Carrying Carrier Screening Into the Future

Screening for pre-clinical disease is a core feature of primary care medicine. On a busy day, we usually do this without much conscious thought – for example, taking blood pressures or measuring developmental milestones. Often, we are measuring a proxy for the individual's propensity for developing a more serious future condition, and the value of the test versus its attendant risks are reasonably straightforward to work out. 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 much more complex. Currently there are no carrier screening programs that are offered on a wide population basis across the United States.

In the U.S. we do offer targeted carrier testing in a specific sub-population: pregnant women. In fact, these individuals are further differentiated by their ethnicity for screening for disorders such as sickle cell disease, cystic fibrosis and the thalassemias. For example, the American College of Obstetrics and Gynecology cystic fibrosis screening guidelines 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 importantly, the prenatal period is not the ideal time for a patient to find out that their offspring might be affected by a serious genetic condition, as options are frequently limited to preparing to have an affected child, which for severe disorders can be devastating to a family, or termination.

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.

To examine these issues in light of rapidly decreasing costs for high throughput testing technologies, the National Human Genome Research Institute recently co-sponsored 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.

What were some of the main themes of the conference? We are rapidly developing the ability to test large numbers of patient samples for large numbers of genetic variants,

including carrier status for recessive conditions, at very low cost. Specific applications such as screening for disorders like fragile X 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.

As the conference progressed, the discussion of attendees moved from being focused on "what can we do?" to "what should we do?" in terms of carrier screening. Several speakers outlined past experiences dating back to the 1960's with screening programs targeted to specific sub-populations with high prevalence of disease. For example, Tay-Sachs screening has been well received among some Ashkenazi Jewish populations in the U.S. This experience contrasts sharply with that of African-American 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 lingering hesitation to engage with the genetics community on a variety of issues.

Several prerequisites for future carrier screening programs were identified by conference attendees. First, the success of any carrier program is fundamentally tied to an understanding of the preferences of the population – which might be as broad as the entire U.S. Engaging populations (ideally including their health care providers) as stakeholders will be a key to determining which disorders are candidates for screening and by what yardstick success of the programs should be measured. It is unclear if any forum currently exists that would allow broad engagement of the U.S. population on a topic of this complexity. Second, extensive education of the public, health care providers, and policymakers 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 do with the science.