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## Putting science over supposition in the arena of personalized genomics

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In this Commentary, we explore the process of going from genome discovery to evaluating medical impact and discuss emerging challenges faced by the scientific community. The need to confront these challenges is heightened in a climate where unregulated genetic tests are being marketed directly to the general public.<sup>1,2</sup> Specifically, we will characterize the delicate balance of deciding when genomic discoveries such as gene-disease associations are “ready” to be evaluated as potential tools to improve health. We will recommend that a considerable research commitment is needed now if we are to successfully bridge the rapidly widening gap between gene-disease association research and the critical (but slower and more involved) investigations into public health and clinical utility. Lastly, we will describe a large, ongoing early phase research project, the Multiplex Initiative, which is examining issues related to the utility of genetic susceptibility testing for common health conditions.

### The state of the discussion

With the completion of the sequence of the human genome, scientific experts have characterized a rapidly approaching future in which genomic risk information might be used by individuals and health care providers to facilitate decision-making, personalize treatment, motivate lifestyle improvements and adherence to screening recommendations. However, skeptics submit that it will take decades to unravel the gene-by-gene and gene-by-environment interactions underlying common disease and that this understanding is needed before personalized health recommendations regarding disease prevention and risk reduction can be provided.<sup>3,4,5</sup>

Ironically, this debate about whether and when genomic discovery will yield tangible public health and clinical benefits at costs society can afford echoes the spirited debate over the wisdom of investing public research funds into the Human Genome Project (HGP).<sup>6</sup> This debate shaped the way that the HGP was implemented. Proponents and opponents exchanged views and opinions were converted into hypotheses and benchmarks. Strategies shifted iteratively as data were accumulated; these data, not polemics, caused many to shift from Genome Project critic to supporter.<sup>7</sup>

In the case of this latest debate, advances in genetic technology have introduced capabilities that critics argue may be pressuring us to put the proverbial cart before the horse. The number of single nucleotide polymorphisms (SNPs) that can be reliably scored in a single experiment continues to climb, while the price per genotype has declined by several orders of magnitude.

This combination of power and economy has led to a flood of genome-wide association studies.<sup>8</sup> Unfortunately, as this technology is moving forward swiftly, the foundation needed to understand the public and clinical utility of these risk markers lags behind.<sup>9</sup>

At the center of the debate (and a significant challenge to initiating research aimed at evaluating the utility of such testing) is the need to return genetic test results to individuals and populations. Many scientists are uncomfortable providing genetic test results when there are no specified robust standards for declaring a genetic association as a “true positive”, especially in the context of clinical decision-making. Such standards could be in the form of gene-disease associations that achieve genome-wide significance (i.e.,  $p < 10^{-7}$ ) in multiple studies, sometimes involving more than 10,000 cases and controls. Evidence could also accrete through repeated replication in a series of small studies tied together via a meta-analysis. Regardless of the specified standard, we expect that gene-disease associations will become widely accepted in the near future.<sup>10</sup>

### Striking a delicate balance: The transition from genomic discovery to translational research

Questions regarding the use of these new technologies to perform genetic tests (and deliver the results directly to individuals) came into sharp focus recently. Several companies began marketing direct-to-consumer tests designed to provide individuals with estimates of their disease risk for a subset of common and rare disorders, based on their genotypes. What sets these new, commercial tests apart from single-gene, single-condition tests is the vast number of genotypes provided directly to individuals. In contrast to Mendelian conditions, the risk associated with complex disease genes are modest. There is a paucity of research on how best to present the latter risk information to individuals, families, and health care providers. Despite this, at least three companies (23andMe, deCODE Genetics, and Navigenics) are using high-density SNP arrays; a fourth (Knome), is offering complete genome sequencing to consumers who seek a personal genetic profile. The launch of these enterprises has prompted important questions with relevance to both the clinical and behavioral arenas.<sup>10</sup>

The marketing of these tests is based on the assumption that obtaining personal genetic information may have value to the general public. Arguably, direct marketing of genetic testing empowers the consumer by maintaining privacy of such information, thus addressing widely documented concerns about the potential for discrimination by health insurers<sup>11</sup>, and is consistent with beliefs about the inherent right of individuals to control personal health information. However, this marketing (and the consumer curiosity that it generates) is occurring against a backdrop of increasing media interest in new genetic discoveries, including near-weekly pronouncements of “the discovery of the gene for” a particular health condition.

