Cancer Survivorship Care: An Opportunity to Revisit Cancer Genetics

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Genetic test results can substantially impact the care of cancer survivors even long after their initial oncologic treatments, and can also lead to testing and initiation of clinical care for their relatives. There are two scenarios in which it is particularly important to assess genetic risk and consider genetic testing during survivorship: (1) in cancer survivors who meet criteria for genetic testing but have not yet had this performed, and (2) in cancer survivors who had genetic counseling and testing previously yet should now consider additional testing because of a new cancer diagnosis (personal or family) or updated testing options (e.g., availability of expanded molecular analyses).

To illustrate the importance of addressing genetic risk in survivors, consider the following patient case. J.S. is a 53-year-old woman who had tested negative for *BRCA1/2* mutations in the late 1990s after having been diagnosed with breast cancer at age 29. Last year, her nieces inquired about her testing history and results because they were concerned about their own risks. When J.S. learned that more extensive testing had become available (including testing for *BRCA1/2* gene rearrangements), she opted for additional testing and was found to carry a deleterious *BRCA1* mutation. Based on this new information, she underwent bilateral salpingo-oophorectomy, at which time she was diagnosed with stage 2 ovarian cancer. In addition to facilitating J.S.'s care, the knowledge of her *BRCA1* mutation allowed her family members to make informed decisions about their own testing and treatment. Thus, genetic testing can play a critical role in optimizing a patient's survivorship care and in mitigating future risks for her and her family. The evolution of testing, as illustrated in this case, is one of several reasons we discuss for revisiting genetics in the care of cancer survivors.

In this article, we describe barriers to genetic testing, which must be considered to address the needs of cancer survivors who meet testing criteria but have not yet been evaluated. Testing for pathogenic mutations in susceptibility genes known to be associated with familial cancer syndromes has been recommended for many cancer patients and their family members for two decades, but not everyone who receives this recommendation is tested. Genetic testing may be appropriate for some people based on concerning family histories or their own characteristics (e.g., young age at diagnosis with cancer, Ashkenazi Jewish heritage, personal diagnosis with a particular cancer site or histology, or a syndromic presentation). However, many individuals who meet criteria for *BRCA* testing, Lynch syndrome testing, and/or testing

for mutations in other cancer-predisposing genes have not been tested for various reasons, including insurability concerns (which are now less relevant thanks to the 2009 Genetic Information Nondiscrimination Act, or GINA, which protects against genetic discrimination in insurance or employment), costs, inadequate access to subsequent care, and emotional distress.¹⁻⁴ Jaggi et al⁵ recently found among survivors of early-stage breast cancer that racial/ethnic minorities were less likely to have discussed genetic testing with a health professional even when they had a strong desire for testing, and that those who had received genetic testing were younger, less likely to be black, and more likely to have a family cancer history. Similarly, Levy et al⁶ reported that young survivors of early-stage breast cancer (diagnosed at age 40 years or younger) were less likely to have had genetic testing if they were black or Latina rather than white (even when Jewish women were excluded). Those enrolled in a health maintenance organization were also less likely to have been tested than those with point-of-service insurance plans.⁶

Some patients may be too sick or distressed by their cancer and/or cancer treatment to pursue testing. Emotional barriers to genetic testing exist even in healthy populations. For example, in 2002, 76 black women at high risk for breast cancer were found to be less likely to agree to genetic testing if they were anticipating negative emotional responses to testing and were more concerned about result-based stigmatization.⁴ A decade later, a qualitative interview study of 120 Latina women at risk for *BRCA* mutations found that logistic concerns (e.g., health insurance coverage), emotional concerns (e.g., distress), and competing life concerns (e.g., caregiving responsibilities for children or other family members) were the biggest barriers to genetic testing.⁷ Historically, fear of loss of health insurance has been one of the greatest barriers to genetic testing. In fact, in a survey in 2000, a majority of 163 genetic counselors reported that they themselves would not have chosen to bill insurance for any genetic testing they might have needed, because of concern about potential discrimination based on the results.⁸ GINA was passed by Congress in 2008 to protect individuals from discrimination based on testing results.⁹⁻¹¹

An interview study of 25 clinicians, 20 insurance executives, and six patient advocates identified poor coordination of tests relative to treatment decisions and reimbursement-related disincentives as the major barriers to *BRCA* testing. Five of the six

advocates in that study explained that out-of-pocket costs for patients are a significant impediment to genetic tests.¹² However, financial and insurability barriers to genetic testing have been reduced recently because of GINA, the Affordable Care Act (ACA), and the US Supreme Court's ruling against gene patenting (removing the single laboratory testing monopoly).¹³⁻¹⁵ Although the ACA allows insurance plans to require cost sharing for *BRCA* testing in cancer survivors,¹⁴ most insurance plans will cover at least part of the cost of *BRCA* testing for survivors who meet criteria, and the ACA has increased the proportion of Americans who are insured. Also, market forces are reducing the cost of gene panels, and there are new companies that are providing genetic testing inexpensively (one assessing 19 genes for approximately \$250).¹⁶ Some survivors may have initially opted not to be tested because of high costs or fear that the results would limit their insurability, but costs are declining rapidly (with modern next-generation sequencing), and survivors should be made aware that a test that may once have been prohibitively expensive is now more affordable.

