

GENOMIC MEDICINE

What Should We Do With Carrier Screening?

Screening for preclinical disease is a core feature of primary care medicine. On a busy day, we usually do this without much conscious thought. For example, we take blood pressures and measure developmental milestones. Often, we are measuring a proxy for the individual's propensity for developing a more serious future condition, and it is reasonably easy to justify the value of the test versus its attendant risks.

In screening for genetic disorders the rationale is essentially the same: testing an asymptomatic individual for a silent (or at least subclinical) DNA variation in order to prevent or mitigate a future harm. However, in carrier screening for recessive genetic disorders, the future harm is not the screened individual's risk of illness but rather a potential risk to the individual's potential offspring. In this setting, the risk/benefit analysis is far more complex. Currently, there are no carrier screening programs that are offered on a wide population basis across the United States.

In the United States, we do offer targeted carrier testing in a specific subpopulation: pregnant women. In fact, these individuals are further differentiated by ethnicity in order to screen for disorders such as sickle cell disease, cystic fibrosis, and the thalassemias. Guidelines from the American College of Obstetricians and

Gynecologists state that cystic fibrosis screening should be offered to European Caucasians and Ashkenazi Jews. Given the extensive admixture among racial and ethnic groups in the United States, determining who qualifies for these types of guidelines is problematic from a clinical standpoint. Perhaps most important, the prenatal period is not the ideal time for patients to find out that their offspring might be affected by a serious genetic condition, since options may be limited to termination or to preparing to have an affected child, which can devastate a family, in the case of severe disorders.

Given that advances in genomic technologies are rapidly lowering the costs of screening for a vast array of recessive genetic disorders, is there a role for population-wide carrier screening at a more appropriate period in an individual's life? Certainly providing individuals with an idea of their carrier status outside of pregnancy allows them many more reproductive options, including choosing not to have children, assisted reproductive technologies, adoption, and, in some very specific settings, avoidance of prospective partners who are carriers for the same disorder.

The National Human Genome Research Institute recently cosponsored a conference on carrier screening entitled, "Population-Based Carrier Screening for

Single Gene Disorders: Lessons Learned and New Opportunities." The conference was attended by a wide range of stakeholders including primary care groups, medical geneticists, lab scientists, patient advocates, commercial testing companies, public health officials, and insurers. As is often the case in emerging areas of medical applications of new technologies, the conference identified more questions than it answered.

An underlying theme of the conference was the fact that we are quickly developing the ability to test large numbers of patient samples for many different genetic variants, including carrier status for recessive conditions, and at very low cost. Specific applications, such as screening for disorders like fragile X syndrome and spinal muscular atrophy, may be nearly ready for scaling to a population level.

Already, direct-to-consumer marketing of genome-wide scans for genetic markers of disease may provide (somewhat unintentionally) insights on recessive genetic conditions in a way that short circuits the traditional informed consent process.

Several speakers outlined experiences dating back to the 1960s with screening programs targeted to specific subpopulations with high prevalence of disease. For example, Tay-Sachs screening has been well received among some Ashkenazi Jewish populations in this country. This experience contrasts sharply with that of black populations targeted by early carrier screening programs for sickle cell disease. These programs, often poorly conceived

and executed, resulted in feelings of stigmatization and disenfranchisement, and a lingering hesitation to engage with the genetics community on a variety of issues.

Several prerequisites for future carrier screening programs were identified at the conference. First, the success of any carrier program fundamentally is tied to an understanding of the preferences of the population. Engaging populations (and ideally including their health care providers) as stakeholders will be key to determining which disorders are candidates for screening and by what yardstick success of the programs should be measured. Second, extensive education of the public, health care providers, and policy makers will be required to establish any effective program. Finally, given the current emphasis on evidence-based medicine, any new screening program should, from the outset, include mechanisms to measure its effectiveness.

Low-cost carrier screening for recessive genetic conditions on a population basis is becoming technically feasible for a wide range of conditions. The hard work will be deciding what we, as a society, want to do with the science. ■

DR. FEERO is a family physician with a doctorate in human genetics from the University of Pittsburgh. He is a senior adviser for genomic medicine in the Office of the Director at the National Human Genome Research Institute. Send comments to fpnews@elsevier.com.



