

VIEWPOINT

Treatment Decision Making and Genetic Testing for Breast Cancer

Mainstreaming Mutations

Steven J. Katz, MD, MPH

Departments of Medicine and Health Management and Policy, University of Michigan, Ann Arbor.

Allison W. Kurian, MD, MSc

Departments of Medicine and Health Research and Policy, Stanford University, Stanford, California.

Monica Morrow, MD

Breast Service, Memorial Sloan-Kettering Cancer Center, New York; and Department of Surgery, Weill Medical College of Cornell University, New York, New York.

Rates of genetic testing for women with diagnosed breast cancer appear to be increasing substantially. More than one-fourth of patients diagnosed today undergo testing,¹ multiple-gene sequencing panels are replacing testing limited to *BRCA1/2* mutations, and genetic counselors report ordering more tests.² Within the next few years it is likely that most patients with newly diagnosed breast cancer will undergo genetic testing to inform their risk of developing a subsequent cancer. There is already a widening gap between the availability of more expansive genetic testing and the relative importance of results to treatment decisions.

This gap is not new. There is a long history of rapid uptake of evaluative testing that outpaces the ability to incorporate results into treatment decisions. Evaluative tests are subject to much less scrutiny and oversight than the treatments they influence. Once evaluative technology is introduced, "off-label" use is determined by clinicians, with few constraints. Logical arguments for additional information from testing can be made,

those occurring among patients' relatives. Clinicians need to discuss the results of these tests with patients. By contrast, pathologic staging tests and tumor biology markers such as ER, PR, and HER2 are performed routinely on all patients without explicit informed consent, and many patients rely on their clinicians to incorporate results into treatment recommendations.

A second major challenge is the unique contribution of germline genetic testing to cancer treatment decision making: genetic results inform the risk of future cancers and potential prevention strategies much more than they guide treatment options for the diagnosed disease. For most patients with invasive breast cancer, the risk of a second primary breast cancer after treatment is extremely low—far lower than the risk of metastatic recurrence of the diagnosed cancer.⁴ Thus, clinicians' recommendations are focused on the disease-free survival trade-offs between cancer treatment options. It is difficult for patients to consider these different schemas: secondary prevention of new cancers vs primary treatment of the one they have. Patients must comprehend information about genetic risk and its implications for local therapy of the primary cancer in addition to information about systemic treatments. This burden on patients is not easily mitigated under the frequently pressured pace of cancer treatment decision making. Obtaining a timely genetic counseling appointment, test results, and follow-up discussion is challenging.

Breast cancer will be the tracer condition to illuminate how early and rapid adoption of expanded genetic testing influences treatment decision making and improves patient health.

and the harms of a test to individual patients are often minimized. Testing charges are generally a small proportion of the total cost of cancer treatment, are subject to less scrutiny than therapeutic charges, and are decreasing in cost. For example, magnetic resonance imaging is widely used to stage breast cancer, despite the lack of evidence for its benefit on treatment outcomes.³ The rapid rise of genetic testing for breast cancer reflects increasing awareness and desire for testing among patients and the substantial discretion that clinicians have to direct evaluative strategies after cancer diagnosis.

The widespread adoption of germline multiple-gene panel testing poses unique challenges for clinicians in navigating breast cancer treatment decisions with patients. First, patients are more involved in determining whether they undergo genetic testing than for other evaluative tests. Furthermore, test results are more formally discussed, primarily because they have implications for the risk of future cancers, especially

Contralateral prophylactic mastectomy (CPM) will serve as an indicator of the effect of genetic testing on treatment decisions, because it is the most effective approach to preventing secondary breast cancer. Rates of CPM began to substantially increase well before the advent of multiple-gene panel testing.⁵ The increase in use of CPM is largely the result of patient demand, fueled predominantly by the desire to leave cancer and its treatments behind forever. This desire is not dampened by the fact that CPM does not increase survival in women at average risk of a second primary breast cancer.

The effect of genetic testing on patient preferences for CPM could be substantial, but the direction is uncertain. For women without a clinically meaningful risk of contralateral breast cancer, negative genetic test results should provide additional reassurance about the threat of future disease and reduce women's desire for the most extensive surgery. By contrast, identifying a deleterious mutation in a gene such as *BRCA1* that confers a well-defined, substantially elevated risk of a new breast

Corresponding

Author: Steven J. Katz, MD, MPH, Departments of Medicine and Health Management and Policy, University of Michigan, North Campus Research Complex, 2800 Plymouth Rd, Bldg 16, Room 430W, Ann Arbor, MI 48109-2800 (skatz@umich.edu).

cancer clearly raises the stakes and informs surgical options for secondary prevention.

However, most of the genes in which mutations are associated with an increased risk of future cancer do not carry the same magnitude of risk as *BRCA1* and *BRCA2*. Furthermore, the magnitude-of-risk estimate for an individual patient varies widely as a function of age and family cancer history. Pathologic mutations for which evidence-based practice guidelines are lacking, and genetic variants of uncertain significance are increasingly more common than *BRCA1/2* mutations.⁶ Clinically ambiguous test results could introduce more uncertainty about future cancer risks, which may further increase patients' desire for the most extensive treatments.

