Breast Cancer Risk Assessment and Genetic Testing: Complexities, Conundrums, and Community

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This special issue of Breast Disease is a testament to how far the field of genetic counseling for breast cancer susceptibility has advanced since the mid-1990s, following the cloning of two major breast (and ovarian) cancer susceptibility genes, *BRCA1* and *BRCA2*. Although perhaps not fully appreciated at the time, individuals who pursued genetic testing shortly after it became available were truly pioneers. They were seeking important, indeed life-changing information, when in fact few specifics about several key issues could be provided. For example, the only available data regarding cancer risks in mutation carriers were derived from the highest risk families, most of which were not representative of the families seen in clinical practice. Then, largely due to the discovery of three founder mutations in Ashkenazi Jews, population-based data revealed a range of breast and ovarian cancer risks in carriers. Subsequently, additional information about mutation penetrance, genetic epidemiology, and risk modifiers, some of which is now integrated into routine clinical counseling, has also facilitated the development of elaborate models to predict the likelihood that an individual will test positive for a *BRCA1/2* mutation. For women who test positive, several recent studies confirm what we suspected early on – namely that prophylactic mastectomy and oophorectomy confer significant protection against the development of breast and ovarian cancer. In premenopausal women, the benefits of oophorectomy are particularly significant, given the associated risk reduction for both breast and ovarian cancer. In addition, for those women who opt against prophylactic mastectomy, screening with a combination of mammography and magnetic resonance imaging appears to frequently detect breast cancer at an early stage. Effective screening strategies for ovarian cancer, however, remain elusive. Ongoing research to develop better screening measures for ovarian cancer is especially critical now given the substantial number of women who are identified by *BRCA1/2* positive status as being at high risk for this disease – a risk not necessarily intuitive based on their family history, which often does not include ovarian cancer.

Perhaps one of the most unanticipated findings subsequent to the identification of *BRCA1* and *BRCA2* was the number of high-risk families who do not harbor a detectable mutation in these genes. Recently, the availability of testing for large rearrangements in *BRCA1* and *BRCA2* has increased the sensitivity of commercial testing; however, the overall yield of deleterious mutations detected with this new method is small. In other high risk families, rare hereditary cancer syndromes may be implicated. Although these syndromes often have a distinct phenotype, they may be underrecognized by clinicians. In addition, we are learning more about other genetic contributions to familial breast cancer risk – including low penetrance gene mutations, SNPs (single nucleotide polymorphisms), and mutations in modifier genes. Given that no other ma-
Major breast cancer susceptibility gene has been identified since the cloning of BRCA1 and BRCA2. It is likely that in many families with breast cancer, the etiology is heterogeneous, comprised of a complex mix of genetic and environmental factors. Thus, it is often difficult to assess cancer risks for concerned individuals and to determine an optimum management plan.

Several articles in this issue illustrate these and other complexities and challenges in hereditary breast cancer risk assessment and management. First, Culver and colleagues describe the nuances of pedigree-based evaluations, drawing attention to qualitative features that can help delineate women who are candidates for genetic testing versus those who are at more moderate risk. They also detail various models for probabilistic estimates of breast cancer risk and BRCA1/2 mutation positivity. Expanding upon this framework, Nusbaum et al. provide a detailed review of hereditary cancer syndromes and low penetrance genes, with an emphasis on key data regarding clinical features, mutation prevalence and penetrance, and genetic epidemiology. The third paper by Smith and Isaacs describes approaches to medical management of women at high risk of developing breast cancer, including measures for surveillance, chemoprevention, and surgical prophylaxis. Vadaparampil et al. and the international team spearheaded by Meiser discuss the utilization and predictors of various risk management strategies. Meiser et al. also provide an overview of international familial cancer services, while many of the other articles in this issue detail the multidisciplinary nature of cancer risk counseling in practice. Despite some of the pitfalls inherent in cancer risk assessment and the availability of sophisticated tools for risk prediction, the articles in this issue collectively underscore the importance of acquiring, verifying, updating, and properly interpreting a family history. To be sure, primary care practitioners, specialist physicians, nurses, and genetic counselors all play pivotal roles in the process of identifying individuals at increased risk and providing them guidance related to risk management.

As demand for cancer susceptibility testing has increased, there has been concomitant interest in exploring options for expanding the reach of genetic counseling and adjunts to such services. To this end, Brown et al. discuss the emerging role of telephone counseling, decision aids, and direct-to-consumer genetic testing, and how these developments may impact upon traditional models of genetic counseling. The same article by Brown and colleagues also ties together the concepts presented in the first three articles by using a novel approach of presenting graduated genetic counseling cases, which serve to illustrate the fundamental and intricate nature of risk assessment and counseling. In particular, they explore key issues affecting newly diagnosed breast cancer patients, young unaffected female mutation carriers, and women who receive uninformative BRCA1/2 test results.

