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Increased Reach of Genetic Cancer Risk Assessment as a Tool for Precision Management of Hereditary Breast Cancer

Kathleen R. Blazer, EdD, MS, LCGC, **Thomas Slavin, MD**, **Jeffrey N. Weitzel, MD**

Division of Clinical Cancer Genetics, City of Hope, Duarte, California.

Genetic cancer risk assessment (GCRA) is an interdisciplinary clinical practice that incorporates genetics, oncology, and counseling skills to quantify risk and implement more precise care for individuals with inherited cancer predisposition.[1] GCRA is warranted for individuals with features suggesting he-Related article page 730 reditary cancer, such as early age at onset, triple-negative breast cancer, and/or a family history of breast or ovarian cancer. The cloning of the *BRCA1* gene on chromosome 17 in 1994, and of a second high-risk locus (*BRCA2*) on chromosome 13 in 1995, ushered in an era with increasing appreciation of the potential for oncogenetics to influence breast cancer screening, treatment, and prevention. The subsequent decades have been marked by an ever greater understanding of gene-specific pathology and age-specific risk for *BRCA*-associated breast cancers, as well as a growing understanding of hormonal and genetic modifiers of risk.[1]

Commercial testing for *BRCA1* and *BRCA2* became available in the United States in 1996, and professional society policy statements and practice guidelines affirm the value of *BRCA* testing for identifying and managing high-risk individuals and families.[2,3] In this issue, Rosenberg and colleagues[4] describe *BRCA* gene testing and surgical decision-making outcomes among participants in the Young Women's Breast Cancer Study (YWS), a multicenter cohort of women 40 years or younger who had limited-stage breast cancer (ie, stage 0-II) and received GCRA at academic and community clinics between 2006 and 2014. Participants were mostly white, well educated (85% completed college and/or graduate school), and virtually all had health insurance.

One positive finding of the study was a relatively robust reach, in that most of the YWS study participants (87%) received *BRCA* gene testing within 1 year of their breast cancer diagnosis. While concerns have been expressed about proposed population-based *BRCA* testing for unaffected young women,[5] we are heartened by the increasing participation in standard-of-care GCRA by young women with breast cancer. We concur with the authors[4] that, unfortunately, it is unlikely that this level of access to, or participation in, GCRA would be found in the community setting or among the economically underserved or ethnic minorities.

Corresponding Author: Jeffrey N. Weitzel, MD, Division of Clinical Cancer Genetics, City of Hope, 1500 E Duarte Rd, Modular No. 173, Duarte, CA 91010 (jweitzel@coh.org).

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It is disconcerting that 48% of those who did not get testing indicated that they and/or their physician did not think a *BRCA* mutation was likely, despite the fact that the National Comprehensive Cancer Network (NCCN) guideline[2] has recommended genetic counseling and *BRCA* testing for women with breast cancer diagnosed at 40 years or younger since the outset of the YWS study. The study results did not identify added distress as a reason for declining *BRCA* testing at the time of cancer diagnosis, but the authors[2] suggest this as a potential factor, referencing previous studies that examined and reported on this finding. The authors[2] note the need to explain the practical purpose for genetic testing at the time of a new breast cancer diagnosis and address patient concerns. These issues are most consistently addressed as an essential component of pretest counseling when conducted by clinicians with expertise in GCRA. Comprehensive GCRA also addresses the challenges of conveying complex, uncertain or un-informative test results in a way that reduces confusion and uncertainty about risk management decision-making.

