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