The rapid increase in genetic testing and its unique role in the evaluative strategies for breast cancer treatment require better integration of testing into patient care. There is pressing need to improve test validity to maximize the benefit of use in treatment settings. Ambiguous test results, such as variants of unknown significance, may do more harm than good if they increase patients' concerns about a new cancer. Furthermore, there is need to align genetic test metrics with those of other evaluative testing: focusing on absolute risk for an individual patient over a fixed period and incorporating competing mortality risks (including that of the diagnosed cancer).

It will be critically important to improve clinician approaches to risk-benefit communication with patients. The widespread uptake of genetic testing will further increase the complexity of treatment decision making in clinical encounters; the demand for clinicians to navigate this reinforces the need to improve clinician skills in risk-benefit communication, especially approaches to addressing drivers of patient preferences for treatments. Deliberation tools need to be developed to assist clinicians in the challenging task of integrating disparate risk and benefit information into a coherent narrative for patients.

The role of and approach to genetic counseling must be reengineered to maximize its effectiveness in treatment settings. The first priority is mainstreaming counseling expertise. Genetic counseling may be poorly utilized owing to insufficient care coordination or limited access. Addressing this potentially growing problem will require new investment for training counselors and new

approaches to integrating their services into practice. It will be especially important to slow the pace of treatment deliberation to allow adequate time to triage patients and incorporate genetic counseling services efficiently into clinic workflow. The second priority is to update the framework and perspective from which counseling is delivered. The basis of genetic counseling involves addressing the implications of test results on future disease risk in families. Such assessments anchor on estimates of cumulative lifetime risk and generally do not consider competing mortality risk.⁷ By contrast, treatment options for the diagnosed cancer are framed in terms of differences in disease-free survival over a 5- to 10-year period (the most stable estimates generated from clinical trials), and competing mortality is considered in assessment of net benefit. These important differences in framing the outcomes and the period over which they occur complicate the task of integrating information from these disparate perspectives into a management plan. This calculus will become even more complicated as genetic test results are increasingly used to select cancer treatment. The need to reconcile these perspectives should motivate reexamination of the role of and approach to genetic counseling in cancer treatment.

There is growing concern that clinicians are falling behind in their understanding of fundamental aspects of genetic testing and their confidence in discussing results with patients. An alternative viewpoint is that the use of genetic tests is outpacing the applicability of their findings to cancer treatment decisions. The rapid dissemination of testing obligates research to determine the influence of testing on patient experiences and treatment decisions. This will require population-based approaches in partnership with physicians, other clinicians, and industry. Essential questions include test performance across patient subgroups that vary by race/ethnicity; personal and family cancer history; disparities in testing of vulnerable populations; and the effects of testing and results on the experiences and perspectives of patients and their families.⁸ Last, there is a pressing need to study the benefits of genetic test results on treatment decision making from both patients' and clinicians' perspectives. Breast cancer will be the tracer condition to illuminate how early and rapid adoption of expanded genetic testing influences treatment decision making and improves patient health.

ARTICLE INFORMATION

Published Online: July 23, 2015.
doi:10.1001/jama.2015.8088.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Kurian reported receiving research funding from Myriad Genetics and Invitae. No other disclosures were reported.

REFERENCES

- Jagsi R, Kurian AW, Griffith KA, et al. Genetic testing decisions of breast cancer patients: results from the iCanCare study. Abstract presented at: The American Society of Clinical Oncology Annual Meeting; June 2015; Chicago, Illinois.
- Hooker GW, Nagy R, Buchanan A, et al. Cancer genetic counseling and testing in an era of rapid change. Abstract presented at: The American College of Medical Genetics Annual Meeting; March 25, 2014; Nashville, Tennessee.
- Morrow M, Waters J, Morris E. MRI for breast cancer screening, diagnosis, and treatment. *Lancet*. 2011;378(9805):1804-1811.
- Nichols HB, Berrington de González A, Lacey JV Jr, Rosenberg PS, Anderson WF. Declining incidence of contralateral breast cancer in the United States from 1975 to 2006. *J Clin Oncol*. 2011;29(12):1564-1569.
- Tuttle TM, Habermann EB, Grund EH, Morris TJ, Virnig BA. Increasing use of contralateral prophylactic mastectomy for breast cancer patients: a trend toward more aggressive surgical treatment. *J Clin Oncol*. 2007;25(33):5203-5209.
- Maxwell KN, Wubbenhorst B, D'Andrea K, et al. Prevalence of mutations in a panel of breast cancer susceptibility genes in *BRCA1/2*-negative patients with early-onset breast cancer [published online December 11, 2014]. *Genet Med*. doi:10.1038/gim.2014.176.
- Easton DF, Pharoah PD, Antoniou AC, et al. Gene-panel sequencing and the prediction of breast-cancer risk. *N Engl J Med*. 2015;372(23):2243-2257.
- Kurian AW, Ford JM. Multigene panel testing in oncology practice: how should we respond? *JAMA Oncol*. 2015;1(3):277-278.