Point/Counterpoint

Point: Genetic Risk Feedback for Common Disease—Time to Test the Waters

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Genetic research is yielding bounties of significant gene-disease associations (i.e., common allelic variations associated with increased risk of common health conditions). Whereas these studies will face issues of reproducibility and generalizability for some time to come, such “genetic risk markers,” supported by a large and convincing body of evidence, are clearly beginning to emerge (1-4). Given that such “validated” markers will become part of our knowledge base, our next challenge is easy to anticipate. How might we use this knowledge to guide the design of interventions that will improve public health? At the outset, the clinical utility of these markers will not be known. The path to decide which markers make sense in terms of clinical utility must pass through research. As new risk markers are discovered, this research will include investigation into new areas of biology and may lead to new pharmacologic interventions. Nevertheless, despite the excitement over genetic risk research, diseases presenting the greatest public health burden—heart disease, diabetes, and many cancers—can be prevented “simply” by altering lifestyle behaviors. However, as any who have tried know, motivating such behavior change is far from simple.

A looming question then is how might individualized genetic risk information be integrated with established behavior change interventions to improve health? Answering this and other important and related research questions will require us to inform individuals about their genetic risk. Providing such genetic risk results to subjects as part of research protocols is currently a hotly debated topic [see the American Journal of Bioethics Nov-Dec 2006 edition] because most genetic markers under study have uncertain clinical significance (5).

We add to this debate by suggesting that although the field is immature, now is the critical time to be evaluating the effects of genetic risk communications, undoubtedly characterized by ambiguity and small disease risk associations, on important health outcomes. However, before we take this argument further, let us be clear: we are not advocating the wholesale return of any and all genetic information. Clearly, genetic markers chosen for feedback should meet some standard of evidence for association. Moreover, we agree with others that feedback based on disease-associated genetic markers with uncertain clinical utility (6) should only be available in the context of research studies. This ensures the added protections of standardized informed consent and Institutional Review Board review.

That said, we submit that research, earlier rather than later, into the perceived benefits of and response to test feedback is essential to maximize the likelihood that future genetic technologies will result in public health benefit. Evaluation of the effects of feedback of genetic susceptibility to common diseases on psychological and behavioral outcomes has been based on analogue studies wherein participants are asked to imagine that they have undergone actual testing and anticipate how they might respond (7). These hypothetical genetic testing scenarios have been associated with reports of increased motivation to adopt health recommendations. Yet, the few studies to evaluate actual feedback have not shown improvements in health behaviors and accurate understanding of feedback is not always achieved (8). Thus, evaluating hypothetical testing scenarios may not be very informative for understanding the effects of feedback on preventive behaviors or use of other health services.

The majority of what we know about behavioral responses to actual genetic susceptibility testing for common diseases has been confined to hereditary breast and colon cancer syndromes for which valid genetic tests are available and whose relative risks are high (up to 80% increased lifetime risk). Studies evaluating genetic testing for these syndromes suggest that individuals do not consistently respond “rationally” to test results by accepting the meaning of such feedback and adopting associated health recommendations. One must also consider that risk associations for the variants that are expected to influence common disease risk will be substantially lower, closer to 20% to 30%. Thus, understanding the potential clinical utility of future genetic testing will require us to evaluate whether target populations perceive any benefits to such testing, how best to communicate results to those interested in testing, and whether communicating modest gene-disease risk associations improves important health outcomes.

Additionally, Khoury et al. (9) point out that genetic susceptibility testing will have the greatest potential for public health benefit when we can simultaneously test for multiple-risk alleles that have modest joint effects. To date, the research on genetic risk communication has

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been focused exclusively on communicating risk based on single gene polymorphisms. Thus, we have no information about how target populations might respond to feedback on multiple risk alleles and multiple diseases. Conveying genetic susceptibility test results for such multiplex genetic testing is likely to face many challenges. The development of feedback approaches that are comprehensible, not contradictory, and might motivate positive behavior change will require systematic and rigorous research. This research could lead to evidence-based communication approaches before testing becomes clinically available. The recent Institute of Medicine report that nearly half of Americans lack the skills needed to evaluate the risks and benefits of health-related technologies makes it especially important to anticipate and begin this line of research (10).