Complementing many of the themes covered in this issue, Quillin and Lyckholm provide a principle-based framework for analyzing and determining practical solutions to ethical quandaries that arise in the context of genetic counseling and testing. They also apply this approach to some of the most controversial issues in clinical genetics which are relevant to predictive testing for cancer risk, namely the duty to warn at-risk relatives, genetic testing of children for susceptibility to adult-onset cancer, and preimplantation diagnosis.

Another critical dimension to be considered within the genetic counseling process is the psychological and familial impact of risk notification, particularly after genetic testing. When genetic testing for hereditary breast cancer risk first became available, it was unclear whether or to what extent individuals might experience undue psychological distress or anxiety. Now, after more than a decade of research, it appears that most people who undergo predictive testing for breast cancer risk cope fairly well with the information. However, several important caveats must be noted: (1) most of the data about the psychological effects of testing are derived from research studies that offered comprehensive genetic counseling; (2) individuals who present for genetic testing are often self-selected in that they tend to have good coping skills at the outset; (3) certain subgroups may be at risk for heightened distress, and identifying them is of interest to practitioners in clinical as well as research settings, as highlighted by Vadaparampil et al. and Meiser et al.; and (4) findings from international studies described by Meiser et al. suggest that it is important to examine cultural and health system-related factors that could contribute to various outcomes associated with genetic testing.

Relatedly, there is growing interest in examining the long-term outcomes that impact individuals who undergo genetic testing. Questions have emerged about long-term quality of life, the best way to measure it, and how and why it might change over time. Several articles in this compilation address these topics from various perspectives. From a medical standpoint, increasing attention is focused on whether genetically high risk newly diagnosed breast cancer patients should be referred for pre-surgical genetic counseling and
Another subgroup of interest is young BRCA1/2 mutation carriers who undergo prophylactic oophorectomy, as they often struggle with persistent menopausal symptoms and difficult questions regarding the role of hormone replacement therapy versus non-hormonal alternatives in alleviating these symptoms. From a psychosocial perspective, questions remain about long-term support needs, especially as genetic information diffuses within the family and relatives grapple with new diagnoses or deaths from cancer as well as complex decisions about risk management. Another element to be considered is the impact of genetic testing on young children, particularly daughters of mothers who have a BRCA1 or BRCA2 mutation. How do parents decide about communicating genetic risk information to their children? What is the effect of this knowledge on children, particularly as they enter adolescence and young adulthood? The article by DeMarco and McKinnon nicely outlines the multifaceted issues involved in family communication about hereditary cancer risk. In addition, they describe the availability of support resources and describe alternative approaches such as a one day educational and support retreat for individuals and family members affected by hereditary breast cancer. Finally, Ms. Rebecca Fisher, a woman who wears many hats as a breast cancer survivor, patient, consumer advocate, wife, and mother (to name a few), poignantly reflects on the impact of genetic testing in an open letter to her young adult daughter.

In closing, the gestalt impression left by all of the articles in this issue is that for individuals who pursue genetic testing, however predictive it may or may not be, their lives are irrevocably touched and perhaps, empowered. Not only does genetic information have profound effects on an individual, often initiating a cascade of feelings and decisions, it also has far-reaching implications for society at large, many of which may not be apparent at the present time. In the wake of the Human Genome Project, as advances in genetic testing are made, increasing numbers of individuals will have the opportunity – and desire – to learn about their propensity for a variety of adult onset conditions, their responses to various medications, and perhaps even their tendencies toward specific behavioral attributes. The “community” aspect of genetics is especially revealed by the final article in this issue – Ms. Fisher’s very personal rendering of how it feels to occupy the space where rapid scientific discovery, and the innumerable spiritual and psychological questions it can raise, meets real life. Indeed, Ms. Fisher’s reflections are a sobering reminder that everyone’s life is tethered to the life of other individuals. Through the lens of our own ideals, our family, our culture, and our society, we will all ultimately grapple with the challenges and benefits reaped by breakthroughs in genetic science. At the same time, we must not lose sight of the significance of knowing that we are so much more than what is in our genes. In this continuum of learning and awareness, it is the shared efforts of policy makers, researchers, health care providers, theologians, ethicists, consumers, and others who together will navigate us through and beyond the genetics nexus. As a community, we have a window of opportunity to embrace lessons learned from cancer genetic counseling and extrapolate them to other pursuits of genetic knowledge. Whether we approach these issues from professional or personal perspectives, it is in all of our best interests to ensure that genetic technology is instilled into the mainstream responsibly and sensitively, and in a way that maximizes potential benefits while diminishing health care disparities and the prospects of physical, social, or psychological harms.