Only a few participants (15) indicated concerns about genetic discrimination as a reason they declined *BRCA* testing. While historically a barrier to genetic testing, additional protections with the Genetic Information and Nondiscrimination Act of 2008 and lack of evidence of genetic discrimination[6] have reduced these concerns in recent years. There is also a broadening social awareness and acceptability of genetic testing for hereditary predisposition. This was most dramatically evidenced during the latter portion of the YWS sampling frame, when in May 2013 actress and director Angelina Jolie announced that she carries a *BRCA1* mutation and chose to undergo a bilateral risk reduction mastectomy (RRM) and reconstruction. This announcement generated considerable interest in testing, evidenced by a surge in uptake of GCRA services and testing noted in the YWS study and others in the United States and internationally.[7,8] It is notable that most of the media sound bites on Jolie's announcement included her clear admonition that although bilateral mastectomy was the answer for her, it is not always the answer—a qualification that is consistent with the NCCN guideline classification of RRM as an *option* for *BRCA* carriers.[2]

The YWS study[2] reported a high uptake of RRM (86%) among the women diagnosed as having a *BRCA* mutation. While the precise timing of genetic testing relative to treatment decision-making was not reported in the study, the authors[2] suggest that because testing took place within 3 months of diagnosis for most, and within 1 year for all participants, it is likely that *BRCA* status was available at the time of surgical decision-making in context of breast cancer treatment. This finding is consistent with those of previous studies[9–11] documenting a high rate of RRM among women with newly diagnosed breast cancer identified as *BRCA* carriers, including an international study[12] that noted significant variation in the uptake of RRM among young women with *BRCA* mutations, with the highest RRM rates among women in North America. These studies affirm the feasibility of GCRA at diagnosis to inform treatment-related surgical decision-making. The receipt of adjuvant chemotherapy affords a window of several months,wherein GCRA can be implemented with adequate time for return of genetic test results.[9] The current trend toward the use of neoadjuvant chemotherapy affords a comparable window of opportunity to obtain genetic risk information prior to deciding on the preferred surgical approach.

We share the concerns of the authors[2] that 51% of women in their study chose bilateral mastectomy despite being *BRCA* negative. While potentially reflecting the overall trend toward increased uptake of bilateral mastectomy among young women in cancer registries,[13,14] this is markedly higher than the 9% to 21% rate reported in previous studies[9–11] focused on presurgical GCRA. The influences of celebrity and other socially mediated trends, young age, family cancer history, lobular histologic characteristics, need for ipsilateral mastectomy, and incidents where the first cancer was not screen detected have all been identified as significant factors contributing to increased uptake of bilateral mastectomy.[12,13] Notably, physician recommendation is recognized as one of the strongest factors influencingcontralateralmastectomy.[10]WhiletheauthorsoftheYWS study[2] acknowledged the need for better clinician communication about the low risk of contralateral breast cancer among *BRCA*-negative women who do not have other risk indicators, the study does not provide specific details about the content of genetic testing and risk management information conveyed to study participants, and it is unclear if it was consistently delivered by clinicians with GCRA training and expertise.

The number of patients with uninformative *BRCA* genetic test results in this study is typical of reported high-risk screening populations. Next-generation sequencing has ushered in a new era of broad-spectrum testing for the growing list of potential genetic etiologies for breast cancer beyond *BRCA*. A few of the cases in the YWS cohort may have an alternate genetic predisposition that confers sufficient new primary breast cancer risk to justify consideration of RRM, such as a pathogenic variant in *TP53*. It should be noted that many of the moderate- and low-penetrance genes currently included on multigene panels do not reach a level of risk to justify RRM.[2,15] The expanded use of multigene panel testing, often by clinicians inadequately trained in GCRA, may exacerbate the uptake of unwarranted RRM.

Affordable next-generation sequencing will help us increase the reach of GCRA, but much work remains. Resources are needed to support clinician contributions to the large-scale data collection required to characterize low- to-moderate-penetrance genes, and to determine the effectiveness of risk appropriate treatment interventions. Furthermore, it is essential to expand evidence-based GCRA training, education, and practice-centered support across the spectrum of health care.

It is encouraging to see the integration of GCRA into standard-of-care clinical treatment of breast cancer over the past 2 decades. The task remains to ensure that the benefits of GCRA reach more individuals and families, including those among underrepresented minorities, with economic disparities, and in low- to middle-income countries. As long as there are growing communities of practice and research collaboration, it won’t take another 20 years to get there.

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