A pressing practical impediment to beginning this research is deciding what the standards should be for providing genetic test results? Several national expert panels have suggested that returning results to subjects is appropriate in the context of the research. When “the findings are scientifically valid and confirmed, the findings have significant implications for the subject’s health concerns, and a course of action to ameliorate or treat these concerns is readily available” (6). However, these criteria do not lend themselves to easy interpretation or implementation. For example, is scientific evidence sufficient when gene-disease associations have been replicated in large studies or in meta-analyses? Many would argue that even this standard is not rigorous enough because research is ongoing and new findings may result in reversals of some of these associations. Similarly, some accepted standards, such as the convention that relative risks approach or exceed 2.0 to indicate significant association, are higher than what we can expect to find for many common disease-genotype associations (relative risk, 1.1-1.3; ref. 11).

Admittedly, accepting the current state-of-the-science and lower relative risks characterized by common diseases increases the uncertainty of risk estimates to be conveyed to research participants. However, most would agree that these limitations will persist even as we learn more about how gene-gene and gene-environment interactions contribute to disease risk. We submit that knowing whether genetic test results can be understood and be used to improve health outcomes is critical to objectively and thoroughly evaluate clinical utility. The importance of these questions could justify including genetic test feedback in research protocols when evidence of risk associations is based on meta-analyses or several large studies. Indeed, such experimental tests would optimally characterize and enable us to anticipate the very challenges of communicating the future genetic test results that are likely to emerge.

Likewise, how do we consider the expert-recommended standard that feedback of genetic test results must have significant implications for the subject’s health concerns and a course of action to ameliorate or treat these concerns? As we said earlier, progress toward our cancer prevention goals will rest heavily on effectively promoting population-level health behavior change. To this end, there is a growing armamentarium of evidence-based interventions to reduce risk for common cancers and other diseases for which genetic susceptibility testing might become available. The burning research question is whether genetic susceptibility feedback targeted to healthy individuals will motivate them to access these interventions and services and/or engage in healthy lifestyles. Paradoxically, answering this question does not require that health recommendations be tailored to an individual’s genetic test results (which clearly the science would not yet support). Thus, recommendations to adopt accepted cancer prevention guidelines present no harm to but great potential benefit for target groups.

Taken together, whereas it is clear that genetic susceptibility testing has yet to meet the rigorous standards for clinical utility, we submit that this standard can only be reached by starting research now into all the elements required for clinical utility. Waiting until we can devise a technically perfect, clinically valid test to learn that patients and physicians do not understand or respond to it in appropriate ways will not advance the field. We know this all too well in the area of cancer where procedures like colonoscopy with well-established clinical utility remain unacceptable to sizable proportions of our target audiences, whereas others with questionable clinical utility such as prostate-specific antigen testing enjoy popular appeal (12).

Thus, we argue that if we are to develop genetic susceptibility testing and feedback approaches with the potential to be clinically useful and feasible for use in primary care settings, we must put forth our best scientific effort to create credible, prototypic genetic tests. Of critical importance to this process is to systematically consider where the evidence for genetic feedback arguably is weighty enough that a researcher could convey a risk message to research subjects. Whereas we acknowledge that this information will be complicated and caveats will abound, the risk of confusion is likely to be no greater than that experienced in daily exposure to competing and ambiguous health messages conveyed to individuals every day. Whether this information is useful or contributes to health benefit is an open question, one that will remain unanswerable until rigorous social and behavioral research can be conducted. Indeed, this research should be conducted in as close to real world circumstances as feasible. The alternative to this research is likely to be piecemeal and nonsystematic introduction of genetic tests directly into clinical practice or via direct-to-consumer marketing (e.g., nutrigenomics). These situations will only make it harder to determine if any of these tests have potential to improve health.

References
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