BY GREG FEERO,
M.D., PH.D.

OncoVue Shown to Rival Gail Model on Cancer Risk Prediction

BY BRUCE JANCIN
Denver Bureau

SAN ANTONIO — A novel test for prediction of an individual's breast cancer risk that incorporates gene-based information along with clinical and lifestyle data significantly outperformed the widely used Gail model in a validation study.

The test, known as OncoVue, utilizes data from a patient questionnaire along with DNA from buccal cells obtained by a mouthwash rinse. The cells are genotyped for 22 single nucleotide polymorphisms (SNPs) located on 19 genes believed to influence breast carcinogenesis. Most of these genes are concerned with steroid hormone synthesis, signaling or metabolism, and DNA repair, Eldon R. Jupe, Ph.D., explained at the annual San Antonio Breast Cancer Symposium. Dr. Jupe is vice president for research at InterGenetics Inc., the Oklahoma City-based developer of OncoVue.

Last July, the Food and Drug Administration authorized commercialization of OncoVue while holding off on formal approval as agency officials deliberate over how best to regulate the emerging

field of molecular testing for cancer risk. At present, OncoVue is offered at 18 U.S. cancer centers at an out-of-pocket cost to patients of \$397. There is no insurance coverage as yet, since the test hasn't received FDA approval.

"We're actively recruiting additional qualified cancer centers with experience in breast cancer risk assessment for our risk testing network," Dr. Jupe said in an interview.

The OncoVue predictive algorithm was developed by applying multivariate logistic regression techniques to a decade-long case-control study involving 5,022 U.S. women, 1,671 of whom developed breast cancer. Through this process, a list of 117 common candidate SNPs was whittled down to the 22 ultimately incorporated in the test.

Dr. Jupe presented at the meeting a validation study in which he compared the risk-prediction performances of OncoVue and the Gail model in 400 women who developed breast cancer and 393 age-matched controls who did not. OncoVue correctly placed more cases and fewer controls in the elevated-risk group. The novel test provided a 62% improvement over the Gail model. ■

Group Advises Against Using Test to Predict Possible Response to SSRIs

BY ALICIA AULT
Associate Editor, Practice Trends

Increasingly possible to determine how patients will likely metabolize antidepressants, including selective serotonin reuptake inhibitors—and thus whether they are more or less likely to benefit from the drugs or to experience side effects. But at least one group is recommending against routine testing at the moment.

The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group evaluated cytochrome P450 testing and concluded that the evidence does not support its widespread and routine use in patients starting treatment with SSRIs.

EGAPP is an independent body supported by the Centers for Disease Control and Prevention. The Agency for Healthcare Research and Quality commissioned the EGAPP Working Group to systematically review the research on P450 testing. The group published its conclusions in December in *Genetics in Medicine* (Genet. Med. 2007;9:819-25).

The CYP450 enzymes belong to a superfamily of genes, usually expressed in

the liver, that are involved in the metabolism of 90% of drugs, including SSRIs. Three are particularly important: CYP2D6, CYP2C19, and CYP2C9. Variants (allele or polymorphisms) of these genes play a role in determining how a drug is metabolized.

The Working Group aimed to determine whether testing would lead to improvement in outcomes, or whether the results might be useful "in medical, personal, or public health decision making."

CYP450 testing is available through "home brew" diagnostics at clinical labs. Eight U.S. labs offer the Food and Drug Administration-approved Roche AmpliChip CYP450 diagnostic. AmpliChip measures CYP2D6 and CYP2C19 polymorphisms and divides patients into four phenotypes: poor metabolizers, intermediate metabolizers, extensive metabolizers, and ultrarapid metabolizers. The test costs \$500, but is not generally covered by insurance.

After analyzing the literature, the Working Group determined that available assays have high sensitivity and specificity for common CYP450 polymorphisms, but that studies did not "consistently identify an association between genotype and clinical response to SSRI treatment." ■