Understandably, this public rhetoric raises expectations about the value of genetic risk information. It is reasonable, then, to raise questions about what *segments* of the population would avail themselves of such testing and how information that previously has not been available to the public might be interpreted and used by different subgroups. Concern also has been raised that inequities in access to these new technologies could exacerbate existing health disparities. The current lack of data needed to address these and other questions about genetic susceptibility testing for common health conditions makes it easy to speculate about such testing having positive, neutral, or negative influences on individuals, health care providers, families, communities, and society as a whole.

Those holding positive views assert that personalized genetic risk assessment could revolutionize medicine, bringing broad benefits to individuals, health care delivery, and the overall health of the population. The skeptics submit that the biology underlying these gene-

disease risk estimates will be unclear or complex and that giving test results to individuals will result in confusion or, worse yet, create unnecessary concerns or provide false reassurances. They also point to the mixed success of current risk communications based on elevated cholesterol, blood pressure, and other biomarkers in motivating behavior change.<sup>12</sup> The added demands of appropriate counseling and referral placed on already-burdened health care providers likely will be an impediment to genomic-informed changes in the standard of care. Moreover, health care providers do not now consistently discuss with their patients evidence-based preventive recommendations for diet, physical activity, or smoking cessation – all of which are unambiguous risk factors for the majority of common health conditions.<sup>13</sup> These recommendations are relatively well-understood and endorsed by the public as avenues for improving health. This leaves skeptics wondering whether more “risk” information will improve the dialog between health care providers and patients.

### Debate shapes science, science settles debate

Each of the above arguments, both pro and con, could be posed as research questions and testable hypotheses. However, no single experiment or project can answer the question of public or clinical utility, and many studies will be required before such genetic tests can be declared “useful.” Thus, a targeted research program to support translational genomics is called for. The Centers for Disease Control's funding to support programs in policy, surveillance, or education related to genomic tests, family history, and other genomic interventions is a good example of the kind of vision needed to evaluate genomic products' potential to improve health (<http://www.cdc.gov/od/pgo/funding/GD08-801.htm>). In developing such a research agenda, scientists must acknowledge the certainty that our current knowledge base will change, and they will need to anticipate both the speed and nature of this change. This is not simply a theoretical issue – economies of scale may lead to studies where individuals are tested for hundreds of thousands of SNPs; this, in turn, will raise additional research questions and testable hypotheses. For example, how will these changes affect what we know about SNPs associated with disease in a year's time? How will advances in whole-genome sequencing methods change the nature of risk assessment? We need not wait for the future to begin answering these questions; the goal is to frame critical research questions *now*, in a way that the results will continue to be applicable as science and technologies evolve.

Posing high priority research questions about the social and behavioral implications of genetic susceptibility testing amidst (and in step) with scientific discovery could aid in shaping genetic risk assessment products. What types of conditions or diseases should be included in research testing? How should we educate individuals about the limitations of genetic testing so they can make informed decisions about participating in research or purchasing a commercially available genetic test? How should we transmit genetic test results in ways that are both understandable and placed in the appropriate context? How will an individual's interpretation of their test results evolve through time? What is the potential impact on the lives of individuals receiving these test results? Will knowing that an “at risk” allele is segregating within a family impact family interaction? As new information on genetic variants is obtained, what would be the best way to inform individuals that the state of science has changed?

The research questions suggested above have the social and behavioral implications of genomics as their fulcrum. However, addressing these questions will require trans-disciplinary collaborations – what Elias Zerhouni, the Director of the National Institutes of Health, has labeled “research teams of the future” – that involve cross-talk and information integration across a broad array of disciplines.<sup>14</sup> These teams must include social scientists, clinicians, epidemiologists, biologists, psychologists, ethicists, and health service researchers to gain an interdisciplinary perspective on the potential impact of genomic risk profiling on important public health outcomes.

Indeed, consider the question about whether multigenic risk feedback will be useful in motivating health improvements or simply confuse those receiving the results and their health care providers. The expertise of human geneticists and epidemiologists is needed to evaluate the evidence base and select markers of sufficient significance to develop a research prototype of a credible test battery. Yet, those involved in the process of selecting appropriate risk markers also must consider what has been learned from decades of social and behavioral research into risk communication and what it takes for specific audiences to understand and accept health-related information.<sup>15,16,17</sup> This is especially relevant in light of the Institute of Medicine report on health literacy<sup>18</sup> showing that nearly half of Americans lack the skills needed to evaluate the risks and benefits of health-related technologies; genomics could raise the bar even higher.

