COMMENTARY | Genetics inMedicine

Multiplex genetic testing: reconsidering utility and informed consent in the era of next-generation sequencing

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Recent advances in the efficiency and economy of genomic sequencing have propelled the growth of personalized medicine. Genetic screening for cancer susceptibility (e.g., *BRCA1/2* testing) is one evidence-based application of "personalized medicine" that improves patient survival.[1] However, most individuals and families in whom hereditary breast cancer is suspected do not have a *BRCA1/2* mutation. Mutations in other genes (e.g., *PTEN*, *TP53*, *PALB2*, and *CHEK2*) have been associated with elevated risks of breast cancer.[2] Thus, multiplex (i.e., multigene) panels have been developed to efficiently screen many cancer susceptibility genes and simultaneously and have been clinically available since 2012.

Panel testing for cancer susceptibility represents the broader transition in clinical genetics from sequential single-gene evaluation to massively parallel (e.g., multiplex) and, in some settings, even whole-exome sequencing. This transition from discrete (i.e., single gene) to broad (i.e., multiplex or whole-genome) applications presents many clinical challenges. Many of the genes included on these "panels" are moderate-penetrance genes that increase the risk of cancer by two- to fourfold, and their clinical utility remains unclear. In many cases, even positive results leave many unknowns regarding cancer risks, optimal management, the impact of multiple moderate-penetrance mutations, and the value of testing unaffected relatives for familial mutations in moderate-penetrance genes.[2] In addition, multiplex testing has been associated with higher rates of variants of uncertain significance, with unknown functional and clinical significance. Thus the outcomes, risks, benefits, and utility of testing for multiple genes of varied risk in the cancer spectrum are unknown. As multiplex testing illustrates, the transition from discrete to broad genomic sequencing presents challenges to traditional conceptualizations of utility, as well as traditional models of informed consent for genetic testing.

DEFINING UTILITY IN THE ERA OF NEXT-GENERATION SEQUENCING

The benefit of a genetic test considered for clinical application has historically been defined by "clinical actionability" or "clinical utility."[3] In the most restricted formulation, clinical utility refers to the ability of the test result to affect a medical outcome or change medical management. As we transition from discrete to broad genomic applications, defining clinical utility is more complex. A test might have clear clinical utility for some genes (e.g., *BRCA1/2*, *MSH1*) but unclear clinical utility for other genes (e.g., *CHEK2*, *ATM*). In addition, given the uncertainty of risks among families without the classic phenotype, clinical utility can vary by family history. For example, *CDH1* testing may have clinical utility for a family with multiple cases of diffuse gastric cancer but unclear utility in a patient with breast cancer with no family history of gastric cancer. Equally important, clinical utility can be considered differently from different perspectives. A provider might ask, "Will this change what I recommend?" Alternatively, a patient or relative might ask, "Will this change what I do?" and a health-care system, "Will this change priorities for reimbursement or investment of value health-care resources?"

Although traditionally valued differently than clinical utility, the increased importance of additional outcomes of broad genetic testing, such as the psychosocial impact (e.g., living with uncertainty; underestimating risk given negative results, impaired family dynamics), have been recognized. Thus there has been increasing endorsement of incorporating individuals' perceptions of personal utility into conceptualizations of utility.[3] There might be additional benefits or utilities that are relevant. Bundling genes that share overlapping phenotypes might be more cost-efficient and less burdensome for patients than sequential testing. In addition, some argue that genes with relatively limited current evidence supporting relationships with clinical phenotypes may be valuable if there is both limited additional cost and a high suspicion that they will ultimately be clinically informative. Thus, even if there is limited immediate utility for some genes or variants on a multiplex panel, there may be a "future utility." Again, these conceptualizations of economic and future utility can be considered differently from the physician, patient, health-care system, and public health perspectives. As we implement next-generation sequencing across a wide variety of clinical settings, new inclusive conceptualizations of utility in which various utilities (clinical, personal,

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economic, future) from various perspectives must be considered to assess the overall risks and benefits of new genomic applications.

NEW MODELS FOR INFORMED CONSENT WITH MULTIPLEX GENETIC TESTING

As we transition from discrete to broad genetic tests, where—at least in the near term—there is unclear utility and an increased potential for uncertainty, adequate informed consent will be an important means to limit potential harms.[4] In cancer genetics, promoting autonomous decision making among patients is traditionally facilitated through counseling with a genetics or other adequately trained professional both before and after testing.[5,6] It has become increasingly recognized that traditional comprehensive models of informed consent, in which specific risks, benefits, and limitations for each gene are described in detail, will not be feasible, applicable, or beneficial to patients as we move to broad genetic testing. "Generic" consent, which includes identifying broad concepts and common-denominator elements indispensible for all patients, has been proposed as an alternative consent strategy for whole-exome sequencing.[7] The intent with this strategy is to minimize information overload and the potential related distress while still providing sufficient information for a wide range of patients to make informed decisions regarding testing or receipt of genetic information. In a "tiered" approach to generic consent, "indispensible" tier 1 information is presented to all patients, whereas tier 2 information is provided to patients who desire or need additional detail to make informed decisions. An additional strategy to address the large amount of relevant information with broad testing is organizing information into clinically relevant "bins."[8]

We propose that these approaches can be combined effectively as a new approach to genetic counseling in the era of multiplex genetic testing. This "tiered and binned" approach has the potential to support informed decisions regarding testing among a wide range of patients with varying informational needs, particularly when there is potential for uncertainty. For example, rather than providing gene-specific information (e.g., certainties and uncertainties regarding cancer risks, cancer spectrums, and medical management), several key themes are emphasized (e.g., testing can identify risk for a wide spectrum of cancers, risks may vary from slightly elevated to high, the potential for uncertainty). This approach recognizes that tier 1 elements may not be sufficient for some patients who will need more comprehensive information. Thus, a key component of this approach is providers' use of knowledge and emotional and information assessments to tailor counseling sessions to an individual patient's informational needs. Equally important, this approach acknowledges that genetic testing is a choice. Although patients and providers are, in most cases, not able to select particular genes to include in or exclude from a panel, patient and provider preferences will determine which genetic test, if any, to pursue.

As multiplex testing illustrates, we are at a critical juncture in medicine, where the breadth and depth of available genetic information is increasing exponentially and holds great promise to improve health outcomes. Panel testing for cancer susceptibility provides an opportunity to begin to consider and navigate many of the ethical and clinical implementation challenges anticipated with whole-exome sequencing.[6] Given the limitations and uncertainties associated with this transition to broad genetic applications, there is an urgent need to better understand the risks, benefits, and utilities of next-generation sequencing applications and how to best deliver services and respect patient preferences as we implement genetic testing for the benefit of diverse patient populations and their families.

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DISCLOSURE

A.R.B. and S.D. report that Myriad Genetics is covering the cost of multiplex testing in an ongoing clinical study. The other author declares no conflict of interest.

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