Inadequate time and expertise on the part of health-care providers regarding the relevance of genetics for optimal clinical care may also impede testing. If providers do not understand or explain why genetic testing is important, patient concerns and confusions will not be adequately addressed. Genetic counseling is often valuable for defusing irrational fears and disseminating accurate information. However, there are few proven behavioral and/or educational interventions that improve the uptake of genetic testing, particularly for cancer survivors.^{17,18} Efforts are ongoing to develop better psychoeducational interventions that will assure that cancer survivors accurately assess the benefits and do not overestimate the risks of *BRCA* counseling and testing.¹⁹

In the following paragraphs, we describe reasons for consideration of additional testing in cancer survivors who already had genetic counseling and testing previously. The indications for genetic testing have expanded over time as molecular and clinical research about familial cancer risk has advanced. Increased understanding of breast cancer molecular phenotypes and their associations with mutations in specific genes has led to consideration of expanded testing.

An example is TP53 testing (often as part of a gene panel) in young women with HER2-positive breast cancer.^{20,21} Indications for testing women with triple-negative breast cancer and ovarian cancer have also expanded in recent years because of therapeutic developments.²² A new cancer diagnosis in a cancer survivor or her close relatives may now render that person a candidate for molecular testing, especially if the additional diagnosis appears to be part of a hereditary syndrome. One example would be a 55-year-old woman with a history of right-sided hormonally sensitive breast cancer but no family cancer history. *BRCA* testing would not be recommended at the time of her initial diagnosis, but testing will be warranted if she is later diagnosed with a left-sided breast cancer or if her sister is diagnosed with ovarian cancer. Changes in testing guidelines can also increase indications for testing; for instance, *BRCA* testing criteria were recently broadened to include all ovarian cancer patients instead of only those with concerning family histories and/or young age.

The evolution of the array of available genetic tests for patients with cancer adds to the complexity of care in this setting. As

illustrated in the case of J.S., the testing available to a patient in the 1990s or early 2000s would not have been as extensive as standard-of-care genetic testing is today. Therefore, patients testing negative more than 10 years ago could warrant further testing now. Evaluation for large genetic rearrangements is now routinely performed as part of *BRCA* testing, and pathogenic mutations have been discovered in genes more recently recognized to confer risks for multiple malignancies, including but not limited to *PALB2*,²³ *PTEN*,²⁴ *CHEK2*,²⁵ and *STK11*.²⁶ Moreover, many variants that were previously termed "variants of unknown significance" have since been more definitively categorized as deleterious or non-deleterious, and efforts are ongoing to understand the clinical implications of as many variants as possible.

Thus, there are a number of reasons why survivors and their family members may wish to consider additional genetic testing long after an initial cancer diagnosis. Therefore, the American Society of Clinical Oncology recommends that cancer family history information be gathered and reassessed periodically in survivors.²⁷ But there is no established mechanism in practice to prompt and facilitate a discussion of genetics in routine oncology follow-up care. Also, while oncologists are generally aware of progress in somatic genetics because of the recent explosion in targeted therapies, they may be less familiar with progress in germline genetics.

Providers caring for cancer survivors should regularly update family histories, consider referral to genetic counselors when new concerning cases of cancer develop in the patient or family members, and inform survivors about relevant changing indications and pros and cons for currently available tests. This may be especially challenging for long-term survivors, whose clinicians may not know what kind of testing they originally underwent, if any. Comprehensive survivorship care plans that prompt clinicians and patients to revisit family history and genetics may play a meaningful role in facilitating this process.^{28,29} To that end, survivorship care plans should include a recommendation for repeated assessments over time of whether modern genetic counseling and testing could impact management strategies for each survivor and his/her family. Even when cancer survivors were tested years ago for a deleterious mutation, it is important that providers and patients keep in mind that cancer genetics has been evolving as rapidly as have other aspects of oncology (i.e., that the comprehensiveness and accuracy of genetic testing have changed over the decades). Furthermore, it is imperative to consider that recommendations for follow-up for patients who have been found to carry a mutation in the past also change over time.

Assuring that all cancer survivors are accurately informed about up-to-date and personalized genetic testing recommendations and implications of testing results should help enhance their access to, and empower their decision-making around, cancer prevention and control. Ultimately, this will improve disease-related outcomes.

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