Integrating genetic susceptibility risk feedback into existing preventive interventions also suggests research questions that could be considered now by transdisciplinary research teams. Previous social and behavioral research in developing and evaluating behavior change interventions for risk reduction has indicated that achieving long-term behavior change is extremely difficult<sup>13</sup>, suggesting that genetic susceptibility feedback is unlikely on its own to result in behavior change, and behavioral impact may differ by disease and attributable risk inferred.

Questions about whether genetic susceptibility testing might create efficiencies in health care delivery that reduce cost without compromising care also could be considered now. For example, it is worth considering whether genetic testing increases patient receptivity to provider recommendations, or allows providers to do more preventive counseling with those found susceptible, or both. To date, studies of genetic testing modalities for Mendelian-inherited conditions (e.g., familial breast and colon cancer syndromes) has been conducted in specialized-care settings, where certified genetic counselors provide one-hour sessions to communicate test results and support patient decision-making. This research tells us little about how susceptibility testing and communication about modest relative risk information might be incorporated into primary care or community health settings. Research is needed to test the balance between what is “best practice” for communicating about common disease markers against what can be effectively integrated into a variety of care settings.

## A multifaceted approach is needed

The complex bio-psychosocial nature of common diseases means that public health interventions will likely increase in complexity as well. Prior social and behavioral research has told us that regardless of the behavior being targeted, interventions that include multiple components and that are sustained over time perform best at promoting long-lasting behavior change.<sup>13</sup> Deciding upon optimal combinations of intervention components that are also cost-effective and not burdensome to individuals and health care providers will continue to require transdisciplinary team research approaches. One such framework<sup>19</sup> calls for scientists to take a more systematic, phased approach to understand and shape improvements in health promotion interventions. There are a number of phases of research that can be conducted linearly or simultaneously to this end. There is the need for early phase studies that serve to develop hypotheses, optimize study design, and specify mechanisms for influencing outcomes. These are “pre-clinical” studies that help to clarify key elements of genetic information that contribute to informed decision-making and optimize interpretation and understanding of feedback. This phase, conducted prior to the widespread deployment of this technology, is important in characterizing the problem and possible solutions, often via mixed approaches that involve both qualitative and quantitative methods. This is followed by exploratory trials wherein comparison groups are added to further clarify the active ingredients and feasibility of intervention approaches. Subsequent phases of research require added research controls and

samples with robust statistical power and typically test hypotheses via randomized controlled trials. Finally, this program of research culminates in a research phase to establish how well these intervention products work in the real world.

## The Multiplex Initiative: A starting point

In keeping with this phased research approach, in the spring of 2006 we launched the Multiplex Initiative, a pre-clinical phase research project with two overarching aims. The first aim was to gain information from a population-based sample of adults (i.e., a sampling frame with a known denominator) about who, when offered genetic susceptibility testing for common health conditions, would be interested in being tested and to explore behavioral responses to test results among those who opted for testing. Specific questions that are being addressed through the Multiplex Initiative include examining whether there are social and psychological differences between those who opt to be tested versus those who decline testing, whether individuals who opt for such testing are able to accurately interpret their test results, whether these individuals' interpretation of their test results is associated with positive or negative emotions or changes in their perceptions about their personal risk for health conditions, and whether receiving their results lead them to seek other personal risk information, either through conversations with health care providers or other means (e.g., family history and behavioral risk assessments). Answering the questions posed above required us to develop a test battery, a standardized approach for offering the test that enabled informed decision-making and provided feedback in a form that could ultimately be applied in a public health setting.

Initial planning for the Multiplex Initiative involved a year's worth of working group meetings with a trans-disciplinary team of scientists who advised us on “best practices” for the prototype test development, methods for obtaining informed decision-making and research consent, and risk feedback approaches. One outcome of this process was the development and deployment of a multiplex genetic susceptibility test prototype for 15 genetic polymorphisms associated with increased risk for eight common health conditions. The health conditions were carefully selected, with consideration given to evaluating the primary prevention potential of genetic susceptibility testing for these conditions. Thus, we selected health conditions (type 2 diabetes, lung, colon, and skin cancer; heart disease, hypercholesterolemia, high blood pressure, and osteoporosis) that are adult-onset and “preventable” – meaning that there are widely accepted prevention recommendations for reducing individual risk for these conditions. Our study subjects are healthy adults ages 25–40 who are all members of the Health Alliance Plan and the Henry Ford Medical Group (both of which are part of a large non-profit health care organization). We decided to conduct this research with an insured population to address our concerns that study participants receiving risk feedback have ready access to prevention services and to enable assessment of patterns of health care use.

Study participants can review in-depth information regarding the testing via a secure Web portal (<http://multiplex.nih.gov>). Those who opt for testing receive additional study-related information during their clinic visit for blood collection. Tested individuals receive their results, along with a report explaining the meaning of their results, in the mail about six months after blood collection. They then receive a telephone call from a research educator who further explains their results and answers any questions the participant may have. Study participants are re-contacted three months after receiving their test results for a follow-up telephone survey.

The Multiplex Initiative represents a modest first step, but will answer basic questions related to comparisons of individuals who do and do not opt for genetic susceptibility testing. This initiative also will provide the first population-based insight into who is most likely to be among the early adopters of genetic susceptibility testing. Since we are surveying and offering testing to a large and diverse sample of individuals, many of whom will not seek testing, we will have



a good deal of information on which we can compare those who do and do not get tested. Additionally, the Web interface will enable us to evaluate an individual's responses to information about genetic susceptibility in real time. This will provide insight into the elements of the information presented that most and least influenced individual's decisions to undergo genetic susceptibility testing. The telephone conversations between participants and research educators to discuss their test results also will lend insight into what individuals perceive to be the take-home messages from their test feedback. For example, are they able to understand caveats about the substantial and greater importance of their *behaviors* above that of their genotypes as contributors to health conditions? Lastly, our considered choice of shorter- over longer-term behavioral outcomes enables us to gain insight into best practices for conveying to individuals the limits and uncertainties of personalized genetic susceptibility test feedback for common health conditions. At this early stage, it is critical to gain insight into the immediate consequences of genetic susceptibility feedback (both positive and negative) on participants' perception of their own personal risk. This can be measured by observing the participants' actions taken after multiplex testing for example their seeking a more complete picture of their personal disease risk (e.g., completion of family history tools, completing behavioral self-assessments, or engaging in conversations with health care providers and other family members).

Recruitment for the Multiplex Initiative began early in 2007. We have approached over 4000 individuals to date, with the goal of accruing 500 who receive the multiplex genetic test. Currently, we have completed over 2000 baseline surveys designed to gather information on how these individuals seek out health information, their beliefs about the role of genetics and behavior in the cause of common health conditions, and their perceptions about their own health. Although recruitment is still underway, preliminary results indicate that, for most, their participation in the Multiplex Initiative is their first experience with clinical research. The majority of individuals who have completed the baseline survey are high school graduates, married, self-report being in excellent or good health, and are relatively familiar with their family's health history. To date, 44% of participants are male and 30% are African-American, which is roughly proportional to the patient population from which the sample was drawn. So far, over 500 individuals have visited the study's Web site to consider testing; to date, about 300 have decided to undergo testing.

The Multiplex Initiative is still in its recruitment phase, so we cannot yet report outcomes. Initial observations by the research educators who have reviewed test feedback reports with the first 50 participants indicate that recipients are not reporting high anxiety about their test results. However, we do not yet have the nuanced understanding of participants' responses that ultimately will be gained from the detailed information we are collecting at each step in the project. We have amassed a comprehensive data set that will enable us to investigate which factors may discriminate the 1500 or more individuals who never logged onto the Web site to consider testing from the 500 who did and, in turn, from the even smaller group that requested testing. Accordingly, we believe that the results of the Multiplex Initiative will provide us with an initial step towards understanding whether healthy individuals use genetic susceptibility testing in ways that could benefit their health.

## In closing

The current climate of vigorous debate is extremely useful for framing research questions and setting rigorous standards for evidence when evaluating the value of genomic discovery for public and clinical benefit. The field has now entered a period where only rigorous experimentation can provide the types of information needed to determine if genetic susceptibility testing should become part of the accepted standard of care. There is a real danger in plunging forward into widespread testing without first performing the kinds of studies

described in this Commentary; doing so will not inform and advance the field. Worse yet, it has the potential to yield a situation where technology alone will drive the market, resulting in products that are not responsive to public health priorities, are limited in reach, and are without benefit to the individuals and populations in greatest need.

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